Symptom burden and health-related quality of life in cancer survivors undergoing hyperbaric oxygen therapy for pelvic late radiation tissue injuries

A mixed-methods study

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SCIENTIFIC ENVIRONMENT

The PhD candidate has been employed at the Department of Occupational Health, Haukeland University Hospital. Throughout the PhD period, the candidate was connected to and located at the Faculty of Psychology, Centre for Crisis Psychology (CCP) at the University of Bergen.

The doctoral training was conducted at the research school 'The Graduate School of Human Interaction and Growth' at the Faculty of Psychology of the University of Bergen. In addition, the candidate was connected to CCP's multidisciplinary research group 'Grief, Trauma and Serious Disease'.

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ABSTRACT

Curative radiotherapy for cancer may lead to severe late radiation tissue injuries (LRTI). However, limited knowledge exists about pelvic cancer survivors' LRTI symptoms, distress and health-related quality of life (HRQOL). Hyperbaric oxygen therapy (HBOT) is an adjuvant therapy for LRTI, but has only been studied to a limited extent. The overall purpose of this thesis was therefore to provide an increased understanding of the symptom burden and HRQOL of cancer survivors undergoing HBOT for pelvic LRTI.

Patients enrolled in the study were recruited from cancer survivors with pelvic LRTI assigned to the Norwegian National Unit for Planned Hyperbaric Oxygen Treatment. Here, participants received HBOT in a mono-place pressure chamber, breathing pure oxygen at a pressure of 2.4 atmosphere absolute for 90 minutes once a day for six weeks.

A mixed-methods approach with an explanatory sequential research design was adopted, whereby data was collected sequentially through self-reported questionnaires at baseline (T1), on completion (T2) and six months after HBOT (T3), and in-depth interviews were performed on completion of HBOT.

Taking a quantitative approach with a descriptive cross-sectional research design, Paper 1 studied the symptom burden, distress and HRQOL in survivors with established pelvic LRTI compared to norm populations, and the relation between these factors at baseline. Here, 107 participants (mean age 64, 53% men) were included. Compared to norms, participants reported more urinary (mean 68.7 vs. 89.5; p=.00; d=1.4) and bowel symptoms (mean 62.5 vs. 92.4; p=.00; d=2.7), increased psychological distress (mean 13.4 vs. 10.3; p=.00; d=0.6), and overall poorer HRQOL (mean 54.9 vs. 71.2; p=.00; d=0.7). A higher symptom burden and higher levels of psychological distress were associated with lower HRQOL (r^2=46%), but psychological distress did not moderate the influence of symptoms on HRQOL.

Taking a qualitative approach with a phenomenological-hermeneutical research design, Paper 2 explored how cancer survivors with pelvic LRTI experienced undergoing HBOT. Data was collected via in-depth interviews with 20 participants. The interviews were audiotaped, verbatim transcribed and analysed using Systematic Text Condensation. Four main themes emerged from the analyses to describe the participants' experience of HBOT: 1) 'Approaching an unknown world'. This theme illuminated that, despite information prior to the treatment, informants were worried about, but highly motivated for HBOT; 2) 'From feeling worried to becoming familiar'. This theme elaborated on HBOT as a process whereby a combination of relevant information, clear routines and person-centred care were important acceptance and coping factors during HBOT; 3) 'A long lasting treatment course'. This theme showed that absence from home and social relations were acceptable, since meeting peer patients allowed a unique community to develop; and 4) 'The treatment course went better than expected'. This theme elaborated on how most participants only experienced minor, temporary and highly tolerable side-effects of HBOT, where most participants described initial symptom relief during the treatment course.

Taking a quantitative approach with a pre-test – post-test research design, Paper 3 studied the development of, and the associations between, symptoms of LRTI and HRQOL, with six-months follow-up after HBOT. Ninety-five participants (mean age 65 years, 52.6% men) were included. Pelvic LRTI, overall HRQOL, and all function scales and the HRQOL symptom scales of sleep, diarrhoea, pain and fatigue improved significantly six months after treatment (*P*-range =0.00-0.04). Changes were already present on the completion of HBOT and were maintained or further improved up to follow-up at T3. Only a weak significant correlation between changes in symptoms and overall HRQOL was found (Pearson *r*-range 0.20-0.27).

In addition to the results from the three papers, the merging of the quantitative and qualitative results provides increased, comprehensive and nuanced understanding and knowledge of the

participants' situation at baseline and in the HBOT process, and the participants' situation on completion of HBOT and at six-month follow-up. Here, the merged findings at baseline show that all areas of the participants' lives were highly impaired, documented as a severe LTRI symptom burden, psychological distress and impaired HRQOL, whereby HBOT was expressed as a hopeful treatment opportunity. The qualitative data describing the HBOT process indicates that it was difficult for the participants to absorb the HBOT information provided before treatment. However, the participants adjusted quickly to the HBOT procedures, whereby the nurses' follow-up and care were crucial. The long-lasting HBOT course away from daily life was to a certain degree outweighed by peer support. On completion of HBOT, the merged results indicated an improved symptom burden and improved HRQOL, and limited side-effects. At six-month follow-up, the quantitative results showed a further improvement from the end of HBOT in pelvic LRTI, and overall HRQOL. However, the participants still had pelvic LRTI and impaired HRQOL at follow-up.

To the best of our knowledge this is the first mixed-methods study which studies the entire process of pelvic LRTI and HRQOL of cancer survivors with pelvic LRTI undergoing HBOT. The knowledge gained from this thesis illustrates the need for increased competence and education of healthcare professionals about pelvic LRTI, the importance of systematic assessment of pelvic LRTI symptoms and HRQOL after radiation, proper symptom management, and educating survivors in adequate symptom management and coping skills. Furthermore, the results provide strong evidence that cancer survivors with pelvic LRTI and impaired HRQOL may benefit from undergoing HBOT. In particular, reduced symptom severity and improved social and role function may influence daily living positively. Even if the results from this study cannot be generalised, the results do provide important knowledge in a field that has only been studied to a limited extent, and an important basis for clinical practice and further research.

SAMMENDRAG

Kurativ strålebehandling for kreft kan føre til alvorlige vevsstråleskader (LRTI). Det finnes imidlertid begrenset kunnskap om bekkenkreft-overleveres LRTI symptomer, psykisk belastning og helse-relatert livskvalitet (HRQOL). Hyperbar oksygenbehandling (HBOT) er en adjuvant, men lite studert, behandling for LRTI symptomer. Derfor var det overordnede formålet med denne studien å få økt forståelse av symptombyrde og HRQOL hos kreft-overlevere som gjennomgår HBOT for stråleskader i bekkenet.

Pasienter som ble inkludert i studien ble rekruttert fra kreft-overlevere med bekken LRTI henvist til Norsk Nasjonal Enhet for Planlagt Hyperbar Oksygenbehandling. Her ble deltakerne behandlet med HBOT i enmannstrykkammer, og pustet rent oksygen ved et trykk på 2.4 atmosfære absolutt i 90 minutter en gang daglig i seks uker.

En mixed-metode med et forklarende sekvensielt forskningsdesign ble benyttet. Data ble samlet inn sekvensielt ved hjelp av selvrapporterte spørreskjemaer på baseline (T1), ved avslutning HBOT (T2) og ved seks måneders oppfølging (T3), og dybdeintervju ved avslutning HBOT.

Gjennom en kvantitativ tilnærming og tverrsnittsdesign studerte vi i Artikkel 1 symptombyrde, psykisk belastning og HRQOL hos kreft-overlevere med etablerte bekken LRTI symptomer sammenlignet med normpopulasjoner, og sammenhengen mellom disse faktorene før oppstart av HBOT. Totalt 107 deltakere (gjennomsnittsalder 64 år, 53% menn) ble inkludert. Sammenlignet med normpopulasjonen rapporterte deltakerne mer urinsymptomer (gjennomsnitt 68.7 vs. 89.5; p=.00; d=1.4) og tarmsymptomer (gjennomsnitt 62.5 vs. 92.4; p=.00; d=2.7), økt psykisk belastning (gjennomsnitt 13.4 vs. 10.3; p=.00; d=0.6), og generelt dårligere HRQOL (gjennomsnitt 54.9 vs. 71.2; p=.00; d=0.7). Høyere

symptombyrde og høyere nivå av psykiske plager var assosiert med lavere HRQOL (r^2=46%), men psykiske plager modererte ikke symptomenes påvirkning på HRQOL.

Gjennom en kvalitativ metode og et fenomenologisk-hermeneutisk forskningsdesign, undersøkte vi i Artikkel 2 hvordan kreft-overlevere med bekken LRTI erfarte å gjennomgå HBOT. Data ble samlet inn via dybdeintervjuer med 20 deltakere. Intervjuene ble tatt opp på lydbånd, ordrett transkribert og analysert ved bruk av Systematisk Tekstkondensering. Fire hovedtemaer fra analysen synliggjorde informantenes erfaringer: 1) 'Tilnærming til en ukjent verden'. Dette temaet belyste at tross informasjon i forkant av behandlingen, var informantene bekymret, men svært motiverte for HBOT, 2) 'Fra å føle seg bekymret til å bli kjent'. Dette temaet utdypet HBOT som en prosess der en kombinasjon av relevant informasjon, klare rutiner, personsentrert omsorg var viktige faktorer for aksept og mestring av behandlingen, 3) 'Et langvarig behandlingsforløp'. Dette temaet belyste at fraværet fra hjemmet og sosiale relasjoner var akseptable ettersom møte med medpasienter tillot et unikt fellesskap å utvikle seg, og 4) 'Behandlingsforløpet gikk bedre enn forventet'. Dette temaet viste at de fleste deltakerne kun opplevde mindre, forbigående og svært tolerable bivirkninger av HBOT, hvorved majoriteten beskrev initial symptomlindring underveis i behandlingen.

Gjennom en kvantitativ tilnærming og et før – og etter forskningsdesign, studerte vi i Artikkel 3 utviklingen av, og assossiasjonene mellom, symptomer på bekken LRTI og HRQOL etter HBOT ved slutten av behandlingen (T2), og ved seks måneders oppfølging (T3). Nittifem deltakere (gjennomsnittsalder 65 år, 52.6 % menn) ble inkludert. Resultatene indikerte at bekken LRTI symptomer, HRQOL symptom skala, søvn, diare, smerte, fatigue, generell HRQOL og alle funksjonsskalaer var signifikant forbedret seks måneder etter behandling (*P*-område =0.00-0.04). Endringer var til stede allerede ved slutten av behandlingen og opprettholdt eller ytterligere forbedret ved 6 måneders oppfølging. Det ble kun funnet en

svak, men signifikant korrelasjon mellom endringer i symptomer og overordnet HRQOL ble funnet (Pearson *r*-område 0.20-0.27).

I tillegg til resultatene fra de tre artiklene, bidrar sammenstillingen av de kvantitative og de kvalitative resultatene til en økt, omfattende og nyansert kunnskap og forståelse for deltakernes situasjon ved oppstart av behandlingen, behandlingsprosessen, deltakernes situasjon ved avslutning og seks-måneders oppfølging etter HBOT. De sammenslåtte resultatene fra før oppstart av HBOT indikerte stor symptombyrde, psykiske belastning, svekket HRQOL, som påvirket alle områder av livet. HBOT representerte en ukjent, men håpefull behandlingsmodalitet. De kvalitative funnene som beskriver selve behandlingsprosessen, viste at det var vanskelig for informantene å absorbere HBOT informasjonen. Deltakerne tilpasset seg imidlertid raskt til HBOT prosedyrene. Her var sykepleiernes oppfølging og omsorg avgjørende. Det langvarige HBOT forløpet, borte fra dagliglivet ble til en viss grad oppveid av støtte fra medpasienter. Ved behandlingsslutt viste de sammenslåtte resultatene forbedrede bekken LRTI symptomer, og de fleste HRQOL dimensjoner, samt at deltakerne erfarte minimale bivirkninger av HBOT. Ved seks måneders oppfølging indikerer de kvantitative resultatene ytterligere forbedrede LRTI symptomer og HRQOL.

Så vidt vi vet er dette den første mixed-metode studien som studerer hele prosessen med symptombyrde, og HRQOL hos kreft-overlevere med stråleskader i bekkenet som gjennomgår HBOT. Kunnskapen fra denne avhandlingen viser behov for økt kunnskap og utdanning av helsepersonell knyttet til stråleskader i bekkenområdet, betydningen av systematisk kartlegging av symptomer på stråleskader og HRQOL etter stråling i bekkenområdet, god symptomlindring og opplæring av kreftoverleverne i adekvat symptombehandling og mestring. Videre gir resultatene fra denne studien sterke føringer for at kreftoverlevere med stråleskader i bekkenområdet og redusert HRQOL kan ha stor nytte av

HBOT. Spesielt kan redusert symptombyrde og forbedret HRQOL med økt rolle – og sosial funksjon ha stor betydning for disse kreftoverleverne hverdagsliv. Selv om resultatene fra denne studien ikke kan generaliseres, bidrar den til viktig kunnskap på et lite utforsket område og en viktig basis både for klinisk praksis og videre forskning.

LIST OF PUBLICATIONS

Paper 1: Velure, G. K., Müller B., Hauken, M. Aa. (2021). Symptom burden psychological distress, and health-related quality of life in cancer survivors with pelvic late radiation tissue injuries. Supportive Care in Cancer. 30(3), 2477-2486. https://doi.org/10.1007/s00520-021-06684-x (Article 1)

Paper 2: Velure, G. K., Müller B., Hauken, M. Aa. (2021). Experiences of patients with pelvic radiation injuries after cancer treatment undergoing hyperbaric oxygen therapy: A phenomenological-hermeneutical study. Nordic Journal of Nursing Research 41(3), p. 131-139. https://doi.org/10.1177/2057158521994405 (Article 2)

Paper 3 Velure, G. K., Müller B., Hauken, M. Aa. Symptom burden and health related quality of life six months after hyperbaric oxygen therapy in cancer survivors with pelvic radiation injuries. Supportive Care in Cancer. https://doi.org/10.1007/s00520-022-06994-8 (Article 3)

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ABBREVIATIONS

CI:	Confidence intervals
EORTC:	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30:	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, version 3.0.
EPIC:	Expanded Prostate Cancer Index Composite
GHQ:	General Health Questionnaire
HBOT:	Hyperbaric oxygen therapy
HRQOL:	Health-Related Quality of Life
LRTI:	Late Radiation Tissue Injuries
RCT:	Randomized controlled trial
STC:	Systematic Text Condensation
WHO:	World Health Organization

DEFINITIONS OF CENTRAL TERMS

- **Cancer survivor:** "Cancer survivors are individuals with a diagnosis of cancer who have completed primary treatment" (1, 2), p. 7.
- **Health-related quality of life:** A multi-dimensional construct that covers six key dimensions such as disease and treatment related symptoms, as well as mental, psychological and social functioning, which in turn influence the individual's overall HRQOL (3).
- **Hyperbaric oxygen therapy:** Hyperbaric oxygen therapy is a treatment modality whereby the patient is placed in a pressure chamber while breathing 100% oxygen, and while exposed to elevated ambient pressure (4).
- **Late and long-term effects:** The terms late and long-term effects are often used interchangeably in the literature. In this thesis, the term late effects is used.

  "Late effects refer to specific toxicities that are absent or subclinical at the end of therapy and become manifest later with the unmasking of hitherto unseen injury because of any of the following factors: developmental process, the failure of compensatory mechanisms with the passage of time, or organ senescence. Late effects appear months to years after the completion of treatment" (5), p. 249.

  "Long term effects refer to any side effects or complications of treatment for which a cancer patient must compensate; also known as persistent effects, they begin during treatment and continue beyond the treatment" (5), p. 250.
- **Pelvic cancers:** Pelvic cancers refer to a variety of cancer diagnoses involving the structures and organs in the pelvic area, representing the pelvic bones, urinary tract, bowel and reproductive organs, such as prostate, testicular and gynaecological cancers (6).

- **Pelvic late radiation tissue injuries:** "Transient or longer term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour in the pelvic region" (6) p. 311.
- **Psychological distress:** Psychological distress refers to emotional distress symptoms such as symptoms of anxiety and depression and is frequently used in research as an indicator of an individual's current mental health (7, 8).

1. INTRODUCTION

This thesis focuses on symptom burden and health-related quality of life (HRQOL) of cancer survivors undergoing hyperbaric oxygen therapy (HBOT) for pelvic radiation tissue injuries (LRTI). There were several reasons for this focus:

Although the number of cancers is increasing, around two thirds of all Norwegian cancer patients survive more than five years after diagnosis, due to a combination of earlier detection and improvements in multimodal treatments (9, 10). However, cancer and its treatment may cause significant physical, psychological, social and vocational late effects and long-term effects, impairing the survivors' health and HRQOL (11, 12). In line with this, the Norwegian Cancer Strategy (2020-2023) underlines the importance of focusing on evaluation and treatment of late effects and cancer survivors' HRQOL (13).

Pelvic malignancies include a variety of cancer diagnoses involving the structures and organs in the pelvic area, such as the pelvic bones, urinary tract, bowels and reproductive organs, and account for around one third of all cancer diagnoses (6, 9). Radiotherapy is an essential part of the curative treatment of pelvic malignancies, often in combination with surgery and chemotherapy (4). Due to the close location of the urinary and gastrointestinal tract and the genitals, survivors of pelvic cancer are particularly exposed to late-effects from the treatment. Radiation may affect surrounding healthy tissues and lead to acute or chronic radiation injury – often referred to as pelvic late radiation tissue injuries (pelvic LRTI) (14, 15). Many of these survivors suffer "in silence" because their LRTI are often not diagnosed and treated, but only handled symptomatically (16, 17). Limited knowledge exists of pelvic cancer survivors' symptom burden from LRTI and how this influences their HRQOL.

Hyperbaric oxygen therapy (HBOT) has traditionally been connected to treatment of decompression sickness. However, increasing evidence supports the use of HBOT as a

treatment for a variety of radiation injuries, based on its ability to increase tissue oxygenation and healing of damaged tissue (14). HBOT is unknown and unfamiliar for many healthcare professionals and patients, and in Norway elective HBOT is only performed at the Norwegian National Unit for planned HBOT located at the Department of Occupational Medicine, Haukeland University Hospital in Bergen.

In general, research of HBOT for LTRI is a relatively new field – especially with respect to the symptom burden of pelvic LTRI and HRQOL. Even if a few previous studies have shown positive effects of HBOT on some types of pelvic LRTI and HRQOL, the field is highly understudied, and more research is needed (18-21).

As a section manager at the Department of Occupational Medicine, the candidate encountered many cancer survivors undergoing HBOT for pelvic LRTI in her daily work. To improve knowledge and patient care, an increasing curiosity emerged as to how LRTI impair HRQOL, and how these survivors experience undergoing HBOT, as well as how their symptom burden and HRQOL develop in the long term after HBOT.

Based on the above considerations, the overall objective of this thesis is to provide increased knowledge and understanding of the symptom burden and HRQOL of cancer survivors undergoing HBOT for pelvic LTRI. More specifically, this thesis aims to explore pelvic survivors' LTRI symptom burden, the patients' lived experience of undergoing HBOT, and the development of pelvic LRTI and HRQOL before and after HBOT. Based on the thesis' aims, a mixed-methods study with an explanatory sequential design was conducted (22).

This thesis is structured around nine chapters. After this introduction, chapter two provides a general description of the thesis' context, including a brief overview of cancer and the consequences of cancer and cancer treatment for survivorship. This is followed by a presentation of pelvic cancer and late effects, with specific focus on pelvic LRTI, including a

presentation of HBOT. Chapter three addresses earlier research on pelvic LRTI, HRQOL and HBOT. The thesis' theoretical framework is presented in chapter four, building on a bio-psychosocial, or holistic, view of health, whereby the concept of HRQOL fulfils this holistic approach. Aims and research questions are presented in chapter five, and chapter six outlines the study's mixed-methods approach. The findings from the three papers, including the merged results, are presented in chapter seven. Since the results from each paper are discussed in the respective papers, the discussion in chapter eight focuses on the merged findings, followed by methodological reflections. The main conclusion, clinical implications and suggestions for further research are presented in chapter nine.

2. CONTEXT OF THE STUDY

To contextualise the thesis, this section first provides a brief and general overview of the cancer trajectory. Then the characteristics of pelvic cancer, treatment and late effects are presented. Finally, HBOT as a treatment modality for LRTI is addressed.

2.1 The cancer trajectory

2.1.1 Cancer and cancer incidents

Cancer is the generic term for a group of diseases characterised by the uncontrolled growth and spread of cells that can affect any part of the body (23). Common to all forms of cancer is failure of the mechanisms that regulate normal cell growth, proliferation and cell death. Consequently, cancer cells have the ability to invade neighbouring tissues, eventually spread to other areas of the body, and if not controlled, cause death (24). Worldwide, cancer is the second-leading cause of death (25), but the leading cause in Norway (26).

The global burden of cancer is expected to grow to annually 27.5 million new cancer cases and 16.3 million cancer-related deaths by 2040 (23), due to a growing and ageing population, lifestyle changes and socioeconomic risk factors (27). In 2020, 35,515 new cancer cases were diagnosed in Norway, most being persons over 50 years of age. In men, 19,223 new cases were detected, with prostate cancer as the most common. In women, 16,292 cases were diagnosed, whereby breast cancer was most common (9). Although the incidence of cancer is increasing, it is estimated that more than 40% of all cancer can be prevented, and common cancers such as cervical, colon and rectum cancer are often cured (24). In Norway, the five-year survival rates are increasing and the relative survival proportion is now more than 70% (all cancer sites) (9).

2.1.2 Cancer survivorship

Modern cancer treatment is often multimodal and long-lasting, and given the advances in screening, detection and treatment, survival rates are increasing. Based on the improved survival rates, the term '*cancer survivor'* has emerged to describe cancer patients living with or beyond cancer. However, no universally accepted definition of 'cancer survivor' exists. Since the mid-1970s the cancer control continuum has been used to describe the various points from cancer prevention, early detection, diagnosis, treatment and survivorship to end of life (28). As modern biology and treatments have changed our understanding of cancer, it is now recognised that the categories are useful labels, but the processes are not so discrete (29). From a biomedical viewpoint, the term survivor has a distinct clinical meaning, referring to individuals who have had a life-threatening disease, but remain disease-free for a minimum of five years (30, 31). In recent years, however, a variety of other definitions have emerged, whereby some refer solely to individuals diagnosed with cancer, while other definitions include next of kin and caregivers (29, 31).

Over the years, the concept of survivorship has also developed, whereby survivorship is currently not only related to the length of survival, but also to well-being and thriving (32). Feuerstein et al. (33) identified six phases of survivorship ranging from diagnosis, treatment, acute effects, sub-acute effects and long-term effects, to end of life. Based on the focus of this thesis, the definition of cancer survivors as individuals with a cancer diagnosis who have completed primary treatment and live with long-term late effects is used (33).

2.1.3 Late effects after cancer and cancer treatment

Many cancer survivors return to normal functioning after treatment. However, cancer and its treatment may also result in a wide range of physical, psychological and social problems that

do not recede over time. (29). It is only in recent years that late effects after cancer treatment have gained more focus internationally and nationally (34, 35). In official documents, in 2013 cancer survivor and survivorship were addressed as a goal in the Norwegian National Cancer Strategy (36), and in the current strategy important goals are to reduce the incidence of late effects, and map and treat late effects, as well as a primary focus on survivors' HRQOL (37). Despite the increased focus, there are still great differences and a lack of screening and management of late effects in the follow-up of cancer survivors, representing a challenge for both patients and the healthcare system (38-43).

The risk of developing late or long-term effects depends on the initial diagnosis, type of cancer treatment, genetic predisposition, lifestyle behaviours, environmental factors and comorbidity (39). Here, the carcinogenic effects of chemotherapy, radiation and/or a combination play a vital role (44).

The terms long-term and late effects are often used interchangeably in the literature. Long-term effects are typically described as treatment complications persisting beyond the end of treatment, while late effects may appear months to years after the completion of treatment (5) (39, 45). Physical late effects may include a range of symptoms, depending on the cancer diagnosis and the treatment. Common physical late effects are fatigue, memory loss, lack of concentration, pain, insomnia, neurological problems, weight loss or weight gain, musculoskeletal problems, lymphedema, bodily impairment, premature-onset menopause, incontinence and gastrointestinal problems such as diarrhoea and constipation (39, 46).

Psychological late effects from cancer treatment are associated with psychological distress, including symptoms such as worry, sorrow, anxiety and depression (39). In addition, cancer survivors often report distress related to fear of cancer recurrence or progression, and problems related to self-esteem, body image, identity and sexuality, and impaired HRQOL (39, 41, 46, 47).

Cancer survivors also report social late effects such as changes in relationships, employment, work-related challenges and economic problems (39, 42, 48). The importance of social support for health is well-known, as a low level of social functioning may impair close relationships, and physical and mental health, as well as HRQOL (49).

2.2 Pelvic cancer

Pelvic cancer involves the lower portion of the trunk, including the pelvic bones, urinary tract, bowel, and reproductive organs, such as prostate and gynaecological cancers (6). In 2020, 13,401 (37.7%) of all cancers in Norway were pelvic. A detailed overview is given in Table 1. (9).

Table 1. New cases of pelvic malignancies in Norway in 2020 (9).

Site	Male	Female	Total
Colon	1,504	1,617	3,121
Rectum/rectosigmoid	821	552	1,373
Anus	38	68	106
Urinary tract	1,410	442	1,852
Prostate	5,030		5,030
Testis and other male genital	340		340
Cervix uteri		328	328
Corpus uteri		764	764
Ovary		487	487
Total			13,401

Prostate cancer has been the most common cancer in men for many decades, with a yearly incidence of around 200 per 100,000 person-years (9). Cancer of the bladder and the urinary tract is the fourth most frequent in men, but less frequent in women. In recent years the incidence of colon cancer has levelled off for men, but is still increasing among women. The incidence of gynaecological malignancies in Norway has decreased in recent years, where

screening programmes, treatment of premalignant conditions and vaccination against human papilloma virus are considered to be the underlying causes (9).

2.2.1 Treatment of pelvic cancers

Early detection and complex treatment have dramatically improved survival from pelvic cancers. The survival rates are approximately 72% for bowel cancers, 77% for urinary tract cancers, 95% for prostate cancer and 82% for gynaecological cancers, except ovarian cancer, which has a survival rate of 51% (9).

Patients diagnosed with pelvic cancers commonly receive multimodal and long-lasting treatment involving radiotherapy, chemotherapy and surgery. Radiotherapy builds on ionising radiation, which deposits energy in the tissue cells it passes through (50). High-energy radiation damages the genetic material of cells and blocks their ability to divide and proliferate further (50, 51). Radiation is used both with a curative intent and in palliative treatment to achieve symptom relief. It may be used pre-operatively, with the aim of shrinking the tumour, and/or post-operatively in order to treat the malignancy itself, but also to reduce the risk of recurrence (51). Radiation can be administered externally and/or internally by probe or radioactive implants (brachytherapy) (51). Prostate and cervix carcinoma are examples that are curable with radiation therapy alone in the early stages (50). Combinations of radiation with other modalities are commonly used for rectal, anal, bladder and endometrial carcinomas (50). The combination of chemotherapy and radiotherapy has been shown to improve survival, but also increases the risk of severe toxicity and radiation-induced problems (6). New methods of radiotherapy techniques are developed to reduce its side-effects, but the number of patients affected with pelvic LRTI is still high (14, 52, 53).

Chemotherapy is another important curative treatment for pelvic cancers. It usually works by keeping the cancer cells from growing, and dividing, thereby inhibiting multiplication and

making more cells (54). Chemotherapy has proved to be effective for a range of epithelial malignancies, including ovarian and bladder cancers, and is also used as an adjuvant in treating patients with colon cancer (55).

Treatment of colon, rectum, anal and urinary tract cancers commonly involves a multimodal approach with surgery, radiotherapy and chemotherapy based on tumour-related characteristics, such as localisation, tumour, comorbidity, prognosis and patient-related factors (e.g. age, general condition) (56-59). Advances in diagnostics and risk assessment, and available treatment of prostate cancer allow clinicians to choose more individualised therapeutic approaches based on cancer prognosis and patient preference (60). The treatment of prostate cancers may thus include active surveillance, surgery, radiotherapy, hormonal therapy, chemotherapy and immunotherapy as single treatments or in combination (59, 60). Brachytherapy (internal radiation) is mainly indicated as a standard treatment in combination with chemo-radiation in patients with gynaecological cancer, often also including surgical interventions (61, 62).

2.2.2 Physical late effects of pelvic cancer, with specific focus on radiation tissue injuries

As for other cancers, pelvic cancer survivors report a range of physical late effects that impair health and well-being. Common physical late effects are urinary and gastrointestinal tract dysfunctions, sexual problems, infertility, pain and fatigue (46, 63-66). Of these, fatigue is described as the most debilitating late effect across different cancer diagnoses, treatments and age (66). Patients treated for gynaecological, colorectal or prostate cancer in particular experience long-lasting fatigue (46, 64, 66, 67).

Radiotherapy is used to treat pelvic cancers more than at any other tumour site. The survivors are therefore particularly prone to develop LRTI, as multiple organs in the pelvic area are

affected across the different cancer types (14, 16, 17, 53). Around 90% of patients receiving pelvic radiation therapy may be affected by gastrointestinal symptoms. (53).

The biological effects of ionising radiation trigger a series of genetic and molecular phenomena, leading to clinically and histologically recognisable injury (68). Progressive oxidative stress and hypoxia may be the driving force behind chronic radiation injury, causing a loss of parenchymal cells, overproduction of collagen, and macro- and microvascular changes (69). Adverse effects of radiotherapy on normal tissue leave approximately 5-15% of patients with long-term pelvic LRTI, which are characterised by tissue damage, fibrosis, hypoxia and poor microcirculation, affecting the urinary tract, gastrointestinal tract, genitalia and pelvic bones (70, 71).

According to Andreyev et al. (6) pelvic LRTI are defined as:

"Transient or longer-term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour of pelvic origin" (p. 311).

The urinary and gastrointestinal tracts are the main sites of pelvic LRTI, and chronic haemorrhagic cystitis is one of the most frequent radiation-induced toxicities (17). Endothelial cell damage and perivascular fibrosis may result in ischemia, leading to a range of symptoms, including urinary frequency, urgency, pelvic pain and haematuria (17). Chronic radiation proctitis may lead to haematochezia, mucus discharge and tenesmus, and often to faecal incontinence. Radiation colitis and enteritis are typically characterised by endarteritis with exaggerated submucosal fibrosis and can be manifested as diarrhoea, digestive problems including food intolerance, pain, fistulae, local abscesses, perforation and bleeding (72, 73). Radiation damage to the vagina may cause stenosis, and shortening and loss of elasticity of the vagina, often with longstanding ulcers and fistulas (74). Radiation-induced reactions in the

bone marrow may include osteitis and osteoradionecrosis. The pathophysiology of this is only partly understood, but is believed to result from toxic response, reduced permeability of endothelial bone marrow sinus, and cytoplasmatic swelling, resulting in bone degeneration (75). Overall, frequent symptoms of pelvic LRTI are diarrhoea, faecal leakage, incontinence, haematuria, increased urinary/bowel frequency, increased urinary/bowel urgency, and sexual dysfunction, which may impose a severe symptom burden and affect their HRQOL (18, 76-78).

2.2.3 Psychosocial late effects of pelvic cancer

In addition to physical problems, pelvic cancer survivors report high levels of psychological late effects, such as anxiety, depression, distress and uncertainty (79-81). Cessna Palas et al. (82) found that both modifiable (perceived risk, self-efficacy, intolerance of uncertainty and social constraints) and non-modifiable (age, gender, disease severity) factors are associated with fear of cancer recurrence. Anxiety-related late effects after pelvic cancer treatment include fear of disease progression, sleep disturbances, psychosexual problems, fertility concerns and body image concerns, adding an extra burden to the survivors (46, 48, 64, 65, 67). A prevalence rate of 12% for clinical anxiety was reported for a sample of 65 cancer survivors at various sites, including gynaecological and testicular malignancies (83). Bergerot et al. (84) found that patients with gynaecological and gastrointestinal cancers report high rates of psychological distress. Up to 32% of survivors of gynaecological, colorectal and prostate cancer are clinically depressed, and women are more likely to experience depressive symptoms than their male counterparts (42, 46). Supporting this, Adams et al. (52) found that more severe pelvic LRTI symptoms across cancer types were associated with higher rates of depression, but not with more anxiety.

Social late effects, such as negative changes in intimate relationships, have been shown to occur after pelvic cancer treatment, due to sexual dysfunctions, infertility and body image problems (42). Debilitating symptoms such as urinary incontinence and faecal leakage significantly impact day-to-day living and cause lifestyle changes related to social activities, family life and household tasks (85). Boelhover et al. (86) found that physical late effects and fatigue after cancer treatment continue to impair work ability, affect career progression and increase financial stress among cancer survivors.

2.2.4 Management of pelvic LRTI

Overall, the treatment options for pelvic LTRI are limited to prophylactic measures for symptomatic treatment once radiation injury is established (14, 16, 17, 53). Pharmacological interventions frequently used for radiation proctitis/enteritis are antidiarrheal agents, analgesics, anticholinergic agents, and nonsteroidal anti-inflammatory drugs. Non-pharmacological interventions include dietary counselling and physiotherapeutic training, particularly training of pelvic floor muscles (14, 87). Antibiotics, vitamin A, laser coagulation and HBOT have proved to be effective for different aspects of radiation injuries (88-90). Although symptomatic treatment can be helpful in the short term, recurrence and re-treatment rates are high. Treatment of haemorrhagic cystitis is mostly conservative and includes hydration, blood transfusions and bladder irrigation with cloth evacuation (91). In refractory severe cases, management options include intra-vesical endoscopic procedures and HBOT. More aggressive management options include cystectomy and urinary diversion, if other conservative measures have failed (87, 91). Overall, treatment options for pelvic LRTI are still limited, with unsatisfactory efficacy, and many cancer survivors seem to live with a high symptom burden (6).

2.3 Hyperbaric oxygen therapy

Besides being well-established for the treatment of decompression sickness, over the last decades HBOT has emerged as a treatment option for radiation injuries (14). Hyperbaric medicine involves breathing pure oxygen in a pressurised environment, representing an important treatment modality for several acute and elective conditions such as decompression sickness, serious infections, diabetic foot wounds and radiation injuries (92). Inhalation of 100% oxygen at an increased pressure of 2 atmosphere absolute or more allows more oxygen to be dissolved in plasma, inducing a steep oxygen gradient between hypoxic tissue and surrounding normal tissue, thereby stimulating angiogenesis mediated by macrophages (93). Repeated HBOT therapy has been shown to increase levels of growth factors, stimulate stem cell mobilisation from the bone marrow in response to oxidative stress, stimulate cellular regeneration and reduce inflammation (94, 95). These mechanisms induce revitalising and healing of hypoxic tissue and finally, alleviate symptoms (96).

HBOT is characterised as a high-technology treatment whereby patients are completely enclosed in a multi- or mono-place pressure chamber, usually for 90-100 minutes once a day for six to eight weeks (4). Strict safety routines are applied, and patients are under constant observation during treatment, as the high ambient oxygen concentration increases the risk of fire (97). Hence, patients must avoid ointments and cosmetics, synthetic clothing, bandages, and titanium glasses, and they are not allowed to bring private possessions, including papers, books or electronic devices, into the chamber.

Overall, HBOT is regarded as a safe treatment, with only a few mild, temporary side-effects related to the increased pressure or hyperoxia (97, 98). Middle ear and sinus barotrauma are the most common side-effects occurring during the compression or decompression phase, and are usually short lasting (99). Hyperoxic myopia occurs frequently and is usually reversible

within 6-8 weeks after HBOT (99). An extremely rare side-effect of HBOT is pulmonary oxygen toxicity, implying tracheobronchial irritation due to the high oxygen concentration, with pleuritic pain and cough/burning, followed by impaired pulmonary function (100). A chest X-ray prior to HBOT can rule out many anatomic abnormalities which increase the risk of active bronchospasm or mucus plugging. Epileptic seizures are also rare, with an incidence of about 1 in 2,000-3,000 treatments (99). In addition, HBOT facilities, with their high technology, unfamiliar surroundings and environmental confinement, may cause claustrophobia and increase patients' distress and anxiety (97, 101).

In Norway, elective HBOT is localised as outpatient treatment at the Norwegian National Unit for Planned Hyperbaric Oxygen Treatment. The treatment is given in mono-place chambers, where patients receive 100% oxygen, breathed in at a pressure of 2.4 atmosphere absolute, for 90 minutes, five times per week, and in cases with radiation injury for six successive weeks. HBOT at the Norwegian National Unit is performed by specialised trained nurses.

3. PREVIOUS RESEARCH ON LATE EFFECTS OF PELVIC CANCER RELATED TO HRQOL AND HBOT

This section provides an overview of previous research regarding pelvic cancer and HRQOL, the use of HBOT for LRTI, patients' experience of undergoing HBOT, and the influence of HBOT on HRQOL.

3.1 Late effects of pelvic cancer impairing HRQOL

Many survivors of pelvic cancer suffer from notable long-term late effects which impair their HRQOL (76, 102). In particular, late effects from pelvic cancers seem to impair HRQOL and everyday life, based on the involvement of the gastrointestinal tract, urinary tract and reproductive organs, including highly sensitive symptoms such as diarrhoea, faecal leakage, incontinence and poorer sexual function (103-106). According to Morris and Haboubi (107), the burden of LRTI impacting the survivors' HRQOL is often under-recognised and sub-optimally managed.

A systematic review by Flyum et al. (108) revealed that patients with colorectal cancer report impaired HRQOL, mainly explained by gastrointestinal symptoms. Significantly impaired overall HRQOL, role and social function, bowel impairment, pain, fatigue and sexual difficulties have also been documented after treatment for anal cancer (76, 104, 109).

Late effects after treatment of cancer in the urinary tract and its influence on HRQOL have mainly been studied in relation to different interventions, whereby survivors who have undergone cystectomy report the most impaired HRQOL (110-113).

Several studies have evaluated prostate cancer treatment and HRQOL showing that bowel symptoms followed by sexual and urinary symptoms have the greatest negative impact on HRQOL (114-117). Song et al. (118) found that prostate cancer survivors reported lower

physical and mental HRQOL, and more comorbidities than control persons. Similarly, Chambers et al. (119) found that prostate cancer predicted poorer long term HRQOL and psychological outcomes, with a greater risk for younger men due to building careers, being more sexually active, and having greater financial responsibilities. Older prostate cancer survivors seem to be at higher risk of poorer physical function, indicating that comorbidities associated with age may increase the physical challenges of treatment (120). According to Punnen et al. (121), men treated with radiotherapy experience more long-term effects on bowel function, while androgen deprivation therapy has the greatest adverse effect on physical HRQOL.

In recent years, HRQOL in gynaecological cancer survivors has received more attention, indicating that late effects impair physical, mental and psychosocial well-being years after treatment (122-127). Deteriorated physical and social functioning, with overweight, comorbidities, deprivation, anxiety and depression, lack of social support and bowel impairment seem to play important roles for impaired HRQOL in gynaecological cancer survivors (77) (128). Reduced overall HRQOL in gynaecological cancer survivors has also been associated with increased symptom burden, age, disease recurrence and several comorbidities (103, 129).

There are several challenges concerning the impact of pelvic LRTI on HRQOL in cancer survivors. As pelvic LRTI are often not reported to healthcare professionals, the symptoms often remain untreated, resulting in increased symptom severity (78). Furthermore, pelvic LRTI are chronic conditions of which the symptoms may vary over time. Consequently, the impact of the symptoms on HRQOL may vary during the course of the disease, although research on this is limited (130). Improved HRQOL over time in survivors of pelvic malignancies have been found, mainly explained by complete disease remission and declined symptoms (102).

The multitude of pelvic LRTI are challenging to investigate, as most studies have focused on the impact of single symptoms or symptom groups, or different treatment modalities' impact on HRQOL. However, limited research exists concerning pelvic cancer survivors experiencing similar pelvic LRTI across different diagnoses. Furthermore, a variety of assessment tools for disease-specific symptoms, as well as HRQOL tools, exist, making the comparability of studies challenging. Consequently, measuring both pelvic LRTI and HRQOL with validated instruments compared to norm populations may be important to understand pelvic cancer survivors' needs, guide efforts in care and clinical treatment, and direct further research.

3.2 Pelvic LRTI, HBOT and HRQOL

3.2.1 HBOT for pelvic LRTI

A Cochrane review (71) concludes that HBOT may improve various LRTI, including bone and soft tissues of the head and neck, proctitis, and may prevent the development of osteoradionecrosis in the jaw. This review also suggests that other tissues impaired by LTRI are likely to respond, e.g. bladder LTRI. Similarly, Nieziegoda et al. (131) found symptom improvement after HBOT in 77-93% of cases in a large study of ten different radiation injuries, including radiation proctitis.

A few randomised controlled trials (RCT) have assessed the effects of HBOT on pelvic LRTI symptoms. Oscarsson et al. (18) found beneficial effects of HBOT for late radiation cystitis. Shao et al. (132) compared HBOT with instillation of hyaluronic acid in patients with haemorrhagic radiation cystitis and concluded that both haematuria and pain decreased in both groups. Furthermore, Clarke et al. (133) found significantly improved symptoms after HBOT for patients with chronic radiation proctitis. Yuan et al. (134) uncovered that HBOT alleviated gastrointestinal complications, including rectal bleeding, diarrhoea and pain, while

Glover et al. (21) found no such evidence. In contrast, Craighed et al.'s review (135) documents symptomatic benefits from HBOT for pelvic LTRI in gynaecological malignancies. Recent publications conclude that HBOT may benefit pelvic LRTI, but more research is needed in this highly understudied field (136, 137, 138).

3.2.2 Cancer survivors' experience of undergoing HBOT for pelvic LRTI

Research of how patients experience undergoing HBOT is surprisingly limited, including the psychological aspects of HBOT. A few previous studies have shown that the technical environment and the confining, uncomfortable space in hyperbaric pressure chambers may cause distinct anxiety and claustrophobia, and lead to terminating or refusing treatment (139-141). In line with this, London et.al. (142) found that nearly one third of patients treated in mono-place chambers required sedative premedication before HBOT, due to claustrophobia. In multi-place chambers, patients have reported discomfort on using the mask or hood for oxygen supply, and a noisy, cold environment, although contact with fellow patients during treatment was experienced positively (143, 144). Yisak et al. (145) found that nursing management plans involving preparation, close follow-up and management of unpleasant feelings associated with HBOT had a positive impact on patient experiences. In a recent mixed-methods study with 29 participants, McInnes et al. (146) showed that many patients experienced anxiety prior to HBOT but, with support, quickly adjusted to treatment, which underlines the need for psychosocial support during treatment.

Cancer survivors with pelvic LRTI often have substantial and complex symptoms in one or multiple organs, and this may create specific concerns when enclosed in a pressure chamber over time (71, 131, 147). However, we have not found prior research on pelvic cancer survivors with LRTI and the experience of undergoing HBOT. This is important knowledge to guide healthcare professionals in how to prepare these survivors for HBOT, to alleviate

anxiety and distress, to meet the patients' needs, and to promote trust and coping ability throughout the treatment course.

3.2.3 HBOT influence on HRQOL of pelvic LRTI

Only a few studies of HRQOL following HBOT for pelvic LRTI are published (18, 133, 148, 149). Here, beneficial effects on HRQOL in patients with both radiation cystitis and proctitis after HBOT have been found (18, 133, 148, 149). In contrast, Lauvrak et al. (20) state in their systematic review that no conclusion about HBOT's influence on HRQOL can be made. Consequently, further research is clearly needed on the impact of HBOT on HRQOL in cancer survivors with pelvic LRTI.

3.3 Why this study?

The foregoing literature review shows limited evidence of HBOT's influence on pelvic LRTI and HRQOL. It can be difficult for patients and healthcare professionals to ascertain the underlying causes of pelvic symptoms. Consequently, LRTI are often underdiagnosed, and this can be a strain and lead to increased uncertainty and stress for those affected. Furthermore, the literature shows that pelvic cancer survivors report high levels of psychological late effects, such as anxiety, depression, distress and uncertainty. However, there seems to be a lack of knowledge in the research field regarding pelvic LRTI's impact on psychological distress in addition to HRQOL, and little is known about how psychological distress may influence the relation of LRTI with HRQOL. Likewise, the physical side-effects of HBOT are well-documented, but there is limited evidence on how patients with pelvic LRTI, with their substantial and complex symptoms, experience undergoing this therapy. Accordingly, there seems to be a lack of in-depth knowledge of pelvic cancer survivors' experience of this high-technology treatment modality. Some studies have demonstrated positive associations between symptom improvement and HRQOL after HBOT, but the

research is conflicting. Hence, there is a clear need to enhance knowledge about the development of pelvic LRTI symptoms and HRQOL following HBOT.

4. THEORETICAL FRAMEWORK

This thesis' theoretical framework builds on a bio-psychological view of health and health promotion, whereby HRQOL is viewed as an important holistic health determinant. This chapter first provides a brief background of health and health promotion before the concept of HRQOL is presented, as well as how the framework is used in this study.

4.1 Health and health promotion

Traditionally, health has often been defined as the absence of physical and mental disease (150). In contrast, in 1949 the World Health Organization (WHO) defined health as a state of complete physical, mental, social and emotional well-being, and not merely the absence of disease (151, 152). Even though it has been criticised for being too ambitious, this definition encompasses a holistic view of health, often referred to as a positive or bio-psychosocial health concept that includes the individuals' own perspective, experiences and context (153, 154, 155). This contrasts the illness paradigm with a pathogenic and biomedical view of health, which emphasises disease rather than health and well-being (154, 156).

The holistic health concept is congruent with health promotion designed to foster health. Here, the World Health Organization (WHO) (153) defines health promotion as the process of enabling people to increase control over, and to improve their health. To reach a state of physical, mental and social well-being, an individual or group must be able to identify and realise aspirations, satisfy needs, and change or cope with the environment. Health promotion thus focuses on promoting the individuals' health, but also emphasises health promotion at the societal and system level, such as health education, identification and reduction of health risks for specific groups and populations, empowerment, advocacy, preventative healthcare and health policy development (157, 158). Consequently, health promotion draws on the

knowledge and methods of various disciplines and is informed by new evidence about health needs and their underlying determinants (159).

4.2 Health-related quality of life

The term quality of life (QOL) originated in the 1960s to describe "what matters to people"; the benefits or experiences that people dream of and hope to realise, including both subjective and objective aspects of life (160). Since then, the concept has developed and is used within several disciplines (155). Within medical and health science, QOL related to health has received special attention, often outlined as HRQOL. Here, HRQOL is generally considered to reflect the impact of disease and treatment on disability and daily functioning (161). However, HRQOL is a complex concept with several different theoretical and philosophical views, including a continuing conceptual and methodological debate about how it should be defined (160, 162-166). Even if several definitions of HRQOL exist, there seems to be agreement that this is an individual, subjective and multidimensional concept that builds on a bio-psychosocial concept of health. HRQOL is often described as a measure of the value assigned to duration of life as modified by disease, treatment, impairments, functional status, perceptions, opportunities and policy (167, 168, 169). Within health promotion and cancer survivorship, the World Health Organization Quality of Life group (WHOQOL) defines HRQOL as an individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, standard of expectations and concerns (170). In line with this, and even more specific and relevant for cancer patients and survivors, the European Organization for Research and Treatment of Cancer (EORCT) defines HRQOL as:

"A multi-dimensional construct that covers six key dimensions such as disease and treatment-related symptoms, as well as physical, psychological and social functioning, which in turn influence the individual's overall HRQOL" (171), p. 142.

This HRQOL concept is illustrated in Figure 1.

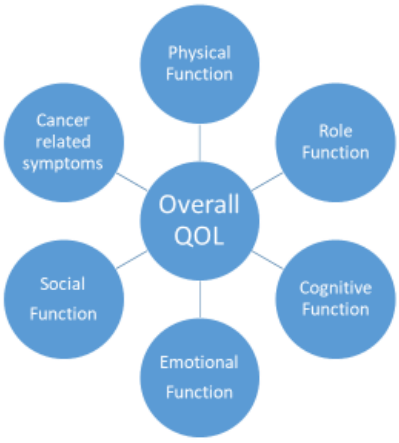


Figure 1: Illustration of EORTC`s HRQOL concept.

Figure 1 illustrates that cancer-related symptoms, together with physical, role, cognitive, emotional and social functions, are important dimensions in overall HRQOL. Consequently, challenges and strengths within each dimension are important contributors to the individual's overall HRQOL (172, 173). This implies that cancer-related symptoms or late effects may negatively influence both the different dimensions and overall HRQOL. Conversely, improvements in cancer-related symptoms or any of the other HRQOL dimensions may positively influence overall HRQOL. Thus, HRQOL may give a holistic picture of the patients' perceived health and overall well-being, shown to be a strong predictor of symptom relief, survival, care and rehabilitation of cancer patients and survivors (155, 161, 167, 174, 175, 176).

However, the EORTC's definition may be criticised for not including a spiritual dimension focusing on religiosity, expectation, suffering and meaning, and hope (176). Here, the

literature shows that HRQOL may be influenced by the difference between the individuals' hope, their outcome expectations, and their actual life (155, 167). In line with this, Rustøen (173) states that hope may be seen as a variable that contributes positively to HRQOL and is regarded as an important coping strategy.

On measuring HRQOL, another critique of the HRQOL concept is that the patients have to distinguish between the part of their life influenced by health and other parts that are not (177). Focusing on HRQOL may thus substantially overestimate the impact of health-related factors and conversely, may seriously undervalue the effect of non-medical factors (177).

Furthermore, another challenge in HRQOL research is the number of different measures, making the interpretation of results complicated (178). In many studies, HRQOL appears as a secondary outcome, while the interventions do not focus on HRQOL (162). Consequently, focusing on symptom- and HRQOL-specific measures may provide more detailed information that is important for clinical practice.

4.3 The theoretical framework's reflection in the three papers

The theoretical framework, with a specific focus on HRQOL, is included as a basis in all three papers, as well as the thesis.

In Paper 1, a theory positing that challenges and strengths within each HRQOL dimension will contribute to the individual's overall HRQOL guided the analysis of baseline data. As a starting point, the level of symptoms, psychological distress and HRQOL, and the influence of these factors on HRQOL, were investigated at baseline, prior to HBOT. Psychological distress was tested as a moderator of the relationship between the cancer survivors' pelvic LRTI symptoms and their well-being, operationalised through overall HRQOL. In Paper 2, the holistic health concept reflected in HRQOL created the basis for exploring the cancer survivors' experience of undergoing HBOT. To gain more insight into the outcome, the

development of symptom severity and HRQOL following HBOT, and the associations between these variables over time, were explored in Paper 3.

Finally, the theoretical framework is included throughout this thesis, when presenting prior research, methods and results, as well as in the discussion section.

5. STUDY AIMS AND RESEARCH QUESTIONS

Based on the identified research gap, the overall aim of this thesis was to provide increased understanding of the symptom burden and HRQOL of cancer survivors undergoing HBOT for pelvic LRTI. More specifically, the study's aims were:

1. To investigate pelvic LRTI symptoms, psychological distress and HRQOL in cancer survivors compared to norm populations.
2. To explore how cancer survivors with pelvic LRTI experience undergoing HBOT.
3. To explore the development of symptom severity and HRQOL following HBOT, and the association between these over time.

Consequently, this thesis sought to answer the following research questions:

1. What is the symptom burden, psychological distress and HRQOL in cancer survivors with pelvic LRTI prior to HBOT compared to the norm population? (Paper 1)
2. Does psychological distress act as a moderator in the relationship between pelvic LRTI symptoms and overall HRQOL? (Paper 1)
3. How do cancer survivors with pelvic LRTI symptoms experience undergoing HBOT? (Paper 2)
4. How do pelvic LRTI symptoms and HRQOL develop from baseline to completion of the six-week HBOT course and at follow-up six months after treatment? (Paper 3)
5. What are the associations between pelvic LRTI and HRQOL over time? (Paper 3)

6. METHODS AND MATERIALS

This chapter presents the study's methods and materials and the underlying rationale for the choices made. First, the research methods and design are presented, followed by a description of the sample, data collection, data analysis and ethical considerations.

6.1 Research methods and design

Various research methodology and design have been used in previous research on LRTI and HBOT. These include RCT, quasi-experimental, survey research and qualitative design (18, 21, 131, 133, 143, 144, 149). The preferred design for evaluation of treatment efficacy is RCT studies. However, the UK Medical Research Council guidelines recommend evaluation of process and implementing several outcomes as an alternative to RCT studies (179). Consequently, mixed-methods are an upcoming method in clinical research because this moves beyond simple hypothesis testing to provide insights into processes and mechanisms to reveal a more complete and nuanced understanding of a topic (22). Furthermore, the choice of research method is primarily dependent on a study's research question and not a specific design per se (22). Based on this study's overall aim and research questions, the research methodology had to reflect both a quantitative and qualitative approach, whereby a mixed-methods approach could provide us with more nuanced and complete knowledge of the topic studied that had not previously been used.

6.1.1 Mixed-methods

Traditionally, quantitative method has dominated the research into pelvic LRTI and HBOT (18, 21, 132-134, 137). Quantitative method is based on the empirical-analytical tradition, addressing objective data, causality or magnitude of effects, and facilitating quantifiable information, and is traditionally connected to the objective bio-medical paradigm (180). The

language of this research is formal and impersonal, the researcher acts in a value-free and unbiased manner and the results are considered to be relatively independent of the researcher, and often have high creditability and are useful for studying large numbers (181, 182). The strengths of the quantitative method include testing of hypotheses and the generalisation of research findings, based on replicated studies with sufficient sample sizes. However, the tools and instruments used may not reflect the participants' experience and understanding, representing a risk of producing general knowledge that is not applicable to clinical practice and for confirmation bias (182).

Qualitative method, in contrast, is based on the historic hermeneutic and emancipatory tradition, which focuses on individuals' experience and understanding (2). In this tradition, reality is viewed as a construct of social interactions and experiences, valuing the context-sensitive and the meaning a person ascribes to a phenomenon (2, 183). The researcher acts in a value-laden, personal, relative and socially-constructed manner (2, 184). The research language is informal, while the research process is inductive, emerging and context-bound, which is useful for studying a limited number of participants in-depth, providing rich and contextual information on a complex phenomenon (2, 183). Furthermore, qualitative method may illuminate dynamic processes and generate theories whereby data may be collected in natural strings in participants' own words or categories. However, findings from qualitative method might not be generalisable, hypotheses are difficult to test, and the researcher can easily influence the result (2, 185).

Combining quantitative and qualitative methods was previously considered to be impossible, as these represent two completely different research paradigms, based on different philosophical underpinnings (167, 186, 187). However, in the 1980s a new paradigm debate emerged, based on how research was increasingly interdisciplinary, complex and dynamic, and acknowledging that both quantitative and qualitative perspectives are needed to facilitate

communication, promote collaboration, and conduct more clinically-relevant research (22, 182). Consequently, the mixed-methods paradigm was developed to support this complexity (188).

Several definitions of mixed-methods have emerged over time, but a widely accepted definition has been developed by Creswell and Plano Clark (22): *"mixed methods, focuses on collecting, analysing and mixing both quantitative and qualitative data in a single study or series of studies. Its central premise is that the use of quantitative and qualitative approaches, in combination, provides better understanding of research problems than either approach alone"* p. 5.

As for the quantitative and qualitative paradigms, the mixed-methods paradigm builds on several philosophical assumptions. The ontology (nature of existence) of mixed-methods builds on both objectivism and constructivism, while epistemology (theory of knowledge) builds on pragmatism. Pragmatism is pluralistic and practically oriented towards "what works" and takes different approaches (22). The axiology (study of underlying values) involves multiple stances, such as that researchers may include both biased and unbiased perspectives (22, 189). The research rhetoric is both formal and informal, and the researcher may employ both formal and informal styles when reporting, valuing both objective and subjective knowledge (22). Thus, mixed-methods focus on research questions closely related to real life, as well as contextual understanding (22, 182). Mixed-methods have the potential to make valid inference, challenge existing theoretical assumptions and develop or create new ones, as well as to move beyond simple hypothesis testing to provide insight into process and mechanisms (22, 182, 190). Mixed-methods benefit from data collection methods from different methodological traditions, but it may be a challenge to shift and use multiple philosophical positions for a researcher with limited experience (180). Furthermore, mixed-methods represent a complex research paradigm, and this may lead to an extended research

period. Mixed-methods research may also be difficult to identify when part of larger study or research programme (189). The latter applies to the current study, where the mixed methodology first becomes visible in this thesis.

6.1.2 Explanatory sequential design

Mixed-methods is a research paradigm in development and, consequently, the research designs have expanded over time. Plano Clark and Creswell (187) provide a classification of different mixed-methods research designs based on the relationship between quantitative and qualitative methods: equal priority, quantitative priority and qualitative priority. Key factors for deciding which design to use are related to the purpose of mixing, the theoretical drive, the timing, the point of integration, the typological use and the degree of complexity (191). Timing of the two methods is classified in three ways: concurrent, sequential and multiphase combination, and strategies may be mixed during interpretation, analysis and collection, as well as mixing at the level of design (22). Six main major mixed-methods designs have emerged: convergent (two independent quantitative-qualitative strands), explanatory (two-phase design, with collection of quantitative and qualitative data at different times), exploratory (the qualitative phase is used to inform the quantitative study), embedded (quantitative and qualitative data collection is within a quantitative or qualitative procedure), transformative (relates more to the content than to the methodology), and multiphase (study 1 - informs study 2 - informs study 3 mixed-methods) (22).

As the main aim of this study was to provide increased understanding of the symptom burden and HRQOL of cancer survivors undergoing hyperbaric oxygen therapy for pelvic LRTI, explanatory sequential design was considered to be most relevant. The intention of this design is to use qualitative data to provide more detail about the quantitative results. In an explanatory sequential design, the quantitative and qualitative data are collected and analysed

independently, before the strands are connected (22). This allows for integration and identification of content represented in both data sets and makes it possible to compare, find contrasts and/or synthesise the results to give a more complete understanding of the outcome (192). Another important intention of this design is to bring together the different and non-overlapping weaknesses and strengths of the quantitative and qualitative strands, viewed from both numerical and narrative perspectives (2, 192). Based on this design, this thesis has a quantitative dominance, as Paper 1 and 3 are based on quantitative methods, while Paper 2 is based on qualitative methods.

However, neither quantitative nor qualitative methods are homogenous fields whereby both the quantitative and qualitative strands are also connected to specific research designs (193). Two different quantitative research designs are used in this thesis. In Paper 1, a descriptive cross-sectional study design, with the purpose of identifying potentially related factors, conveying more knowledge about the condition, and illuminating areas for further studies of HBOT, was performed (194). In Paper 3, a pre-test - post-test design was used to assess changes in the development of pelvic LRTI symptoms and HRQOL following HBOT. This design is linked to a quasi-experimental design, usually used to test causal consequences of long-lasting treatments, in contrast to "true" experiments with random assignment to a treatment and to a control group. (181, 195, 196). To strengthen the chosen design, two samples of norm populations for comparison were included (181).

In the qualitative strand, a phenomenological-hermeneutical design was used (2). This method is particularly suitable when the aim is to understand the meaning of the lived experiences of individuals concerning a phenomenon (2, 197, 198). The design consists of elucidating the individuals' experiences of the life world (phenomenology) and interpreting them (hermeneutic). This is an ongoing process between the individuals' expressed experience and the researchers' preunderstanding and interpretation (the hermeneutic circle) to gain new

insight and understanding of a phenomenon (2, 197, 199). Studying a limited number of individuals in-depth may provide rich and contextual information about complex phenomena (2).

To summarise, Figure 2 illustrates the study's ontological, epistemological, axiological and methodological strands.

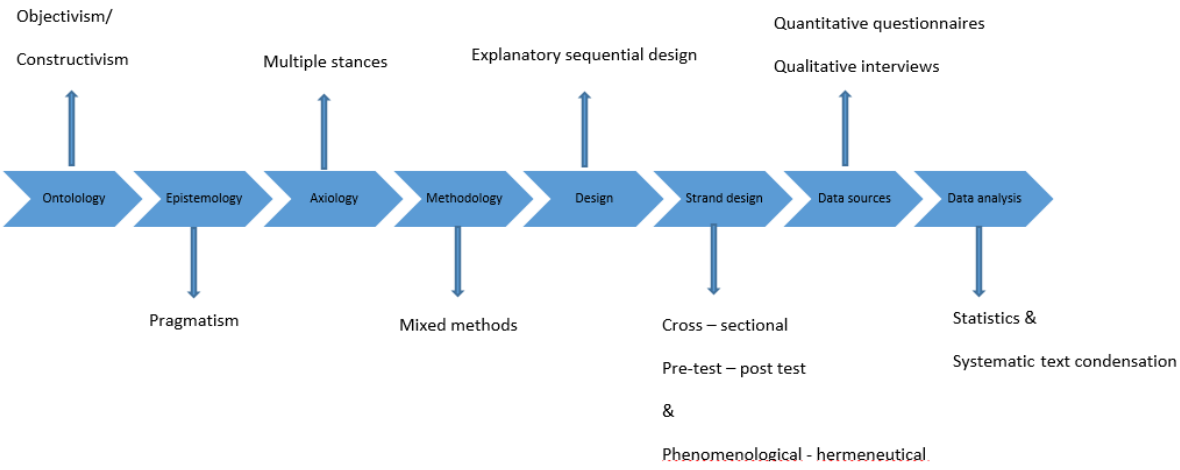


Figure 2. The study's ontological, epistemological, axiological and methodological strands.

6.2 The sample

In the following, participant recruitment, eligibility criteria, sampling procedure and the study sample are presented.

6.2.1 Recruitment and eligibility criteria

The participants were recruited from among all cancer survivors with pelvic LRTI assigned to HBOT at the Norwegian National Unit for Planned Hyperbaric Oxygen Treatment, between 1 August 2018 and 31 March 2021. This unit serves the whole country, and to ensure participant identification that was as complete as possible, the following inclusion criteria were established:

1. Pelvic radiation injury after intended curative radiation for pelvic cancer.

2. LRTI symptoms from bowel, bladder or pelvic area, with signs of radiation injury verified by endoscopy or radiology.
3. ≥ 6 months from completed radiation.
4. Aged ≥ 18 years.

Exclusion criteria were:

1. Severe physical and/or mental comorbidity representing a contraindication for HBOT, including signs of active cancer.
2. Insufficient language skills to complete study questionnaires and/or interviews.
3. Previously treated with hyperbaric oxygen.

Participants in the quantitative studies were recruited from among all those who fulfilled the eligibility criteria and gave their consent to participate. Participants included in the qualitative phase of the study (n = 20) were drawn from the pool of numbers 1- 73 participating at baseline (T1), reflecting a broad variety of demographic and medical backgrounds, as required for qualitative research (2).

6.2.2 The participants

In total, 129 cancer survivors met the eligibility criteria, and 107 participants were included in the study. Non-participation was related to declining to participate (n = 11), withdrawal from treatment (n = 6), and previous HBOT (n = 5). At six-month follow-up, 95 of the participants had completed the entire follow-up plan (T1 to T3). Loss to follow-up (n = 12) was related to death (n = 1), not returning questionnaires (n = 2), discontinued treatment due to other illness (n = 3) and not completing six-month follow-up (n = 6). The demographic and medical characteristics of the study population are outlined in Table 2.

Table 2. Demographic and medical characteristics of the study population (N = 107)

	n (%)
Gender	
Male	57 (53.3)
Female	50 (46.7)
Age, years [mean (SD, range)]	64 (12, 32-84)
Education	
College/University	85 (79.5)
Primary/High School	22 (20.5)
Work Status	
Sick Leave/Disability Pension/Retired	88 (82.3)
Full Time/Part Time Employment	19 (17.7)
Civil Status	
Married/Cohabiting	77 (72.0)
Single	30 (28.0)
Children under 18 Years of Age	
No	94 (87.9)
Yes	13 (12.1)
Medical Characteristics	
Cancer Site	
Prostate	56 (52.4)
Gynaecological	38 (35.5)
Rectum/Anus	13 (12.1)
Referral Diagnosis	
Cystitis and proctitis	9 (9.4)
Cystitis	39 (36.4)
Proctitis	45 (42.1)
Osteoradionecrosis pelvis	11 (10.3)
Wound/fistula	3 (2.8)
Type of Cancer Treatment	
Radiation only	68 (63.6)
Chemotherapy and Radiation	39 (36.4)
Types of Radiation	
External and Internal	30 (28.0)
External only	77 (72.0)
Radiation Dose, Gy [range]	
Internal	7.0-75.0
External	35.0-100.0
Months since Radiation [mean (SD, range)]	70.48 (78.32, 11-511)

Abbreviations: Gy, Gray; Numbers are number of participants (% of total) if not specified otherwise; SD, standard deviation.

The participants in the qualitative study (n = 20), 11 women and 9 men with different civil status, were between 36 and 77 years of age. They were diagnosed with different pelvic cancers, had undergone pelvic radiation, and had developed different LTRI (radiation cystitis, proctitis and osteoradionecrosis).

6.3 The HBOT procedure in this study

In Norway, elective HBOT is localised as outpatient treatment at the Norwegian National Unit for Planned Hyperbaric Oxygen Treatment. During the six-week treatment course most patients are located at a patient hotel within walking distance from the HBOT unit, while local patients stay at home. Patients who are in need of hospitalisation stay in different hospital wards, depending on their underlying medical condition.

As for all medical treatment, hyperbaric medicine is also prescribed by physicians, and HBOT at the Norwegian national unit is performed by specialised trained nurses according to medical regulations and prescriptions. Physicians are available if needed, but are not present during treatment sessions. During treatment, patients are completely enclosed in a mono-place pressure chamber for approximately two hours once a day. Strict safety routines are applied, and patients are under constant observation during treatment, as the ambient oxygen level increases the risk of fire and oxygen seizures (97, 200). Details of the treatment procedures are outlined in Table 3.

Table 3. HBOT procedure at the Norwegian national unit.

Prior to treatment	Written information, by post and electronic - treatment schedule, information about treatment, safety rules, hotel information, travel information
First treatment day	Oral information by HBOT physician - treatment, safety, side-effects, treatment effects Video - to see how treatment is carried out Guided tour - see other patients being treated in mono-place chambers, wardrobe facilities, waiting area, clothing, preparation orders before treatment Individual information and check by an HBOT physician Education by an HBOT nurse - safety rules, information about compression and decompression, instruction in techniques to equalise ear pressure, training in using a mask in connection with air breathing breaks, clarification of individual needs
Daily before treatment	Daily safety check - ensure patients have followed safety rules in accordance with procedure (e.g. avoid ointments, synthetic materials), measures according to medical equipment, secure and comfortable position
Start of treatment	During treatment, patients are totally enclosed, and hands-on care cannot be provided - initially, HBOT nurse checks that the communication system works, starts compression and guides the patient (e.g. how to equalise pressure), compression normally takes seven minutes (slower compression for first treatments)
During treatment	100% oxygen breathed at 2.4 atmosphere absolute for 90 minutes. Five minutes of air breathing via mask twice during each treatment session, to prevent oxygen seizures - HBOT nurse sits outside the chamber to safeguard the patient, communicates by loudspeaker system, with film, TV, or music distraction according to the patient's wishes
End of treatment	Decompression - HBOT-nurse safeguards and observes patient during decompression (five minutes) and closes up the treatment session
After treatment	Assist patients with individual needs (e.g. clothing, urinary catheter, blood samples, transport)

Abbreviations: HBOT, hyperbaric oxygen therapy.

6.4 Data collection

In this study, quantitative data was collected at three time points: at baseline (T1) before HBOT, on completion of the six-week HBOT course (T2), and at six-month follow-up (T3). Qualitative data was collected at one time point, i.e. on completion of the six-week HBOT course (T2). The timeline and data collection are illustrated in Figure 3.

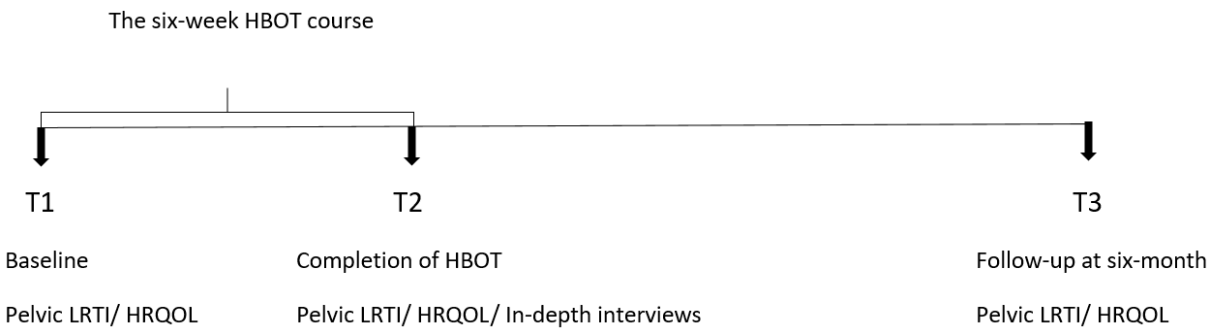


Figure 3. The study's timeline and data collection.

6.4.1 Collection of quantitative data

Quantitative data was collected via self-reported questionnaires. The questionnaires were sent by post at T1 and T3 and participants returned the questionnaires on arriving at the hyperbaric unit for their first treatment, or by post, in a pre-stamped envelope. At T2, the questionnaires were issued to the participants by a study nurse and returned in a mailbox at the treatment unit before departure.

The quantitative outcome measures were chosen on the basis of the definition of pelvic LRTI symptoms, HRQOL and previous research in this field. Here, the following data was collected (Appendix 1):

- *Medical variables* were collected from the medical journal (cancer diagnosis, treatment, radiation injuries).
- *Sociodemographic data* (age, gender, civil status, education, work status) were collected by self-reporting.
- *The Expanded Prostate Cancer Index Composite (EPIC)* (201), urinary and bowel domain, was used to measure pelvic LRTI. This instrument was chosen as it measures perceived urinary and bowel toxicity and complications from radiotherapy for prostate cancer and gynaecological malignancies. Based on the past four weeks, the EPIC urinary domain consists of 12 items addressing a broad range of urinary tract symptoms (e.g. leakage, frequency, incontinence, nocturia, pain and haematuria); while the bowel domain consists of 14 items of bowel function and discomfort (e.g. urgency, leakage, frequency, bloody stools and pain) (201). Items are scored on Likert scales, with different response categories (0-4, 1-3, 1-4 and 1-5), and transformed into a 0-100 score (202). The results are presented as a total score for urinary and bowel symptoms, based on the means of all items, as well as urinary subscales (function, bother, incontinence and irritable/obstructive) and bowel subscales (function, bother). The total score is the mean of all the scores, where lower values indicate more severe symptoms (202). EPIC was previously used in studies of pelvic LRTI, which enables comparison of the results. The instrument has shown to be sensitive to change, valid and reliable, with Cronbach's alpha ranging between 0.82- 0.86 (201, 203, 204).
- *The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30, version 3.0*, was used to measure HRQOL (3). The EORTC QLQ-C30 was published in 1993 and provides established reference data for 50 countries (3, 205-207). In line with the literature, EORTC QLQ-C30 defines HRQOL as a subjective, multidimensional construct operationalised through nine

multi-item scales (3, 161, 173, 176). These include an overall HRQOL scale, five functional scales (physical, role, social, emotional, cognitive), three symptom scales (fatigue, pain, and nausea/vomiting), as well as six single symptom items (dyspnoea, appetite loss, insomnia, constipation, diarrhoea and financial impact). Most of the items are scored on a four-point interval scale ranging from 1 ('not at all') to 4 ('very much'), while overall HRQOL is scored on a seven-point interval scale ranging from 1 ('very bad') to 7 ('excellent'). All items are transformed into a 0-100 score (205). For functional scales and overall HRQOL, a high score reflects a high level of functional capacity associated with better HRQOL. Conversely, high scores on the symptom scales represent a high symptom burden associated with poor HRQOL. This instrument is widely used both internationally and nationally, with documented robust psychometric properties. It has proved to be a reliable and valid measure of HRQOL in cancer patients, and Cronbach's alpha ranges between 0.80 and 0.90 for most multi-item scales and single items (3, 206).

- *The General Health Questionnaire (GHQ -12)* was applied to measure the participants' current mental health (208). The instrument includes questions on the level of general psychological distress, as well as the ability to carry out normal functions. Positively worded items (e.g. "been able to enjoy normal day-to-day activities") are scored from 'more than usual' to 'much less than usual'. Negatively worded items (e.g. "lost much sleep over worry") are scored from 'not at all' to 'much more than usual'. The 12 items are scored on a four-point Likert scale (0-1-2-3), with a possible total score ranging from 0-36. A higher score indicates more symptoms of psychological distress. The instrument is widely used as a reliable screening tool for non-psychotic illness outside a clinical setting, showing generally high validity, sensitivity and specificity, and Cronbach's alpha ranges between 0.82-0.86 (7, 209).

6.4.2 Collection of qualitative data

Individual in-depth interviews were considered to be well suited for exploring the cancer survivors' experience related to undergoing HBOT, since their aim is to collect descriptions of individuals' life world in order to understand the significance of their lived experiences involving a certain phenomenon (2, 183). The first five interviews were conducted by the main supervisor, and 15 interviews by the PhD candidate. To ensure that the interviewers conducted the interviews in a reasonably similar manner, a semi-structured interview guide was developed, piloted and agreed on (Appendix 2). The interview guide consisted of broad topics related to the experience of information, procedures and follow-up during HBOT (210). All interviews took place face-to-face in a quiet office at the hospital, but outside the HBOT chamber area. The interviewers had not met any of the informants prior the interviews. First, the interviewers introduced themselves, and gave a reminder of the purpose and that participation in the study was voluntary, including the right to withdraw and the protection of anonymity, and ensured permission to audiotape. All interviews started with the opening question: "Can you please describe how you have experienced undergoing HBOT?" The informants were encouraged to tell their own stories as freely as possible, and their stories led to new follow-up questions. The context allowed for exploration of the individual participants' experiences whereby they could direct the course of the interview and identify and describe experiences that had not been considered by the researchers. All interviews were audiotaped and lasted approximately one hour.

After each interview, the two interviewers discussed their immediate reflections on special themes, nuances or important clues on which to follow up in the forthcoming interviews. Data saturation was achieved at around the 15th interview, but 20 interviews in total were performed to make sure that no further new topics emerged (211). All interviews were transcribed verbatim. Throughout all transcriptions, emotional reactions (e.g. crying),

stressing of words, sighing and whimpering were explained and outlined at the same manner, to enhance validity and transparency, although identifiable characteristics (e.g. names) were not transcribed, to preserve anonymity (2). The transcripts were not returned for corrections or comments.

6.5 Data analysis

In explanatory sequential design, the quantitative and qualitative data is analysed independently, using approaches best suited for the respective method before the strands are connected (22).

6.5.1 Quantitative data analyses

All data was coded and processed using the IBM SPSS Statistics for Windows version 26.0 (212) software package. Normality for all variables was determined by Q-Q plots, skewness and kurtosis. Internal consistency, measured by Cronbach's alpha, was high for all instruments (α = 0.80 – 0.91) (213). Normally distributed data was reported with the sample mean and standard deviation (SD). All *P* values were two-tailed, and judged to be significant if < 0.05. Correlations were reported with Pearson's *r* and explained variance (r^2) (214). Effect sizes (Cohens *d*) were judged against the following criteria: small ($d \geq 0.2$), medium ($d \geq 0.5$), large ($d \geq 0.8$) or very large ($d \geq 1.3$) (215).

In Paper 1, missing values were handled according to the respective questionnaires' manual (202, 208, 216). For EPIC, the four missing items were calculated via the mean for the actual participant, since at least 80% of the questions for the actual domain were answered (202). For EORTC QLQ-C30, the 12 missing values were calculated via the mean, since at least half of the items from the scale had been answered (216). For GHQ, the three missing items were imputed as a low score (208). Descriptive statistics were used for demographic and medical variables. Predictor variables (age, gender, type of cancer treatment and radiation-related

variables) were analysed regarding the outcome variables (pelvic LRTI symptoms, psychological distress and HRQOL). Correlation analyses, using Pearson's *r* and explained variance (r^2), and *t*-tests were used to assess the possible links between pelvic LRTI symptoms, psychological distress and HRQOL (214). Regression analyses were used to assess the influence of age and clinical variables (cancer site, time since treatment and radiation dose) (217). Multiple linear regression analysis was carried out to explore the relationship between pelvic LRTI symptoms, psychological distress and overall HRQOL. Finally, to examine the influence of psychological distress on the association of pelvic LRTI symptoms with overall HRQOL, a moderation analysis was conducted by adding the product of psychological distress and pelvic LRTI symptoms to the multiple regression analysis (218).

Differences in pelvic LRTI symptoms and HRQOL between the time points T1, T2 and T3 were analysed by paired sample *t*-tests for changes in the mean. As a value of less than 80 points in the urinary and bowel domain of the EPIC indicates a significant symptom burden, separate analyses were performed for the respective subgroups (EPIC <80 at T1) (219). Development over time is presented as a mean change of scores, with 95% confidence intervals (CI). To assess the correlation of the development in pelvic LRTI symptoms with overall HRQOL, Pearson's correlation analysis was used (214). Multiple linear regression was carried out to explore the relationship between changes in overall HRQOL as dependent variables and changes in pelvic LRTI symptoms as independent variables.

As a control group was not included, using references or norm data made it possible to compare the present study's EPIC scores, EORTC QLQ-C30 scores and GHQ-12 scores (205, 220, 221). *Z*-tests were performed to analyse differences between the cancer survivors' mean scores and the mean scores in the reference populations, providing z-scores and two-tailed *P* values (213). Since data from a Norwegian norm population of cancer survivors with pelvic LRTI is not available, the following populations were regarded as suitable for comparison:

EPIC bowel and urinary scores were compared to a sample consisting of controls without prostate cancer (N = 112) (220). Mean scores of HRQOL were compared to the EORTC reference values of a general European population (N = 7802) (205). The GHQ-12 mean scores were compared with a sample consisting of Norwegian married/cohabiting students (N = 1750), studied by Nerdrum et al. (221). Effect sizes of the differences in means between cancer survivors ($Mean_{cs}$) and the other adult populations ($Mean_{norm}$) were defined by Cohen's $d = (Mean_{cs} – Mean_{norm})/ SD_i$, where SD_i was the pooled SD within groups (222).

6.5.2 Qualitative data analysis

In Paper 2, the qualitative data consisted of 20 interviews, representing 168 pages of transcribed text. As the aim of Paper 2 was to understand the individuals' experience of the HBOT process, systematic text condensation (STC) was considered an appropriate method to analyse the data. STC was developed by Malterud (185) as a pragmatic procedure, inspired by phenomenological ideas, presenting the participants' experience as expressed by themselves, rather than by exploring the possible underlying meaning of what was said (185, 197). (185). As various theoretical frameworks can be applied, STC is thus aligned with the philosophical basis for mixed-methods (185, 223).

STC is a four-step analysis: 1) gaining a total impression; 2) identifying units of meaning; 3) abstracting the contents of individual units of meaning; and 4) summarising their importance (185). These four steps start with interviewing and then move into analytical circles, aligning with the study's phenomenological approach (2).

The analysis was performed in collaboration by the two supervisors and the candidate, emphasising the importance of working both systematically and creatively to capture the essence of the informants' experiences. First, the three authors of Paper 2 read the interviews separately to obtain a general overview related to the study aim. Then, the individual's

general impression was discussed in common until consensus was reached. Secondly, the interviews were re-read and eight representative units of meaning were extracted. The units of meaning were transferred into NVivo12 software for further coding and sorting of the data (www.qsrinternational.com). Thirdly, the coded units of meaning were condensed into abstracted themes, engaging the researchers in an analytical circle between the identified themes, transcribed interviews and discussions. On the conclusion of this process, four themes were agreed on, each having two subthemes. The analyses were discussed among the supervisors and the candidate until all interpretations achieved consensus (2, 185). The findings were summarised and quotations from participants were used to illustrate the findings and ensure the participants' exact meaning (185). The quotes were translated from Norwegian to English as accurately as possible, and the procedures for the analysis of the findings are outlined in Table 1 in Paper 2, to allow for transparency (2, 185, 224). The three researchers represented different disciplines; two of them had a nursing background, and one researcher had a physician background. Two of the researchers had extensive experience from HBOT, while one of the researchers had no knowledge within this field, but was an experienced qualitative researcher. During the analyses, both the candidate and the supervisors were aware of the researchers' pre-understandings, specifically those related to previous professional and personal experience, as well as the theoretical and professional standpoints, and these pre-understandings were included in the discussion throughout the analyses (185).

6.5.3 Merging quantitative and qualitative results

As previously described, the first two analysis steps in an explanatory sequential design are to analyse the quantitative and qualitative data separately. The quantitative data was analysed at baseline (T1) and in relation to the development of pelvic LRTI symptoms and HRQOL from T1-T3. The qualitative data was analysed after completion of all the in-depth interviews at T2.

The third step in this analysis was to identify content areas that were present in both data sets and to compare, find contrasts and/or synthesise the results to provide a more complete understanding of the data (22). During this process, the amounts and content that were present in both the quantitative and the qualitative data sets were examined and structured. The aim of merging the results was to provide a more comprehensive picture of the participants' situation at baseline (T1/Article 1), of the HBOT process (T2/Article 2) and of the outcome during and after HBOT (T1-T3/ Article 3).

6.6 Ethical considerations

Research focused on human beings is governed by strict ethical and legal regulations (225, 226). The management at the Centre for Crisis Psychology, Faculty of Psychology, University of Bergen and at the Department of Occupational Medicine, Haukeland University Hospital, approved the study. The present study is part of a prospective longitudinal study with the overarching aim of increasing the understanding of, and knowledge about, pelvic LRTI in cancer survivors undergoing HBOT. The main study was pre-registered in ClinicalTrials.gov. (Identifier: NCT03570229) (Appendix 3) and approved by the Regional Committee of Medical Research Ethics in Northern Norway (ID 2018/706) (Appendix 4). The study was conducted in compliance with the Declaration of Helsinki and the requirements for data processing and handling of the data (226, 227). The participants received written information about the study concerning how participation was voluntary, all data would be treated confidentially, that they could withdraw from the study at any time, and that data could be deleted on request. All participants gave written consent (Appendix 5).

Confidentiality was ensured in several ways. A coding system was used whereby numbers replaced the participants' names and the list connecting names and numbers was stored on the hospital's research server, and only the research team had access to the list. The

numbered questionnaires (T1 and T3) were sent by post and delivered (T2) to the participants by a study nurse, who was not involved in the analysis of the data. Questionnaires were returned by post, in pre-stamped envelopes (T1 and T3), and/or in a mailbox at the hyperbaric unit (T2). All completed questionnaires were stored in a locked cabinet at the university, separate from the data file. Data plotting was performed by a scientific assistant or by the candidate, and the data file was stored on the university's research server, with no identification beyond participant numbers. The sound recorder used to record the interviews was stored in a locked cabinet. Recordings that were converted to mp3 files and the anonymised interview transcripts were stored on the research server at the hospital.

Quantitative and qualitative methods may entail different ethical issues regarding confidentiality, closeness and potential stress (2, 22, 210). All professionals involved in the study had extensive experience either as researchers, clinicians, or both, as well as the competence to ensure ethical and safe conditions for all participants.
The interviewers only met the participants during the interviews, and they were not involved in the HBOT process.

Four specific ethical issues require careful consideration when undertaking research consisting of qualitative interviews: 1) impose no harm, 2) use relationship-based ethics, 3) disclose the research intent, and 4) ensure the right to privacy and confidentiality (228). The interviewers sought to diminish any risk of subtle injury, such as decreasing a participant's self-esteem or exposing a participant to undue stress via their experiences during the interview (229). The interviewers made sure the study was understood and gave the participants the opportunity to ask questions and make comments, communicated that their participation was valuable and appreciated, and sought to provide safe and comfortable interview frames, interact in a polite manner, and encourage participants to speak freely. (2, 228).

As the participants were outpatients for six successive weeks, skilled healthcare professionals could immediately attend to any problems arising during the HBOT course. The majority

reported only minor, temporary and highly tolerable side-effects of HBOT, and those who experienced adverse events were immediately seen by a physician for management and follow-up. In addition, all patients treated at the national unit had access to a physician on duty and medical requests were managed and followed up rapidly and successively. In addition, during the entire study period, all three researchers were available for telephone contact. All enquiries were discussed within the group, with subsequent feedback to the participant.

7. FINDINGS

In this section, the findings from the three papers are presented, followed by the merged results, in which the findings are connected.

7.1 Paper 1: Symptom burden, psychological distress, and health-related quality of life in cancer survivors with pelvic late radiation tissue injuries

Curative radiotherapy for pelvic cancer may lead to severe LRTI. However, limited knowledge exists about pelvic cancer survivors' LRTI symptoms, distress and HRQOL.

The aim of this study was to assess the symptom burden, psychological distress and HRQOL in survivors with established pelvic LRTI compared to norm populations, and to investigate the relationship between these factors.

A descriptive cross-sectional study design with the purpose of identifying potentially related factors was used. Cancer survivors referred for treatment of established pelvic LRTI were recruited nationwide. A total of 107 participants were included (53% were men, n= 57) with a mean age of 64 (range 32-84 years, SD=12). Pelvic LRTI were assessed according to EPIC urinary and bowel domain, compared to a sample consisting of controls without prostate cancer (N=112). Psychological distress was assessed by GHQ-12, compared with a sample consisting of Norwegian married/cohabiting students (N=1750). Finally, HRQOL was assessed by EORTC QLQ-C30, and compared with a general European population (N=7802).

The participants reported more urinary (mean 68.7 vs. 89.5; $p< 0.00$; d=1.4) and bowel symptoms (mean 62.5 vs. 92.4; $p<0.00$; d=2.7) than norms with large to very large effect sizes. Survivors treated with both chemotherapy and radiation reported more bowel symptoms than participants treated with radiation only (mean 58.8 vs. 65.0, p=0.02). Women reported more bowel symptoms than men (mean 58.6 vs. 65.7, $p<0.00$). The cancer survivors

also scored higher, with medium effect size on psychological distress than the norms (mean 13.4 vs. 10.3; $p<0.00$; $d=0.6$). Overall HRQOL score (mean 54.9 vs. 71.2; $p<0.00$; $d=0.7$) and all sub-dimensions were lower compared to norms, except for emotional symptoms. The greatest differences were found for social function (mean 48.3 vs. 87.5; $p<0.00$; $d=1.7$), physical function (mean 69.1 vs. 89.8; $p<0.00$; $d=1.2$), and role function (mean 59.9 vs. 84.7; $p<0.00$; $d=0.9$), with large or very large effect sizes. The cancer survivors also scored significantly higher than the norms on all HRQOL symptom scales, with very large or large effect sizes for diarrhoea (mean 50.5 vs. 7.0; $p<0.00$; $d=2.3$), constipation (mean 28.6 vs. 6.7; $p<0.00$; $d=1.2$), fatigue (mean 49.8 vs. 24.1; $p<0.00$; $d=1.1$), and insomnia (mean 47.1 vs. 21.8; $p<0.00$; $d=0.9$). A higher symptom burden and higher levels of psychological distress were associated with lower HRQOL ($r^2=46\%$), but psychological distress did not moderate the influence of symptoms on HRQOL.

In conclusion, the results indicate that cancer survivors with established pelvic LRTI experience a severe symptom burden, moderate levels of distress, and highly impaired HRQOL compared to norm populations, several years after radiotherapy. To improve HRQOL, treatment of pelvic LRTI symptoms and interventions related to coping are of great importance. Systematic assessment of symptoms and HRQOL after radiation should be part of routine follow-up and be confirmed by objective measures and available treatment options, such as HBOT. In addition, educating survivors in adequate coping skills may be of importance.

7.2 Paper 2: Experiences of patients with pelvic radiation injuries after cancer treatment undergoing hyperbaric oxygen therapy – a phenomenological-hermeneutical study

Radiotherapy for pelvic cancers may cause pelvic LRTI, and HBOT is one of few treatment alternatives. However, we have limited knowledge of how cancer survivors with pelvic LRTI experience undergoing HBOT.

The aim of this study was to explore how cancer survivors with pelvic LRTI experienced undergoing HBOT.

The study was anchored in qualitative methods, using a phenomenological-hermeneutical approach. To capture the lived experience of undergoing HBOT, in-depth, individual, face-to face interviews of 20 cancer survivors were conducted on completion of six-week HBOT. The interviews were audiotaped and lasted for approximately one hour. STC was used to analyse the transcribed data.

Four main themes emerged from the analyses of the participants' experience of undergoing HBOT: 1) approaching an unknown world; 2) from feeling worried to becoming familiar; 3) a long-lasting treatment course; and 4) the treatment course went better than expected. Each of the main themes was further elaborated as two sub-themes.

In relation to the first main theme, "approaching an unknown world", the participants reported that they knew very little of what to expect on arriving at the HBOT unit and that they experienced entering a totally unknown environment. This was elaborated on in the sub-theme "I got information but still I felt unprepared", describing that even if they had received written information, they still experienced being unprepared. Even though HBOT was highly unknown and unfamiliar, the participants expressed that they were eager to start treatment. This was identified as the sub-theme "HBOT may be my chance", where they articulated a common hope that HBOT would reduce their LRTI symptoms.

Main theme two “from feeling worried to becoming familiar”, describes a gradual process from being worried about towards becoming familiar with HBOT. This was further outlined in the sub-theme “I had to learn how to dive”, whereby learning by doing was important to reducing the participants’ anxiety and distress. Another important facet was identified in the sub-theme “the nurses made me feel safe”, describing the importance of the nurses’ competence and close follow-up.

The third main theme “a long-lasting treatment course” elaborated on how the participants experienced HBOT as protracted and time consuming. This experience was expressed by the sub-theme “being away from daily life”, describing how their absence from home greatly affected their everyday life. Another facet was identified as the sub-theme “the importance of peer patients”, describing the crucial importance of meeting other survivors with pelvic LRTI.

The fourth main theme identified was “the treatment course went better than expected”. This positive experience was based on two main features. The first facet was outlined in the sub-theme “experiencing limited side-effects” showing few, mild and transient side-effects, even if some patients experienced fatigue. In the second facet “the beginning symptom relief”, the participants experienced improvement in LRTI during the HBOT course, with pain relief, less bleeding, and reduced urge and frequency of urine and faeces.

In conclusion, many participants experienced starting HBOT as unfamiliar, and detailed information was needed to prevent distress and anxiety. Clear routines, highly specialised personnel with a reassuring attitude, person-centred care, and distraction during treatment seemed to be important factors to make the patients feel safe and to promote coping during treatment. The long HBOT course seemed to be outweighed by the benefits of meeting peer patients. Overall, HBOT was experienced as a safe treatment with limited side-effects, with many patients noticing initial symptom relief.

7.3 Paper 3: Symptom burden and health-related quality of life six months after hyperbaric oxygen therapy in cancer survivors with pelvic radiation injuries.

Radiotherapy is an important aspect of the multimodal curative treatment for pelvic cancers, but LRTI may develop months or years later. HBOT has shown positive effects for a range of LRTI, but limited research exists concerning HBOT for pelvic LRTI and how this influences survivors' HRQOL.

The aim of this study was to explore the development of and association between symptoms of pelvic LRTI and HRQOL following HBOT.

A quantitative method with a pre-test – post-test design was used to evaluate the changes in pelvic LRTI and HRQOL from baseline (T1), on completion of the six-week HBOT course (T2), and at six-month follow-up (T3). EPIC urinary and bowel domain and EORTC QLQ-C30 were used to assess pelvic LRTI symptoms and HRQOL.

Cancer survivors referred for treatment of established pelvic LRTI were recruited nationwide. Ninety-five participants were included in the study (52.6% were men) with a mean age of 65 years (range 32-84 years, SD=11.6).

Participants reported a high LRTI symptom burden at baseline (urinary EPIC, mean (SD) 70.0 (17.2); bowel EPIC 63.4 (13.4)), while this improved statistically and clinically significantly six months after treatment (p = <0.00), representing minimal clinically important changes. Participants with the highest symptom burden (EPIC < 80) at baseline reported moderate improvement of bowel symptoms.

The participants reported severely impaired HRQOL, including overall HRQOL, all functions and symptom scales at baseline. At six-month follow-up, overall HRQOL, all functional scales and most symptom scales/scores increased statistically and clinically significantly. Here, scores for overall HRQOL, social and role function, sleep disturbance, diarrhoea, pain,

and fatigue improved the most after HBOT. This increase was already present at the end of the HBOT course, except for physical and cognitive function and fatigue.

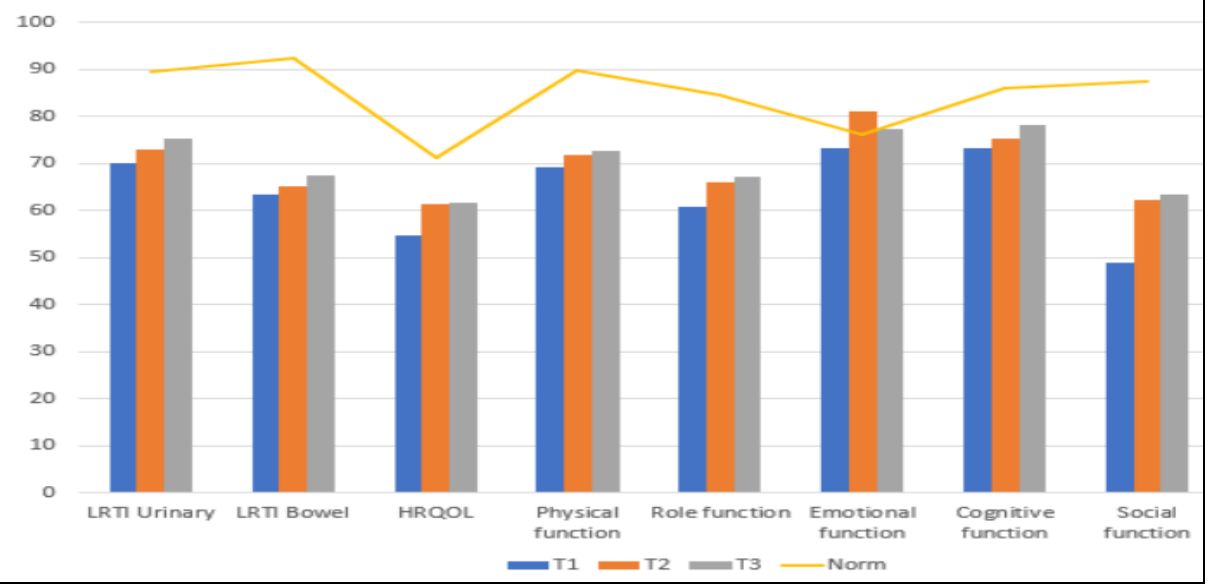
The correlations between the changes in LRTI symptoms and HRQOL were positive, but weak, and the changes in LRTI symptoms from baseline to six-month follow-up explained only 10% of the variance in overall HRQOL.

In conclusion, the results indicate a beneficial, but small outcome for pelvic LRTI symptoms and HRQOL after HBOT at six-month follow-up, and already with a noticeable improvement at the end of HBOT. Changes in pelvic LRTI were associated with changes in HRQOL.

7.4 Merging the results from the three papers

Merging the findings from the three papers may provide a more comprehensive picture of the participants' situation at baseline (T1), from the HBOT process (T2) and from the outcome after undergoing HBOT (T2 and T3), as presented in Table 4 and elaborated below.

Table 4. The merged results from the three papers

	Baseline (T1)	**The HBOT process**	**End of Treatment (T2)**	**6 Months Follow-up (T3)**
Quantitative results Papers 1 and 3	Significantly (*P*<.00) greater pelvic LRTI symptoms (*d*=1.4- 2.7), psychological distress (*d*=0.6) and impaired HRQOL (*d*=0.7) compared to norms. Psychological distress did not moderate the influence of symptoms on HRQOL.		Statistically and clinically significantly (*P*<.00) improved LRTI symptoms and overall HRQOL, and all the functional dimensions, except for physical function, and most HRQOL symptoms from baseline	Statistically and clinically significantly (*P*<.00) improved LRTI symptoms, HRQOL and all the functional dimensions and most HRQOL symptoms from baseline A further significant improvement in LRTI symptoms (*P*<.00) and HRQOL symptoms and fatigue and dyspnoea were found, where emotional function decreased, while the other dimensions were stable
				
Qualitative results Paper 2	Approaching an unknown world: b) 'HBOT may be my chance'	Approaching an unknown world: a) 'I got information, but I still felt unprepared' From feeling worried to becoming familiar: a) 'I had to learn how to dive' b) 'The nurses made me feel safe'	The treatment course went better than expected. a) 'Experiencing limited side-effects' b) 'Experiencing the beginning of symptom relief'	

		A long-lasting treatment course: a) 'Being away from daily life' b) 'The importance of peer patients'		
Merged results	High pelvic LTRI symptom burden, psychological distress, impaired HRQOL, all areas of life affected. HBOT represented an unknown, but hopeful treatment modality.	Difficult to absorb the HBOT information. Adjusted quickly to HBOT procedures, and nurses' follow-up and care were crucial. Long-lasting treatment away from daily life outweighed by peer support.	Improved LRTI symptoms and most HRQOL dimensions and symptoms. Positive experience of HBOT, with limited side-effects and with symptom improvement.	Further improved LTRI symptoms. All HRQOL dimensions and most symptoms improved from baseline and were maintained from T2-T3. From T2- T3 fatigue improved, and emotional function decreased.

Abbreviations: *d*, effect size, judged as small ($d \geq 0.2$), medium ($d \geq 0.5$), large ($d \geq 0.8$) or very large ($d \geq 1.3$); EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; EPIC, The Expanded Prostate Cancer Index Composite; Overall HRQOL, overall health-related quality of life; *P*, statistically significance difference < .05.

At baseline, participants reported a high symptom burden, psychological distress and impaired overall HRQOL, with all function and most symptom scale scores compared to norms indicating that all areas of their lives were impaired. The qualitative findings support the quantitative results, describing vast physical, emotional and social implications of pelvic LRTI. However, the participants described HBOT as an important and hopeful opportunity for symptom relief.

The qualitative data describe the HBOT process. These findings indicate that participants received limited information about HBOT from the referring physician. Even if they got information from the HBOT section, they still felt unprepared about what to expect. However, the nurses' information, individual follow-up and holistic care, in addition to learning by doing, were important factors in reducing the participants' initial anxiety and distress. The participants experienced that the daily, long-lasting treatment course greatly affected their everyday lives. However, meeting other survivors of pelvic cancer greatly outweighed the absence from home and family.

At the end of HBOT, pelvic LRTI symptoms, overall HRQOL and all functional scales, except physical and cognitive function, and most HRQOL symptom scales, improved. The

qualitative findings support these quantitative results, as the participants experienced symptom improvement and limited side-effects – even if some experienced fatigue.

Six-month follow-up were assessed via quantitative data. Here, a further improvement in pelvic LRTI symptoms, overall HRQOL, all HRQOL functional and most symptom scales from the end of HBOT was found. Participants with the most severe symptom burden at baseline improved the most. The findings indicate, however, that as a mean, the participants still had severe pelvic LRTI symptoms and impaired HRQOL, except for the emotional function, for which participants align with the norm population.

8. DISCUSSION

This thesis covers a limited studied field, and to the best of our knowledge, this is one of the first studies in Norway contributing to knowledge about the symptom burden and HRQOL of cancer survivors undergoing HBOT for pelvic LRTI. It is the first mixed-methods study to follow pelvic LRTI survivors' outcomes and the process following HBOT that may contribute to more comprehensive understanding and knowledge.

In the following, the merged results from the three papers are discussed, including the participants' situation at baseline, the HBOT process, and participants' status at the end of treatment and at six-month follow-up. This section ends with reflections on the study's methodological strengths and limitations.

8.1. A highly burdened sample at baseline

The quantitative results from this study show that the participants reported a severely high symptom burden compared to norms. This was supported and outlined by qualitative data, and described as high levels of pain, diarrhoea, urge for urine and faeces, bleeding and sleep disturbance.

Previous research indicates that radiotherapy to the pelvic area may cause severe side-effects (78, 81, 104, 127, 230). However, studies of long-term pelvic LRTI are sparse. Previous research has documented a decline in pelvic LRTI symptoms over time, mainly explained by complete disease remission (102, 231). However, the participants in our study reported severe impacts at mean six years after radiation, indicating a long-term symptom burden, whereby the symptoms had not, or had not sufficiently, declined over time. In line with the literature (6, 52, 230), the high symptom burden may indicate that, although it is well-known that LRTI may occur after radiotherapy, these late effects seem to be severely underdiagnosed. This is

supported by the qualitative findings outlining that most of the participants had been unaware of their LRTI diagnosis, and that in many cases the diagnosis was not objectively verified before referral to HBOT. A major problem may be limited knowledge of pelvic LRTI among both healthcare professionals and survivors, and, consequently, that the symptoms may be misinterpreted as normal aging symptoms (6, 52). In addition, the limited spectrum of symptomatic treatment for pelvic LRTI often seems to have only a short-term effect, leaving the survivors with a severe symptom burden over time (230). Even if pelvic LRTI only affect 5-15 % of cancer survivors and newer radiotherapy modalities seek to limit the debilitating effects on normal tissue, the symptom burden of cancer survivors with pelvic LRTI is highly worrisome (6).

Previous research indicates that LRTI generally have a negative impact on HRQOL (6, 52, 230). In line with this, our participants reported low levels of overall HRQOL, as well as impaired physical, role, cognitive and social function compared to norms at baseline. These results are supported and outlined by the qualitative findings, where the participants expressed that their pelvic LRTI particularly impaired their physical activity, social participation and work ability. Together, the quantitative and qualitative findings indicate that all aspects of the survivors' lives were negatively impacted. Both quantitative and qualitative findings also revealed that the participants in particular experienced high levels of diarrhoea, pain, urge, sleep disturbance and fatigue. In general, pain, fatigue, and sleep difficulties are the most common late effects in cancer survivors, documented as impairing everyday life and social interaction, and increasing the risk of poor health and disability (39, 46, 232-239).

The quantitative results revealed that the participants reported moderately more psychological distress than norms. This supplements earlier findings suggesting that a combination of cancer-related symptoms, pain, fatigue and psychological distress adds to the total burden of cancer survivors, impairing their coping with everyday life (240, 241, 242). Previous research

has shown that late effects of cancer treatment, especially radiotherapy, are associated with psychological distress and contribute to impaired HRQOL (79-81). In addition, our results revealed a stronger correlation between the participants' overall HRQOL and distress than between overall HRQOL and pelvic LRTI. This is an important finding suggesting that other factors than LRTI may also add to the cancer survivors' distress. Such factors may be related to experience in the cancer trajectory (81, 82), fear of cancer recurrence, having elevated levels of psychological distress before cancer treatment, being about to start a new and unknown treatment, or other factors unrelated to cancer (101, 141). However, the high correlation between psychological distress and overall HRQOL reflects the strong interrelatedness between these factors (41, 52, 84, 243).

An interesting finding was that the participants' emotional function was comparable to the norm population, which may have several explanations. First, the participants may have adapted and developed several coping strategies in dealing with pelvic LRTI (244). Secondly, in the qualitative study the participants expressed that HBOT was their chance for symptom improvement, whereby any improvement would be welcomed. Hope and outcome expectations are important resources in coping, playing a predominant role in mediating distress and promoting HRQOL (173).

The merged results indicate that the participants experienced multidimensional challenges, which hampered their overall HRQOL, and provide a comprehensive picture of the cancer survivors' situation. This complies with the theoretical concept of HRQOL, underpinning that impairment in one dimension may negatively influence other dimensions, as well as overall HRQOL (3). Furthermore, the interaction and complexity between pelvic LRTI, psychological distress and HRQOL underpin the importance of a bio-psychological or holistic view in survivorship follow-up, screening and treatment interventions. In line with the theory

of HRQOL and health promotion, our findings indicate a need for holistic interventions to promote long-term health.

Despite an increased focus on cancer survivors, late effects and HRQOL, our results support prior research stating that this area is in need of improvement (34, 35, 36, 38, 39, 107). In line with prior research (34, 36, 37, 245, 246), our findings indicate that healthcare professionals need increased knowledge related to pelvic LRTI and their holistic consequences. In particular, the transition from cancer treatment to survivorship is documented as crucial for cancer survivors' long-term health, highlighting the importance of information and screening for late effects, individual survivorship plans, holistic follow-up care, and health-promoting interventions (29) (34, 37). Here, research indicates that nurse-led follow-up appears to provide a more holistic focus, in line with cancer survivors' complex needs in combination with medical follow-up (247-249).

8.2 Positive experiences of HBOT

The qualitative findings indicate that the participants experienced entering the HBOT facilities as approaching an unknown and rather scary world. The participants expressed that they had received limited information from the referring physician and that the information from the HBOT unit was difficult to absorb. Previous research shows that entering a high-technology treatment, including HBOT, may increase the level of distress and anxiety, so that patients would like more information in advance, as this may reduce treatment-related distress (141, 143, 144). HBOT is a highly-specialised treatment at national level, so that our results indicate that it may be challenging to reach out with information to different levels of healthcare services; and that efforts are needed to make this treatment visible to both healthcare professionals and patients as a treatment modality for LRTI (250). However, participants also found it difficult to relate in advance to the information from the HBOT unit,

consisting of written information and a video link. This may indicate a need for critical review of the information provided from the HBOT unit, for example by involving user representatives, or by a telephone call from an HBOT nurse, to clarify misunderstandings, before admission to the unit.

The findings revealed that participants quickly adapted to the safety routines and the pressure chamber treatment. Here, an important factor seems to be 'learning by doing', as it may be difficult to imagine the treatment procedures beforehand (144, 146). However, the findings indicate that the most important factor to ensure smooth adjustment was the individualised care and close follow-up by the nurses, as well as distraction during treatment. The importance of predictability and person-centred care are essential for positive coping experiences, where psychoeducation and close follow-up have been documented to facilitate patients' feeling of safety (145, 146). In addition, the close follow-up by the nurses over the course of six weeks may have enhanced coping and empowerment, which have been shown to be important factors for cancer survivors' HRQOL (155, 167, 173).

Furthermore, the findings elaborated that participants experienced the six-week treatment as protracted and time-consuming, and that absence from home, family and friends affected their everyday lives. Interestingly, they expressed that meeting other cancer survivors to some degree outweighed their absence from ordinary life. They experienced that meeting peers gave them someone to spend time with, while for many this was the first time they had the opportunity to share their experiences. This finding is supported by a range of studies linking peer support to better psychosocial outcomes in cancer survivors (38, 251-254). Consequently, this highlights the importance of organising HBOT in a way that promotes peer support.

To sum up, the findings from the HBOT process show the importance of a holistic approach to the pelvic LRTI survivors' complex needs, in alignment with the HRQOL concept and health promotion (3).

8.3 Decreased symptom burden and increased HRQOL at the end of HBOT

The quantitative findings from EPIC and HRQOL symptoms already showed a statistically significant and clinically relevant improvement in the participants' symptom burden on completion of HBOT, even though the regeneration of tissue was expected to take longer (71, 89, 255). The results are supported by the qualitative findings, where the participants experienced rather specific and quasi-objective symptom relief during the treatment course, such as fewer toilet visits and less sleep disturbance, which may indicate structural improvement (18). In line with the literature (97, 98), participants experienced highly tolerable and limited side-effects from HBOT, such as barotrauma and visual disturbance. However, several participants described debilitating fatigue during the treatment course. This may be related to oxygen toxicity and pre-existing fatigue, but is not described in previous literature. Consequently, this may be important for the information given patients, any more research may be needed.

The findings revealed that participants with the most severe baseline symptoms improved the most, which was in line with previous studies (18, 19, 133). This is important knowledge for healthcare professionals and may indicate which patients might benefit the most from HBOT. In addition, this is important patient information with respect to clarifying expectations in advance of HBOT. Even though the changes observed were of rather small magnitude, the symptom development corresponds to noticeable and clinically relevant improvement (205, 256).

Furthermore, major statistically significant and clinically relevant changes in overall HRQOL and most functional scales were found on completion of HBOT. This may have several explanations, such as a reduction of LRTI beginning to fulfil the participants initial hope of improvement, being in a setting that facilitates increased knowledge of their condition, promotion of coping, positive experiences, interaction and social support – which are all important factors for facilitating HRQOL (155, 167, 173). In line with the Norwegian cancer strategy (13) these results indicate the importance of focusing on HRQOL and not merely on pelvic LRTI symptoms.

8.4 Further decreased symptom burden and increased HRQOL at six-month follow-up

The quantitative results revealed a further improvement in specific LRTI symptoms and in less specific symptoms such as sleep disturbance, diarrhoea, pain and fatigue at six-month follow-up. However, even if the improvement was statistically significant, it was small and less than shown in the RICH-ART study by Oscarsson et al. (18). This may indicate that our sample was more heterogeneous, as it included several LRTI symptoms, while the RICH-ART study focused solely on radiation-induced cystitis (18). It must also be considered that our results are based on group means, which can mask that a significant proportion of patients may have experienced greater improvement. More research is still needed to clarify which patients will benefit most from HBOT.

Even if the pelvic LRTI improvement was small, it was clinically significant, entailing a noticeable change for the participants. This is in line with the participants' expressed hope at baseline, when they expressed that all symptom relief, no matter how small, would be of importance, and coincident with health promotion and the health continuum stating the importance of bringing participants closer to health than illness (157, 158, 257). This is also supported by the HRQOL symptoms, showing significant improvement in diarrhoea, sleep

disturbance, pain and fatigue. Furthermore, an improvement in overall HRQOL, and in social and role function, indicates improvement in all areas of the participants' everyday life, which must be seen as important. This adds to the knowledge that, beyond LRTI symptoms, HBOT may also have a positive impact on HRQOL (18, 20, 133, 149). However, the development in HRQOL from the end of HBOT to six-month follow-up was limited, indicating that the treatment course was most important for HRQOL, as discussed above. In contrast, fatigue improved the most from the end of HBOT to six-month follow-up. In this case, an explanation may be that HBOT triggers fatigue, and that it takes time to improve fatigue (97, 258, 259). Furthermore, the participants' emotional function score declined significantly from the end of HBOT to six-month follow-up, but was then still significantly better than at baseline. Again, several explanations may be relevant, such as disappointment that symptoms persisted, returning to the challenges of everyday life, a lack of peer support and less professional follow-up. This underlines the importance of local survivorship follow-up, for example from GPs, cancer care coordinators and/or municipal rehabilitation.

The merged results provide valuable supplementary information about the HBOT process on completion of treatment and at six-month follow-up. Although the causal direction could not be determined from this pre-test – post-test data, the findings suggest that HBOT may be useful for improving pelvic LRTI symptoms, as well as improving the survivors' HRQOL. Furthermore, the mixed-methods design and multiple points of measurement also add to the reliability of the results, because the different strands shed light on each another and therefore provide a more comprehensive view of the baseline results, the HBOT process and the outcomes. Together, the merged results support the interpretation that the results are most likely related to HBOT, indicating decreased symptom severity and enhanced HRQOL after treatment. However, the results also indicate that the participants' pelvic LRTI symptoms and

HRQOL were still substantially below the norms, indicating a further need for symptom management and holistic follow-up to promote health and HRQOL (3, 260-262).

8.5 Methodological considerations

Mixed-methods research involves both quantitative and qualitative approaches and these methods also differ in terms of how they verify the quality of the data and results. In the methodological considerations, the candidate followed Creswell and Plano-Clark's (22) recommendations for verification checks for each strand, as well as for the merged data. In addition, this section must also be viewed in connection with the choices and description in the methodology section.

8.5.1 Reflections on the quantitative results

Quantitative data were used in Papers 1 and 3. Reflections on the methodological strengths and limitations of quantitative research include discussion of the study's validity (how accurately a method measures what is intended), and reliability (whether the results can be reproduced under the same conditions) (263, 264). Consequently, reflections on the quantitative sample, the HBOT treatment, research designs, data collection, statistics and the researcher's role are presented as follows.

The sample consisted of participants with established pelvic LRTI, verified by endoscopy or radiology. This ensured a correctly diagnosed population, but also a selected group of those with the most severe LRTI symptoms. By inviting all patients referred to the Norwegian National Unit for planned HBOT in a period when few (n=11) declined to participate, the study samples in Papers 1 and 3 are regarded as large within this field, particularly in view of the Covid-19 pandemic and the periods of lockdown of HBOT. The gender distribution was quite even, but nearly 80% of the sample had higher education. The latter may indicate social inequality, as survivors with higher education to a greater extent seek and ask for treatment

(265). The inclusion of different cancer diagnoses might also represent a limitation, due to the heterogeneity of the applied treatment other than radiation (16, 17, 266).

HBOT treatment. All participants received HBOT daily for six weeks, conducted in mono-place chambers at a pressure of 2.4 atmosphere absolute, with each session lasting two hours. All participants were subject to the same established safety routines before, during and after HBOT. Furthermore, all participants were observed closely by a specialised trained HBOT nurse and at three routine appointments with an HBOT physician. Consequently, all participants received the same treatment provided in the same manner.

Research designs. Paper 1 included a cross-sectional study design, as this is a recommended design to study the targeted population at a specific point in time. As we sought to study the broader aspects of established LRTI, investigations had to take place before HBOT. Here, the use of an external comparison group is regarded as a strength of the study (194).

Paper 3 included a pre-test - post-test design. To examine the effects of an intervention, RCT are often applied as a standard study design (181, 225). Not including a control group may thus compromise the external validity, and the quantitative results may be taken to represent a measure of treatment efficacy. However, a pre-test – post-test design with external group comparisons is considered a suitable option for testing the feasibility of new methods and interventions (181). Therefore, the applied pre-test – post-test design provides a valuable indication of the feasibility and development of LRTI symptoms over time after HBOT. The use of three points of assessment contributed to illuminating the longitudinal course of LRTI symptoms after treatment, adding to the robustness and reliability of the results (181, 205, 220, 221, 225).

Data collection. For Papers 1 and 3, data was collected using three self-reported instruments,: EPIC, EORTC QLQ-C30 and GHQ-12, which are all widely used, with documented robust

psychometric properties, and have been shown to be valid, reliable and sensitive instruments for this use (201, 204, 205, 208, 209). A limitation here may be that EPIC is only validated for prostatic and gynaecological cancers, but as we focused on the symptom burden and not on diagnosis, we deemed this instrument to be most relevant. Another limitation may be that EORTC QLQ-C30 is developed for cancer patients, and therefore might not capture all aspects of HRQOL among cancer survivors. However, HRQOL instruments for cancer survivors are under development, but were not yet available for our study. Other limitations of EORTC QLQ-C30 are the lack of capturing the participants' hope and sexuality, which also represent important aspects of survivors' HRQOL. Collection of medical data from patients' medical journals, the pretesting of the instruments for four pelvic cancer survivors not participating in the study, and a dedicated study nurse in charge of collecting the data, are regarded as study strengths. Participants filled out paper-based questionnaires, which may represent both a strength and a limitation. Some participants may prefer paper-based, while others may prefer digital versions. On planning the study, we anticipated that using paper-based questionnaires filled out at the unit and receiving these by post in pre-stamped envelopes in follow-ups, would reduce missing data. The high completion rate and low rates of missing items support this anticipation and strengthen the data. However, digital questionnaires, especially for the follow-ups, might have yielded even better completion rates.

Statistics. All data in Papers 1 and 3 was normally distributed, with few missing values and high internal consistency for all instruments (Cronbach's $\alpha = 0.80– 0.91$). In addition, the statistical procedures were closely discussed with the supervisors and an external statistician, while the candidate has statistics skills, so that the chosen statistical tests, procedures and interpretations are judged to be reliable and transparent.

To strengthen the results of a cross-sectional pre-post study it is recommended to compare with norm populations. Here, a limitation may be that groups are likely to differ for many

relevant variables besides symptom burden, distress and HRQOL, whereby the estimated effects may be either under- or overestimated (3, 225). However, the EPIC norm population and the EORTC QLQ-C30 norm population have been used in previous Norwegian studies of cancer survivors, as well as a multicentre study of radiation cystitis and HBOT, and this enables comparison between studies (18, 205, 220, 267). The reference population for GHQ-12 consisted of Norwegian married/cohabiting students, which may represent a limitation compared to our older sample. However, no other reference sample exists, and we had to use the one that was available.

Researchers' role. The researchers' role in quantitative research is ideally objective and distanced, and does not influence the results (181, 225). A strength is that the candidate did not meet the participants and was not involved in collecting the quantitative data. A limitation may be that the candidate collected and analysed the qualitative data before the quantitative data, which may have influenced the interpretation of the latter. However, both the candidate and supervisors were highly aware of this pitfall, and furthermore, the results were discussed with a statistician. In addition, the STROBE guidelines, aiming to strengthen the quality and transparency of healthcare research (268), were followed in both papers. Based on these considerations, it is not likely that the candidate influenced the quantitative results.

8.5.2 Reflections on the qualitative results

Paper 2 is based on a qualitative method, whereby different strategies to assure quality exist (2, 183, 223, 225). Here, we followed Creswell's (2) recommendation to reflect on reflexivity, researchers' bias for prolonged engagement, member checking, thick and rich descriptions, peer review and external audits. These are presented after reflection on the sample.

The sample. Qualitative studies typically examine small samples in depth, to generate rich information about the participants' lived experience of a phenomenon (2, 182, 183, 223, 225).

In Paper 2, we included 20 participants, who represent a relatively large qualitative sample (269). However, more than sample size, data saturation is an important feature of qualitative research. This is reached when no new information appears from the data collection (2, 223, 270). In Paper 2, data saturation was achieved after 15 interviews, while data collection continued until 20 interviews had been held, to ensure that no new topic emerged, which is regarded as a study strength (211). Another argument was that several peer-reviewed journals within this field do not publish qualitative research with fewer participants. In line with the recommendations, the sample was selected on the basis of a wide variety of gender, demographic and medical variables, increasing the likelihood that the findings captured the participants' lived experiences (2, 270).

Reflexivity. The researcher is "the instrument" in qualitative research, which underlines the importance of elucidating the researcher's qualifications, experience and reflexivity throughout the research process, in order to understand any biases or assumptions that may influence the findings(2, 183, 223, 271-274).

Previous experience and potential biases. The candidate's motivation for this study was based on the possibility of conducting "in-depth" research and increasing knowledge of pelvic cancer survivors' HBOT process. The candidate's background as a specialised trained HBOT nurse, extended clinical experience as a nurse in different clinical settings, as well as in HBOT, and employment at the HBOT unit where the study took place, may represent both a study strength and a limitation. The candidate's prior knowledge and clinical experience may have made it easier to understand the participants' needs and views and may thereby have given access to richer and thicker descriptions of the participants' experience of HBOT. Another strength is the candidate's extensive experience in communicating with patients about serious illness and personal matters, and coping with emotional outbursts (210). Moreover, the candidate's private experience, for example related to the death of close family

members and experience of own serious illness, may have made the candidate more aware of the informants' overall situation. On the other hand, the candidate's professional and private experience may also represent potential biases, as important information, specific challenges, nuances or ambiguities in the data may have been overlooked. However, these issues were closely and repeatedly discussed while studying the literature, during the PhD courses, and in close follow-up by the main supervisor, who is an experienced qualitative researcher without specific HBOT experience (199).

Prejudices and orientations. Based on the pre-understandings outlined concerning awareness of the candidate's interpretations and decisions made during the research process, the candidate wrote short field notes during the research process. These notes include reflections on choices of method, design, transcription of audiotapes to text, and how to capture the participants' intended meaning, which facilitated awareness of the researchers' perspective (2, 210). Moreover, the procedures related to splitting the interviews between the candidate and the main supervisor, the discussions and critical questions from the supervisors representing different professional and methodological standpoints, the presentation to and discussions in the research group and advisory board, and discussions with other PhD candidates, were all important issues to enhance the candidate's awareness and reflexivity during the collection and analysis of data. The candidate's professional training, 35 years of clinical experience, as well as her private experience, clearly influenced the theoretical choices to focus on health promotion, HRQOL, and the mixed-methods design, as these represent important ways of reflecting on and capturing a holistic and individual health concept (2, 223). These also represent important ways of overcoming potential biases in the candidate's pre-understandings (2, 223).

Prolonged engagement and persistent observation is an important validation strategy in qualitative research (2). The candidate did not meet the informants before the interviews, and

each lasted for approximately one hour. It might be discussed whether this is considered to be enough time to gain an in-depth understanding, to build trust to test for misinformation and distortion, and to achieve saturation of key categories (2). Here, creating a calm and private setting in the interview situation, preparing the participants for the interviews both in writing and before commencing the interview, providing identical information about the content, timeframe, and voluntary and confidentiality aspects of the interviews, with two interviewers conducting the interviews, are seen as important factors. As the candidate and the main supervisor were not involved in HBOT, it was assumed that the participants could talk freely about their HBOT experiences. Furthermore, at the end of each interview the participants were asked whether they had anything more they wanted to share, and the researchers followed up on the thoughts and reflections shared by the participants. They were also asked how they experienced the interview situation. Only positive experiences and a genuine motivation to help others were revealed.

Member checking, as another qualitative validation strategy, was performed in several ways in this study (2). First, the interview guide was pilot tested to target its usefulness. This was an important opportunity to test the information, practical arrangements and the interview guide in a real-life setting. In addition, this helped the candidate to feel more confident, ask open and fewer questions, and focus on the participants' narratives (210). Secondly, during the interviews the participants were asked follow-up questions to clarify statements and opinions (22). Thirdly, the analysis and the researchers' interpretations were repeatedly checked against the transcribed interviews to verify that these represented the participants' intended meaning. The findings were also unanimously validated by the study's advisory board, consisting of user representatives and healthcare providers with and without HBOT experience, where the feedback indicated high validity (22).

Thick and rich descriptions (transparency) is a qualitative validation strategy promoting the voices, feelings and opinions of the participants (223). In this study, transparent descriptions of the participants, data collection, verbatim transition, data analyses and quotations representing multiple voices in the results are all viewed as important measures to ensure this validation. To prevent bias related to pre-understanding, NVivo12 software (www.qsrinternational.com) for coding and sorting of the data was used to ensure that the participants' perspective came through. The informants were given pseudonyms, whereby anonymity was ensured (2). Connecting the quotes to a pseudonym may give a better connection to the informants and thereby reflect the phenomenological-hermeneutical design by exploring the individual's lifeworld. These quotes also represent a validation of the participants' experiences, allowing for transparency of the findings (185). The table of the analysis process and the candidates' closeness to the participants in conducting, transcribing and analysing, and being the paper's first author, also adds to accuracy and transparency (2).

Peer review and external audits. In addition to the collaboration and peer review by the supervisors and co-authors, Paper 2 was published in the *Nordic Journal of Nursing Research.* This is a peer-reviewed journal, for which two reviewers, in addition to the editorial manager, reviewed the paper, adding to an external check of the research process and exchanging its validity (2, 22).

The findings from Paper 2 cannot be generalised due to the specific content or the limited number of participants studied (22). In contrast, qualitative research focuses more on transferability, whereby the context-bound findings are of most interest (225). In Paper 2, the findings represented originate from a specific treatment at a specific treatment centre and may be context bound. However, the participants were recruited nationwide, with a variety of backgrounds and medical variables suggesting that we captured a valid sample of the experiences of cancer survivors with pelvic LRTI undergoing HBOT in mono-place pressure

chambers. Furthermore, the common themes in Paper 2 were consistent, suggesting that we captured a valid sample of the participants' HBOT process. Based on this and the strategies of validity and reliability, it is probable that the qualitative results are trustworthy.

8.5.3 Reflections on the merged results

In mixed-methods research, potentially threats to validity are related to data collection, analysis and the interpretation of the merged strands (190, 275). Strategies to enhance the validity and reliability of this study were conducted for both strands, and below the validation strategies for merging the data are presented (22).

The sample. In line with the recommendations for mixed-methods research, the same sample was used in both the quantitative and qualitative strands, to enhance validity. (22). Here, the participants included in the qualitative phase of the study were drawn from the pool of participants included in the quantitative phase.

Data collection. Using different data collection procedures, i.e. collection of quantitative data through validated and reliable self-reported questionnaires and collection of qualitative data through in-depth interviews, reduced the risk of potential bias from one data collection to the other (22). This study used an explanatory sequential design, in which qualitative data helped to explain the mechanism underlying the quantitative results (22, 192) in more depth. The main supervisor is an experienced mixed-methods researcher who supported the candidate through guidance and follow-up during the entire study. Furthermore, both supervisors had complementary expertise in quantitative and qualitative research, backgrounds in cancer care and research, as a senior neurologist/HBOT physician. The candidate had longstanding clinical experience within the field, as well as prior experience in qualitative research from her master's degree. As discussed above, recommended strategies for enhancing validity and reliability for each strand were used and were viewed as strengths of the research.

Data analyses. To enhance the reliability of the merged data, a data display to link major quantitative and qualitative findings, and identify points of convergence, was developed (Table 4). In addition, several other measurements to enhance validity and reliability in a mixed-methods approach were performed. The transformation was kept straightforward, the distribution of scores was examined, statistical procedures were discussed closely with the supervisors and an external statistician, each research question was addressed, and all sets of results were presented and published. In addition, quantitative and qualitative data was collected and analysed separately, and techniques traditionally associated with each data type increase the strengths of each methodology (22).

Interpreting the data. Merging the results from the two strands was challenging, especially since the quantitative strand was dominant and gave more weight than the qualitative strand (22, 186). The researchers had this issue in focus during the entire research process. All three papers were independently peer reviewed and published, adding to the reliability of the findings and interpretations. Furthermore, the comprehensive and transparent exposition of the study's methodology and presentation of the merged results add to the quality of the interpreted data. No major disagreements or unresolved divergent findings between quantitative and qualitative data were encountered during the data analyses. This made the merging of the data easier and provided a comprehensive picture of the complexity of the multimodal challenges of cancer survivors with pelvic LRTI undergoing HBOT.

The different phases of this study were based on a theoretical framework, which also enhances the study's reliability (225). The merged results indicate that a mixed-methods approach focusing on positive health outcomes may provide important and increased knowledge of the baseline and the HBOT process, as well as the development of symptom burden and HRQOL. The use of EORTC's HRQOL concept (3) was important and helpful for providing a structure of and interpreting the complex results. The candidate found that this

concept explained and met the stated complexity in a suitable manner and thereby added to the comprehensive picture of the results.

The researcher's role in a mixed-methods study is challenging because it requires knowledge of both strands, as well as the time involved (22). The candidate was aware of these challenges and sought to resolve these issues as described in the respective strands.

9. CONCLUSION

In the following, main conclusions from the study will be drawn, followed by the study's implications for clinical practice and further research.

9.1 Main conclusions

The purpose of this thesis was to achieve a greater understanding of the symptom burden and HRQOL of cancer survivors undergoing HBOT for pelvic LRTI. To the best of our knowledge, this is the first study of cancer survivors with pelvic LRTI undergoing HBOT using mixed-methods and interpreting this in the light of HRQOL. In this context, the merged results are viewed as more than the sum of the individual quantitative and qualitative parts.

The merged findings from this study indicate that cancer survivors with established pelvic LTRI may experience a severe symptom burden compared to norms, including pain, fatigue and insomnia. Consequently, these survivors' HRQOL seems to be greatly impaired, particularly in relation to overall HRQOL and their physical, role, and social functions compared to norms, whereby a higher symptom burden is associated with lower HRQOL. Furthermore, the findings show that cancer survivors with pelvic LTRI may experience higher distress levels than norms, whereby a higher distress level is associated with lower HRQOL.

The study also brings new knowledge of how cancer survivors with pelvic LTRI experience the HBOT process. These findings show that cancer survivors seem to have great motivation and hope for HBOT. The information about HBOT from referring physicians seems to be limited and the information given in advance by the HBOT unit makes it difficult for the patients to understand what the treatment really involves. However, highly specialised personnel, daily follow-up and person-centred care seem to be important factors to make the participants feel safe and promote their coping abilities during the HBOT course. Moreover,

the findings show that the patients may experience the treatment course as long-lasting, but highly tolerable, with limited side -effects. Being absent from their ordinary everyday lives may to a certain degree be outweighed by meeting survivor peers, and socialising and sharing experience.

The merged findings furthermore indicate that patients may already experience a significantly improved symptom burden from pelvic LRTI, insomnia and pain on the completion of HBOT, with those with the highest symptom burden experiencing the greatest improvement. Furthermore, the results also indicate a concurrent and significant improvement in HRQOL, particularly for social and role functions.

The results from the six-month follow-up indicate further significant, although small, symptom relief from LTRI, pain, fatigue and sleep problems. Concurrently, changes in overall HRQOL and most functional scales were maintained or further improved slightly six months after HBOT. Interestingly, the changes in pelvic LRTI were associated to a relatively small degree with changes in HRQOL. Here, both the remaining symptoms and the extent of improvement may be relevant, but no conclusion can be drawn.

The results from this study point to the usefulness of building research of survivors with pelvic LRTI undergoing HBOT for health promotion and HROQL on a theoretical basis, using a mixed-methods design, as this may provide a more comprehensive and nuanced picture of the survivors' situation at baseline, during the HBOT process and on follow-up.

However, the focus on a selected population referred to HBOT, and the single-centre approach, may limit the generalisation of the study's findings. Still, the merged findings and quality assessments add to the study's reliability, suggesting that findings may be transferable to other individuals and settings. However, this study did not include participants refusing HBOT or study participation, meaning that we captured participants who were highly

motivated for HBOT and research participation. We furthermore only included participants treated in mono-place pressure chambers, where patients' experience of multi-place pressure chambers may differ, even if our clinical experience does not support this.

9.2 Implications for clinical practice

The findings from this study raise several implications for clinical practice.

First, the baseline results add to the discussion of limited survivorship follow-up in Norway. Here, the merged findings call in particular for increased competence and education of healthcare professionals about LRTI, and systematic assessment of pelvic LRTI symptoms and HRQOL after radiotherapy, where such impairment should be addressed with proper symptom management and by educating survivors in coping skills. Increased holistic survivorship follow-up in primary healthcare, for example from GPs, cancer care coordinators and/or municipal rehabilitation, and implementation of follow-up plans, are recommended. Cancer nurses should play a vital role in holistic screening and survivorship follow-up, in both specialist and primary healthcare, for example as cancer coordinators or by participating in developing nurse-led survivorship clinics or rehabilitation programmes.

Secondly, the study provides insights into how cancer survivors with pelvic LRTI experience the HBOT trajectory. The results indicate a need for increased knowledge about HBOT as a relevant treatment for pelvic LTRI among both healthcare professionals and survivors. The improvement in HRQOL during the course of the therapy emphasises the importance of following up cancer survivors, in combination with proper symptom management, as well as organising the treatment in a way that enables peer support to promote coping and social support. Furthermore, the results emphasise the importance of holistic care and close follow-up by specialised trained nurses during HBOT for promoting the patients' safety, coping and well-being.

Thirdly, the significant improvement in symptoms and HRQOL following HBOT indicates that this treatment may be relevant for cancer survivors with pelvic LRTI. In particular, reduced symptom severity and improvement in social and role function may positively influence the survivors' day-to-day functioning. This is important knowledge for healthcare professionals that may provide an important basis for realistic information to survivors, with the study suggesting that those with the most severe symptoms may benefit the most from HBOT.

9.3 Suggestions for future research

In general, there is limited evidence concerning the use of HBOT for survivors with pelvic LRTI, and more research within this field is greatly needed. Research regarding healthcare professionals' current knowledge of late effects of cancer survivorship, as well as interventions to increase this knowledge, seems to be of importance. The study's results support the use of regular screening of HRQOL to identify pelvic LRTI, and cancer survivors' need for interventions and rehabilitation, so that research into adequate screening tools and screening timelines is needed. Research concerning patients' expectations, and which information prior to HBOT they need, so as to be prepared for the treatment, are highly relevant to reduce patients' distress and to promote coping.

Furthermore, there is a need for RCT studies to assess the effect of HBOT for cancer survivors with pelvic LRTI, whereby the results from our study may represent an important starting point. In addition, research into individual responses to HBOT is of importance to uncover who will benefit the most from the treatment. In addition, satisfaction with care and important factors for good perceived care along the HBOT trajectory are of interest. The study results indicated that most participants reported a high level of fatigue during the HBOT process, and more research should be directed at this issue. Furthermore, studies focusing on

these cancer survivors' sexual health are lacking, as well as studies focusing on whether HBOT may also have a positive impact on sexual health.

Focusing on all areas of life seems to support the multidisciplinary approach for cancer survivors with pelvic LRTI. Moreover, longitudinal studies with several points of assessment of symptom burden and HRQOL during and in the long-term after HBOT are important to determine more accurately when any improvement occurs. Here, qualitative research of long-term experience following HBOT would also add valuable knowledge.

Additionally, our study has demonstrated that further mixed-methods studies within this field may add valuable comprehensive and nuanced knowledge within the field.

10. REFERENCES

1. Feuerstein M. Defining cancer survivorship. J Cancer Surviv. 2007;1(1):5-7. https://doi.org/10.1007/s11764-006-0002-x
2. Creswell JW, Poth CN. *Qualitative inquiry and research design: Choosing among five approaches*. 4 ed. Thousand Oaks, Calif: Sage publications; 2017. 488 pp.
3. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a Quality-of-Life Instrument for Use in International Clinical-Trials in Oncology. J Natl Cancer Inst. 1993;85(5):365-376. https://doi.org/10.1093/jnci/85.5.365
4. Moon R, (ed). Hyperbaric oxygen therapy indications. 14 ed. North Palm Beach, FL: Best Publishing Company; 2019. 399 pp.
5. Aziz NM, Rowland JH. Trends and advances in cancer survivorship research: challenge and opportunity. Semin Radiat Oncol; 200313(3):248-266. https://doi.org/10.1016/S1053-4296(03)00024-9
6. Andreyev HJN, Wotherspoon A, Denham JW, Hauer-Jensen M. Defining pelvic-radiation disease for the survivorship era. Lancet Oncol. 2010;11(4):310-312. https://doi.org/10.1016/S1470-2045(10)70026-7
7. Goldberg DP. A classification of psychological distress for use in primary care settings. Soc Sci Med. 1992;35(2):189-193. https://doi.org/10.1016/0277-9536(92)90166-N
8. Payton AR. Mental Health, Mental Illness, and Psychological Distress: Same Continuum or Distinct Phenomena? J Health Soc Behav. 2009;50(2):213-227.
9. Cancer Registry of Norway. *Cancer in Norway* 2020 - *Cancer incidence, mortality, survival and prevalence in Norway*. Oslo: Cancer registry of Norway; 2020. [Accessed 3. December 2021] Available from: cin-2020.pdf (kreftregisteret.no)
10. World Health Organization. *World Cancer Report 2020.* International Agency for Research on Cancer (IARC). Geneva, Switzerland: World Health Organization: 2020. [Accessed 4. January 2022] Avaiable from: World Cancer Report – IARC (who.int)
11. World Health Organization. *Shanghai Declaration on promoting health in the 2030 Agenda for Sustainable Development.* Shanghai, China: World Health Organization; 2018. [Accessed 4. January 2022] Avaiable from: Promoting health: guide to national implementation of the Shanghai Declaration (who.int)
12. McGuire S. World cancer report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr. 2016;7(2):418-419. https://doi.org/10.3945/an.116.012211

13. Norwegian Cancer Society. Cancer Strategy 2020- 2023. Oslo, Norway: The Norwegian Cancer Society; 2019. [Accessed 4. January 2022] Available from: Kreftforeningens-strategi-2020-2023-engelsk.pdf
14. Lawrie TA, Green JT, Beresford M ea. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev. 2018. https://doi.org/10.1002/14651858.CD012529.pub2
15. Sipaviciute A, Sileika E, Burneckis A, Dulskas A. Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review. Int J Colorectal Dis. 2020;35(6):977-983. https://doi.org/10.1007/s00384-020-03595-x
16. Paquette IM, Vogel JD, Abbas MA, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Chronic Radiation Proctitis. Dis Colon Rectum. 2018;61(10):1135-1140. https://doi.org/10.1097/dcr.0000000000001209.
17. Pascoe C, Duncan C, Lamb BW, Davis NF, Lynch TH, Murphy DG, et al. Current management of radiation cystitis: a review and practical guide to clinical management. BJU Int. 2019;123(4):585-594. https://doi.org/10.1111/bju.14516
18. Oscarsson N, Müller B, Rosén A, Lodding P, Mölne J, Giglio D, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. Lancet Oncol. 2019;20(11):1602-1614. https://doi.org/10.1016/s1470-2045(19)30494-2
19. Pereira D, Ferreira C, Catarino R, Correia T, Cardoso A, Reis F, et al. Hyperbaric oxygen for radiation-induced cystitis: A long-term follow-up. Actas Urol Esp. 2020;44(8):561-570. https://doi.org/10.1016/j.acuro.2020.03.010
20. Lauvrak V, Frønsdal KB, Ormstad SS, Vaagbø G, Fure B. Effectiveness of Hyperbaric Oxygen Therapy in patients with Late Radiation Tissue Injury or Diabetic Foot Ulcer. Oslo: Nasjonalt kunnskapssenter for helsetjenesten; 2015. Report No.: 9788281219458. [Accessed 20 January 2021] Avaiable from: Effectiveness of Hyperbaric Oxygen Therapy in patients with Late Radiation Tissue Injury or Diabetic Foot Ulcer - NIPH (fhi.no)
21. Glover M, Smerdon GR, Andreyev HJ, Benton BE, Bothma P, Firth O, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. Lancet Oncol. 2016;17(2):224-233. https://doi.org/10.1016/S1470-2045(15)00461-1
22. Creswell JW, Clark VLP. *Designing and conducting mixed methods research.* 3 ed. Los Angles, Am: Sage publications; 2017. 520 pp.

23. American Cancer Society. *Global Cancer facts & figures*. 4 eds. Atlanta: American Cancer Society; 2018. [Accessed 4. January 2022] Available from: Global Cancer Facts and Figures 4th Edition
24. World Health Oranization. *National cancer control programmes*: *policies and managerial guidelines*. Geneva, Switzerland: World Health Organization; 2002. [Accessed 12. January 2022] Available from: Cancer Back Matter.ind (who.int)
25. World Health Oranization. *Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region. 2000-2019.* World Health Organization; 2020. [Accessed 13. January 2022] Available from: Global Health Estimates (who.int)
26. Norwegian Institute of Public Health. *Cause of Death Registry for 2020.* Oslo, Norway: Norwegian Institute of Public Health; 2020. [Accessed 6. January 2022] Available from: Norwegian Cause of Death Registry - NIPH (fhi.no)
27. Sung H, Ferlay J, Siegel RL, Lawersanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021:71(3):209- 249. https://doi.org/10.3322/caac.21660
28. The National Cancer Institue. Cancer Control Continuum [Webpage]. [Accessed 4. January 2022]. Available from: https://cancercontrol.cancer.gov/od/continuum.html.
29. Hewitt M, Greenfield S, Stovall E. National Cancer Policy Board (US). Committee on Cancer Survivorship: *Improving care and quality of life. From cancer patient to cancer survivor: Lost in transition.* Washington, DC: National Academies Press; 2006.
30. Marzorati C, Riva S, Pravettoni G. Who is a cancer survivor? A systematic review of published definitions. J Cancer Educ. 2017;32(2):228. https://doi.org/10.1007/s13187-016-0997-2.
31. Rowland JH. *Survivorship Research: Past, Present, and Future.* New York, USA: Springer; 2007. p. 28-42.
32. Leigh S. *Cancer Survivorship: A Nursing Perspective.* New York, USA: Springer; 2007. p. 8-13.
33. Feuerstein M, Nekhlyudov L. *Handbook of Cancer Survivorship.* 2 ed. Boston: Springer International Publishinger; 2018. 407 pp.
34. Norwegian Directorate of Healt. *Late effects after cancer treatment.* Oslo, Norway: The Norwegian Directorate of Health, 2020. [Accessed 12. December 2021] Available from: Seneffekter etter kreftbehandling (helsedirektoratet.no)
35. Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al. Pelvic complications after prostate cancer radiation therapy and their management: an international collaborative narrative review. Eur Urol. 2019;75(3):464-76. https://doi.org/10.1016/j.eururo.2018.12.003

36. Norwegian Ministry of Health and Care Services. *NCD-Strategy 2013 – 2017. For the prevention, diagnosis, treatment and rehabilitation of four noncommunicable diseases: Cardiovascular disease, Diabetes, COPD and Cancer*. Oslo, Norway: The Norwegian Ministry of Health and Care Services; 2012. [Accessed 4. January 2022] Avaiable from: ncd_strategy_060913.pdf (regjeringen.no)
37. Norwegian Ministry of Health and Care Services. *Norwegian National Cancer Strategy 2018 – 2022.* Oslo, Norway: Norwegian Ministry of Healt and Care Services, 2017. [Accessed 6. January 2022] Avaiable from: Leve med kreft. Nasjonal kreftstrategi (2018–2022) (iccp-portal.org)
38. Kreftforeningen. *Å leve med og etter kreft. En undersøkelse blant kreftpasienter og pårørende i Kreftforeingenes brukerpanel.* Oslo, Norway: Kreftforeningen; 2019. [Accessed 12. January 2022]. Avaiable from: Rehabiliteringsrapporten-2018_web.pdf (kreftforeningen.no)
39. Treanor C, Donnelly M. Late effects of cancer and cancer treatment—the perspective of the patient. Supportive Care in Cancer. 2016;24(1):337-346. https://doi.org/10.1007/s00520-015-2796-4
40. Schover LR, van der Kaaij M, van Dorst E, Creutzberg C, Huyghe E, Kiserud CE. Sexual dysfunction and infertility as late effects of cancer treatment. European Journal of Cancer Supplements. 2014;12(1):41-53. https://doi.org/10.1016/j.ejcsup.2014.03.004
41. Hulbert-Williams N, Neal R, Morrison V, Hood K, Wilkinson C. Anxiety, depression and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? Psyco-oncology. 2012;21(8):857-867. https://doi.org/10.1002/pon.1980
42. Foster C, Wright D, Hill H, Hopkinson J, Roffe L. Psychosocial implications of living 5 years or more following a cancer diagnosis: a systematic review of the research evidence. Eur journal of cancer care. 2009;18(3):223-247. https://doi.org/10.1111/j.1365-2354.2008.01001.x
43. Ma JL, Hennessey DB, Newell BP, Bolton DM, Lawrentschuk N. Radiotherapy-related complications presenting to a urology department: a more common problem than previously thought? BJU Int. 2018;121 Suppl 3:28-32. https://doi.org/10.1111/bju.14145
44. Aziz NM. Cancer survivorship research: State of knowledge, challenges and opportunities. Acta Oncol. 2007;46(4):417-432. https://doi.org/10.1080/02841860701367878
45. Hjermstad M, Knobel H, Brinch L, Fayers P, Loge J, Holte H, et al. A prospective study of health-related quality of life, fatigue, anxiety and depression 3–5 years after stem cell transplantation. Bone Marrow Transplant. 2004;34(3):257-266. https://doi.org/10.1038/sj.bmt.1704561
46. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors—a systematic review. Int J Psychiatry Med. 2010;40(2):163-181. https://doi.org/10.2190/pm.40.2.c

47. Silver JK, Baima J, Mayer RS. Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. CA Cancer J Clin. 2013;63(5):295-317. https://doi.org/10.3322/caac.21186
48. Ganz PA. Late effects of cancer and its treatment. Semin Oncol Nurs; 2001;17(4):241-248. https://doi.org/10.1053/sonu.2001.27914
49. Cohen S, Underwood LG, Gottlieb BH. *Social support measurement and intervention: A guide for health and social scientists*, Oxford: Oxford University Press; 2000. https://psycnet.apa.org/doi/10.1093/med:psych/9780195126709.001.0001
50. Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9(3):193-199. https://doi.org/10.7150/ijms.3635
51. Abbas Z, Rehman S. An overview of cancer treatment modalities. Neoplasm. 2018;1:139-157. https://doi.org/10.5772/INTECHOPEN.76558
52. Adams E, Boulton MG, Horne A, Rose PW, Durrant L, Collingwood M, et al. The Effects of Pelvic Radiotherapy on Cancer Survivors: Symptom Profile, Psychological Morbidity and Quality of Life. Clinical Oncology. 2014;26(1):10-17. https://doi.org/10.1016/j.clon.2013.08.003
53. Andreyev HJN, Davidson SE, Gillespie C, Allum WH, Swarbrick E. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut. 2012;61(2):179-192. https://doi.org/10.1136/gutjnl-2011-300563
54. DeVita VT, Chu E. A history of cancer chemotherapy. Cancer Res. 2008;68(21):8643-8653. https://doi.org/10.1158/0008-5472.can-07-6611
55. Chabner BA, Roberts TG. Chemotherapy and the war on cancer. Nature Reviews Cancer. 2005;5(1):65-72. http://dx.doi.org/10.1038/nrc1529
56. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen Y-J, Ciombor KK, et al. Rectal cancer, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(7):874-901. [Accessed 20. January 2022]. Available from: Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology in: Journal of the National Comprehensive Cancer Network Volume 16 Issue 7 (2018) (jnccn.org)
57. Dee EC, Eyler CE, Sanford NN, Wo JY. Local Therapy Options for Recurrent Rectal and Anal Cancer: Current Strategies and New Directions. Curr Colorectal Cancer Rep. 2019;15(6):157-169. https://doi.org/10.1007/s11888-019-00445-z
58. Yaxley JP. Urinary tract cancers: An overview for general practice. J Family Med Prim Care. 2016;5(3):533-538. https://doi.org/10.4103/2249-4863.197258
59. Helsebiblioteket. Prostata [Webpage]. Oslo, Norway; Helsebiblioteket. 2020. [Accessed 17. January 2022] Available from: https://kreftlex.no/Prostata

60. Litwin MS, Tan H-J. The diagnosis and treatment of prostate cancer: a review. JAMA. 2017;317(24):2532-2542. https://doi.org/10.1001/jama.2017.7248

61. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Jan;17(1):64-84. https://doi.org/10.6004/jnccn.2019.0001

62. Johnson CA, James D, Marzan A, Armaos M. Cervical Cancer: An Overview of Pathophysiology and Management. Semin Oncol Nurs. 2019;35(2):166-174. https://doi.org/10.1016/j.soncn.2019.02.003

63. Ganz PA. Monitoring the physical health of cancer survivors: A survivorship-focused medical history. J Clin Oncol. 2006;24(32):5105-5111. https://doi.org/10.1200/jco.2006.06.0541

64. Brearley SG, Stamataki Z, Addington-Hall J, Foster C, Hodges L, Jarrett N, et al. The physical and practical problems experienced by cancer survivors: A rapid review and synthesis of the literature. Eur J Oncol Nurs. 2011;15(3):204-212. https://doi.org/10.1016/j.ejon.2011.02.005

65. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. Cancer. 2008;112(S11):2577-2592. https://doi.org/10.1002/cncr.23448

66. Fosså SD, Vassilopoulou-Sellin R, Dahl AA. Long term physical sequelae after adult-onset cancer. J Cancer Surviv. 2008;2(1):3-11. https://doi.org/10.1007/s11764-007-0039-5

67. Jansen L, Koch L, Brenner H, Arndt V. Quality of life among long-term (⩾5 years) colorectal cancer survivors – Systematic review. Eur J Cancer. 2010;46(16):2879-2888. https://doi.org/10.1016/j.ejca.2010.06.010

68. Dent P, Yacoub A, Contessa J, Caron R, Amorino G, Valerie K, et al. Stress and radiation-induced activation of multiple intracellular signaling pathways. Radiat Res. 2003;159(3):283-300. https://doi.org/10.1667/0033-7587(2003)159[0283:sariao]2.0.co;2

69. Anscher MS, Chen L, Rabbani Z, Kang S, Larrier N, Huang H, et al. Recent progress in defining mechanisms and potential targets for prevention of normal tissue injury after radiation therapy. Int J Radiat Oncol Biol Phys. 2005;62(1):255-259. https://doi.org/10.1016/j.ijrobp.2005.01.040

70. Denham JW, Hauer-Jensen M. The radiotherapeutic injury–a complex 'wound'. Radiother Oncol. 2002;63(2):129-145. https://doi.org/10.1016/s0167-8140(02)00060-9

71. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev. 2016;4(4):CD005005. https://doi.org/10.1002/14651858.cd005005.pub4

72. Ramakrishnaiah VPN, Krishnamachari S. Chronic haemorrhagic radiation proctitis: A review. World J Gastrointest Surg. 2016;8(7):483. https://doi.org/10.4240/wjgs.v8.i7.483

73. Harb AH, Abou Fadel C, Sharara AI. Radiation Enteritis. Curr Gastroenterol Rep. 2014;16(5):1-9. https://doi.org/10.1007/s11894-014-0383-3

74. Leitao Jr MM. Management of vulvar and vaginal melanomas: current and future strategies. Am Soc Clin Oncol Educ Book. 2014;34(1):e277-e281. https://doi.org/10.14694/edbook_am.2014.34.e277

75. Meixel AJ, Hauswald H, Delorme S, Jobke B. From radiation osteitis to osteoradionecrosis: incidence and MR morphology of radiation-induced sacral pathologies following pelvic radiotherapy. Eur Radiol. 2018;28(8):3550-3559. https://doi.org/10.1007/s00330-018-5325-2

76. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. Eur J Oncol Nurs. 2015;19(5):479-485. https://doi.org/10.1016/j.ejon.2015.02.007

77. Mamguem Kamga A, Dumas A, Joly F, Billa O, Simon J, Poillot ML, et al. Long-Term Gynecological Cancer Survivors in Côte d'Or: Health-Related Quality of Life and Living Conditions. Oncologist. 2019;24(7):e490-e500. https://dx.doi.org/10.1634%2Ftheoncologist.2018-0347

78. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol. 2007;8(11):1007-1017. https://doi.org/10.1016/s1470-2045(07)70341-8

79. Han CJ, Gigic B, Schneider M, Kulu Y, Peoples AR, Ose J, et al. Risk factors for cancer-related distress in colorectal cancer survivors: one year post surgery. J Cancer Surviv. 2020;14(3):305-315. https://doi.org/10.1007/s11764-019-00845-y

80. Joshy G, Thandrayen J, Koczwara B, Butow P, Laidsaar-Powell R, Rankin N, et al. Disability, psychological distress and quality of life in relation to cancer diagnosis and cancer type: population-based Australian study of 22,505 cancer survivors and 244,000 people without cancer. BMC Med. 2020;18(1):372. https://doi.org/10.1186/s12916-020-01830-4

81. Lotfi-Jam K, Gough K, Schofield P, Aranda S, Jefford M. A longitudinal study of four unique trajectories of psychological distress in cancer survivors after completing potentially curative treatment. Acta Oncol. 2019;58(5):782-789. https://doi.org/10.1080/0284186x.2018.1562209

82. Cessna Palas JM, Hyland KA, Nelson AM, Small BJ, Jim HSL, Jacobsen PB. An examination of the relationship of patient modifiable and non-modifiable characteristics with fear of cancer recurrence among colorectal cancer survivors. Support Care Cancer. 2021;29(2):869-876. https://doi.org/10.1007/s00520-020-05552-4

83. Thomas SF, Glynne-Jones R, Chait I, Marks DF. Anxiety in long-term cancer survivors influences the acceptability of planned discharge from follow-up. Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer. 1997;6(3):190-196. https://doi.org/10.1002/(sici)1099-1611(199709)6:3%3C190::aid-pon274%3E3.0.co;2-0

84. Bergerot CD, Razavi M, Clark KL, Philip EJ, Pal SK, Loscalzo M, et al. Emotional problem-related distress screening and its prevalence by cancer type: Assessment by patients'

characteristics and level of assistance requested. Psychooncology. 2021;30(8):1332-1338. https://doi.org/10.1002/pon.5685

85. Gillespie C, Goode C, Hackett C, Andreyev HN. The clinical needs of patients with chronic gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther. 2007;26(4):555-563. https://doi.org/10.1111/j.1365-2036.2007.03405.x
86. Boelhouwer IG, Vermeer W, van Vuuren T. The associations between late effects of cancer treatment, work ability and job resources: a systematic review. Int Arch Occup Environ Health. 2021;94(2):147-189. https://dx.doi.org/10.1007%2Fs00420-020-01567-w
87. Nicholas S, Chen L, Choflet A, Fader A, Guss Z, Hazell S, et al. Pelvic Radiation and Normal Tissue Toxicity. Semin Radiat Oncol. 2017;27(4):358-369. https://doi.org/10.1016/j.semradonc.2017.04.010
88. Vanneste BGL, van de Voorde L, de Ridder R, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. Int J Colorectal Dis. 2015;30(10):1293-1303. https://doi.org/10.1007/s00384-015-2289-4
89. Oscarsson N, Arnell P, Lodding P, Ricksten SE, Seeman-Lodding H. Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery. Int J Radiat Oncol Biol Phys. 2013;87(4):670-675. https://doi.org/10.1016/j.ijrobp.2013.07.039
90. Siow S, Mahendran H, Seo C. Complication and remission rates after endoscopic argon plasma coagulation in the treatment of haemorrhagic radiation proctitis. Int J Colorectal Dis. 2017;32(1):131-134. https://doi.org/10.1007/s00384-016-2635-1
91. Smit SG, Heyns CF. Management of radiation cystitis. Nat Rev Urol. 2010;7(4):206-214. https://doi.org/10.1038/nrurol.2010.23
92. Neuman TS, Thom SR. *Physiology and medicine of hyperbaric oxygen therapy.*1 ed. Philadelphia: Saunders/Elsevier; 2008. p. 599- 606.
93. Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science. 1983;221(4617):1283-5. https://doi.org/10.1126/science.6612342
94. Fok TC, Jan A, Peel SA, Evans AW, Clokie CM, Sándor GK. Hyperbaric oxygen results in increased vascular endothelial growth factor (VEGF) protein expression in rabbit calvarial critical-sized defects. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(4):417-422. https://doi.org/10.1016/j.tripleo.2007.07.015
95. Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol. 2006;290(4):H1378-1386. https://doi.org/10.1152/ajpheart.00888.2005

96. Macdonald HM. Hyperbaric oxygenation in the patient with malignancy: friend or foe? Diving Hyperb Med. 2007;37(3):133-138.

97. Camporesi EM. Side effects of hyperbaric oxygen therapy. J Undersea Hyperb Med. 2014;41(3):253-257. [Assessed: 13. June 2021]. Avaiable from: Side effects of hyperbaric oxygen therapy - PubMed (nih.gov)

98. Hadanny A, Zubari T, Tamir-Adler L, Bechor Y, Fishlev G, Lang E, et al. Hyperbaric oxygen therapy effects on pulmonary functions: a prospective cohort study. BMC Pulm Med. 2019;19(1):148. https://doi.org/10.1186/s12890-019-0893-8

99. Heyboer M. Hyperbaric Oxygen Therapy Side Effects - Where Do We Stand? J Am Coll Clin Wound Spec. 2016;8(1-3):2-3. https://dx.doi.org/10.1016%2Fj.jccw.2018.01.005

100. Thomson L, Paton J. Oxygen toxicity. Paediatr Respir Rev. 2014;15(2):120-312. https://doi.org/10.1016/j.prrv.2014.03.003

101. Barnard A, Sandelowski M. Technology and humane nursing care: (ir)reconcilable or invented difference? J Adv Nurs. 2001;34(3):367-375. https://doi.org/10.1046/j.1365-2648.2001.01768.x

102. Pate A, Lowery J, Kilbourn K, Blatchford PJ, McNulty M, Risendal B. Quality of life and the negative impact of comorbidities in long-term colorectal cancer survivors: a population-based comparison. J Cancer Surviv. 2020. https://doi.org/10.1007/s11764-020-00876-w

103. Korfage IJ, Essink-Bot M-L, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-Related Quality of Life in Cervical Cancer Survivors: A Population-Based Survey. Int J Radiat Oncol Biol Phys. 2009;73(5):1501-1509. https://doi.org/10.1016/j.ijrobp.2008.06.1905

104. Bentzen AG, Balteskard L, Wanderås EH, Frykholm G, Wilsgaard T, Dahl O, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. Acta Oncol. 2013;52(4):736-744. https://doi.org/10.3109/0284186x.2013.770599

105. Das P, Cantor SB, Parker CL, Zampieri JB, Baschnagel A, Eng C, et al. Long-term quality of life after radiotherapy for the treatment of anal cancer. Cancer. 2010:116(4):822-829. https://doi.org/10.1002/cncr.24906

106. Provencher S, Oehler C, Lavertu S, Jolicoeur M, Fortin B, Donath D. Quality of life and tumor control after short split-course chemoradiation for anal canal carcinoma. Radiat Oncol. 2010;5(41):5-41. https://doi.org/10.1186/1748-717x-5-41

107. Morris KA, Haboubi NY. Pelvic radiation therapy: between delight and disaster. World J Gastrointest Surg. 2015;7(11):279-288. https://doi.org/10.4240/wjgs.v7.i11.279

108. Flyum IR, Mahic S, Grov EK, Joranger P. Health-related quality of life in patients with colorectal cancer in the palliative phase: a systematic review and meta-analysis. BMC Palliat Care. 2021;20(1):1-18. https://doi.org/10.1186/s12904-021-00837-9

109. Welzel G, Hägele V, Wenz F, Mai S. Quality of Life Outcomes in Patients with Anal Cancer after Combined Radiochemotherapy. Stralenther Onkol. 2011;187(3):175-182. https://doi.org/10.1007/s00066-010-2175-5

110. Gilbert SM, Wood DP, Dunn RL, Weizer AZ, Lee CT, Montie JE, et al. Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). Cancer. 2007;109(9):1756-1762. https://doi.org/10.1002/cncr.22556

111. Somani BK, Gimlin D, Fayers P, N'dow J. Quality of life and body image for bladder cancer patients undergoing radical cystectomy and urinary diversion—a prospective cohort study with a systematic review of literature. Urology. 2009;74(5):1138-1143. https://doi.org/10.1016/j.urology.2009.05.087

112. Hedgepeth RC, Gilbert SM, He C, Lee CT, Wood Jr DP. Body image and bladder cancer specific quality of life in patients with ileal conduit and neobladder urinary diversions. Urology. 2010;76(3):671-675. https://doi.org/10.1016/j.urology.2010.01.087

113. Gerharz EW, Månsson Å, Månsson W, editors. Quality of life in patients with bladder cancer. Urologic Oncology: seminars and original investigations. 2005;23(3):201-207. https://doi.org/10.1016/j.urolonc.2005.03.005

114. Ward-Smith P, Kapitan D. Quality of Life Among Men Treated with Radiation Therapy For Prostate Cancer. Urol Nurs. 2005;25(4):263-268.

115. Hamilton A, Stanford J, Gilliland F, Albertsen P, Stephenson R, Hoffman R, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. J Clin Oncol. 2001;19(9):2517-2526. https://doi.org/10.1200/jco.2001.19.9.2517

116. Van Andel G, Visser A, Hulshof M, Horenblas S, Kurth K. Health-related quality of life and psychosocial factors in patients with prostate cancer scheduled for radical prostatectomy or external radiation therapy. BJU Int. 2003;92(3):217-222. https://doi.org/10.1046/j.1464-410x.2003.04321.x

117. Penson DF, Litwin MS, Aaronson NK. Health related quality of life in men with prostate cancer. J Urol. 2003;169(5):1653-1661. https://doi.org/10.1097/01.ju.0000061964.49961.55

118. Song L, Ji Y, Nielsen ME. Quality of life and health status among prostate cancer survivors and noncancer population controls. Urology. 2014;83(3):658-663. https://doi.org/10.1016/j.urology.2013.12.009

119. Chambers SK, Ng SK, Baade P, Aitken JF, Hyde MK, Wittert G, et al. Trajectories of quality of life, life satisfaction, and psychological adjustment after prostate cancer. Psychooncology. 2017;26(10):1576-1585. https://doi.org/10.1002/pon.4342

120. Song L, Mishel M, Bensen JT, Chen RC, Knafl GJ, Blackard B, et al. How does health literacy affect quality of life among men with newly diagnosed clinically localized prostate cancer? Findings from the North Carolina-Louisiana Prostate Cancer Project (PCaP). Cancer. 2012;118(15):3842-3851. https://doi.org/10.1002/cncr.26713

121. Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol. 2015;68(4):600-608. https://doi.org/10.1016/j.eururo.2014.08.074

122. Janicek MF, Averette HE. Cervical cancer: prevention, diagnosis, and therapeutics. CA Cancer J Clin. 2001;51(2):92-114. https://doi.org/10.3322/canjclin.51.2.92

123. Distefano M, Riccardi S, Capelli G, Costantini B, Petrillo M, Ricci C, et al. Quality of life and psychological distress in locally advanced cervical cancer patients administered pre-operative chemoradiotherapy. Gynecol Oncol. 2008;111(1):144-150. https://doi.org/10.1016/j.ygyno.2008.06.034

124. Nout RA, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, van Der Steen-Banasik EM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. Eur J Cancer. 2012;48(11):1638-1648. https://doi.org/10.1016/j.ejca.2011.11.014

125. Kobayashi M, Ohno T, Noguchi W, Matsuda A, Matsushima E, Kato S, et al. Psychological distress and quality of life in cervical cancer survivors after radiotherapy: do treatment modalities, disease stage, and self-esteem influence outcomes? Int J of Gynecol Cancer. 2009;19(7): 1264-1268. https://doi.org/10.1111/igc.0b013e3181a3e124

126. Abayomi J, Kirwan J, Hackett A. The prevalence of chronic radiation enteritis following radiotherapy for cervical or endometrial cancer and its impact on quality of life. Eur J Oncol Nurs. 2009;13(4):262-267. https://doi.org/10.1016/j.ejon.2009.02.007

127. Sekse RJT, Dunberger G, Olesen ML, Østerbye M, Seibæk L. Lived experiences and quality of life after gynaecological cancer—An integrative review. J Clin Nurs. 2019;28(9-10):1393-1421. https://doi.org/10.1111/jocn.14721

128. Barker CL, Routledge JA, Farnell DJ, Swindell R, Davidson SE. The impact of radiotherapy late effects on quality of life in gynaecological cancer patients. Br J Cancer. 2009;100(10):1558-1565. https://doi.org/10.1038/sj.bjc.6605050

129. Zhou Y, Irwin ML, Ferrucci LM, McCorkle R, Ercolano EA, Li F, et al. Health-related quality of life in ovarian cancer survivors: Results from the American Cancer Society's Study of

Cancer Survivors — I. Gynecol Oncol. 2016;141(3):543-549. https://doi.org/10.1016/j.ygyno.2016.04.006

130. Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. Urology. 2005;65(4):649-653. https://doi.org/10.1016/j.urology.2004.10.050

131. Niezgoda JA, Serena TE, Carter MJ. Outcomes of Radiation Injuries Using Hyperbaric Oxygen Therapy: An Observational Cohort Study. Adv Skin Wound Care. 2016;29(1):12-19. https://doi.org/10.1097/01.asw.0000473679.29537.c0

132. Shao Y, Lu Gl, Shen Zj. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012;109(5):691-694. https://doi.org/10.1111/j.1464-410x.2011.10550.x

133. Clarke RE, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. Int J Radiat Oncol Biol Phys. 2008;72(1):134-143. https://doi.org/10.1016/j.ijrobp.2007.12.048

134. Yuan JH, Song LM, Liu Y, Li MW, Lin Q, Wang R, et al. The Effects of Hyperbaric Oxygen Therapy on Pelvic Radiation Induced Gastrointestinal Complications (Rectal Bleeding, Diarrhea, and Pain): A Meta-Analysis. Front Oncol. 2020;10:390. https://doi.org/10.3389/fonc.2020.00390

135. Craighead P, Shea-Budgell MA, Nation J, Esmail R, Evans AW, Parliament M, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. Curr Oncol. 2011;18(5):220-227. https://doi.org/10.3747/co.v18i5.767

136. Sarin A, Safar B. Management of radiation proctitis. Gastroenterol Clin North Am. 2013;42(4):913-925. https://doi.org/10.1016/j.gtc.2013.08.004

137. Tanaka T, Minami A, Uchida J, Nakatani T. Potential of hyperbaric oxygen in urological diseases. Int J Urol. 2019;26(9):860-867. https://doi.org/10.1111/iju.14015

138. Villeirs L, Tailly T, Ost P, Waterloos M, Decaestecker K, Fonteyne V, et al. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature. Int J Urol. 2020;27(2):98-107. https://doi.org/10.1111/iju.14130

139. Plafki C, Carl UM, Glag M, Hartmann KA. The treatment of late radiation effects with hyperbaric oxygenation (HBO). Strahlenther Onkol. 1998;174 Suppl 3:66-68.

140. Allen KD, Danforth JS, Drabman RS. Videotaped modeling and film distraction for fear reduction in adults undergoing hyperbaric oxygen therapy. J Consult Clin Psychol. 1989;57(4):554-558. https://doi.org/10.1037//0022-006x.57.4.554

141. Clark C, Rock D, Tackett K. Assessment of the magnitude of anxiety in adults undergoing first oxygen treatment in a hyperbaric chamber. Mil Med. 1994;159(5):412-415.

142. London SD, Park SS, Gampper TJ, Hoard MA. Hyperbaric oxygen for the management of radionecrosis of bone and cartilage. Laryngoscope. 1998;108(9):1291-1296. https://doi.org/10.1097/00005537-199809000-00005

143. Lee A, Forner L, Jansen EC. Patient's perspective on hyperbaric oxygen treatment of osteoradionecrosis. Int J Technol Assess Health Care. 2014;30(2):188-193. https://doi.org/10.1017/s0266462314000038

144. Chalmers A, Mitchell C, Rosenthal M, Elliott D. An exploration of patients' memories and experiences of hyperbaric oxygen therapy in a multiplace chamber. J Clin Nurs. 2007;16(8):1454-1459. https://doi.org/10.1111/j.1365-2702.2006.01700.x

145. Yisak A, Frank K, Maryam M, Mesomeeh I, Sanaz Akhavan R. Hyperbaric Oxygen Therapy: Indications, Benefits and Nursing Management. Int J Caring Sciences. 2019;12(1):567-571.

146. MacInnes L, Baines C, Bishop A, Ford K. Patient knowledge and experience of hyperbaric oxygen treatment. Diving Hyperb Med. 2021;51(1):72-77. https://doi.org/10.28920/dhm51.1.72-77

147. Viswanathan AN, Lee LJ, Eswara JR, Horowitz NS, Konstantinopoulos PA, Mirabeau-Beale KL, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. Cancer. 2014;120(24):3870-3883. https://doi.org/10.1002/cncr.28849

148. Safra T, Gutman G, Fishlev G, Soyfer V, Gall N, Lessing JB, et al. Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity. Clin Oncol (R Coll Radiol). 2008;20(4):284-287. https://doi.org/10.1016/j.clon.2007.12.005

149. Irgens A, Vaagbo G, Aanderud L. Quality of life--the effect of hyperbaric oxygen treatment on radiation injury. Undersea Hyperb Med. 2013;40(6):479-485.

150. Larson JS. The conceptualization of health. Med Care Res Rev. 1999;56(2):123-136. [Accessed: 24. April, 2022] Available from: The conceptualization of health - PubMed (nih.gov)

151. World Health Organization. *Constitution of the World Health Organization.* New York: World Health Organisation: 1948. [Accessed 7. February 2022] Available from: Constitution of the World Health Organization (who.int)

152. Callahan D. The WHO definition of 'health'. Stud Hastings Cent. 1973:1(3):77-88. Accessed 7. February 2022] Available from: The WHO Definition of 'Health' (jstor.org)

153. World Health Organization. *The Ottawa Charter for Health Promotion*. Ottawa: World Health Organization; 1986. [Accessed 7. Februsry 2022] Available from: Health Promotion (who.int)

154. Nordenfelt L. The concepts of health and illness revisited. Med Health Care Philos. 2007;10(1):5-10. https://doi.org/10.1007/s11019-006-9017-3

155. Davis S (ed). *Rehabilitation: the use of theories and models in practice*. London: Elsevier Health Sciences; 2006. 208 pp.

156. Gammersvik Å, Larsen TB (ed). *Helsefremmende sykepleie : i teori og praksis. 2. utg.* Bergen: Fagbokforl; 2018. 284 pp.
157. Raingruber B. *Contemporary health promotion in nursing practice.* Burlington: Jones & Bartlett Publishers; 2014. 421 pp.
158. World Health Organization. *The World health report 2000: health systems: improving performance.* World Health Organization. [Accessed 12. February 2022] Available from: https://apps.who.int/iris/handle/10665/79020
159. Smith BJ, Tang KC, Nutbeam D. *WHO health promotion glossary: new terms.* Health Promot Int. 2006;21(4):340-345. https://doi.org/10.1093/heapro/dal033
160. Helsedirektoratet. *Gode liv i Norge. Utredning om måling av befolkningens livskvalitet.* Oslo: Helsedirektoratet IS-2479; 2016. [Accessed 17. February 2022] Available from: Rapportmal logofigur - enkel (helsedirektoratet.no)
161. Wahl AK, Hanestad BR. *Måling av livskvalitet i klinisk praksis: en innføring.* Bergen: Fagbokforl.; 2004. 152 pp.
162. Haraldstad K, Wahl A, Andenæs R, Andersen JR, Andersen MH, Beisland E, et al. A systematic review of quality of life research in medicine and health sciences. Qual Life Res. 2019;28(10):2641-2650. https://doi.org/10.1007/s11136-019-02214-9
163. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34(7):645-649. https://doi.org/10.1007/s40273-016-0389-9
164. Gold MR, Siegel JE, Russell LB, Weinstein MC (eds). *Cost effectiveness in health and medicine.* Harward: Oxford University Press; 1996. 448 pp.
165. Ebrahim S. Clinical and public health perspectives and applications of health-related quality of life measurement. Soc Sci Med. 1995;41(10):1383-1394. https://doi.org/10.1016/0277-9536(95)00116-o
166. Torrance GW. Utility approach to measuring health-related quality of life. J Chronic Dis. 1987;40(6):593-603. https://doi.org/10.1016/0021-9681(87)90019-1
167. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol. 2003;56(5):395-407. https://doi.org/10.1016/s0895-4356(03)00044-1
168. Mayo N. *Dictionary of quality of life and health outcomes measurement.* Milwaukee: International Society for Quality of Life Research; 2015. 185 pp.
169. World Health Organization. The World Health Organization quality of life assessment (WHOQOL): Position Paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-1409. https://doi.org/10.1016/0277-9536(95)00112-k

170. Nutbeam D, Muscat DM. Health promotion glossary 2021. Health Promot Int. 2021;36(6):1578-1598. https://doi.org/10.1093/heapro/daab067

171. Velikova G, Coens C, Efficace F, Greimel E, Groenvold M, Johnson C, et al. Health-related quality of life in EORTC clinical trials—30 years of progress from methodological developments to making a real impact on oncology practice. European journal of cancer supplements. 2012;10(1):141-149. https://doi.org/10.1016/S1359-6349(12)70023-X

172. Robinson PG, Carr AJ, Higginson IJ. *Quality of Life.* London: BMJ Books; 2003. 133 pp.

173. Rustoen T. Hope and quality of life, two central issues for cancer patients: a theoretical analysis. Cancer Nurs. 1995;18(5):355-361.

174. Fayers PM, Machin D. *Quality of Life: The Assessment, Analysis and Reporting of Patient-Reported Outcomes.* 3 ed. Hoboken: Wiley & Sons; 2016. 566 pp.

175. Van Leeuwen M, Husson O, Alberti P, Arraras JI, Chinot OL, Costantini A, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health and quality of life outcomes. 2018;16(1):1-15. https://doi.org/10.1186/s12955-018-0920-0

176. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. Qual Life Res. 1995;4(6):523-531. https://doi.org/10.1007/bf00634747

177. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: A review and evaluation of different conceptual approaches. Int J Nurs Stud. 2006;43(7):891-901. https://doi.org/10.1016/j.ijnurstu.2006.03.015

178. Bratt E-L, Moons P. Forty years of quality-of-life research in congenital heart disease: Temporal trends in conceptual and methodological rigor. Int J Cardiol. 2015;195:1-6. https://doi.org/10.1016/j.ijcard.2015.05.070

179. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655. https://doi.org/10.1136/bmj.a1655

180. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs—principles and practices. Health Serv Res. 2013;48(6pt2):2134-2156. https://doi.org/10.1111/1475-6773.12117

181. Cook TD, Campbell DT, Shadish W. *Experimental and quasi-experimental designs for generalized causal inference*. Boston: Houghton Mifflin company; 2002. 656 pp.

182. Johnson RB, Onwuegbuzie AJ. Mixed methods research: A research paradigm whose time has come. Educational researcher. 2004;33(7):14-26. https://doi.org/10.3102/0013189X033007014

183. Malterud K. Qualitative research: standards, challenges, and guidelines. Lancet. 2001;358(9280):483-488. https://doi.org/10.1016/s0140-6736(01)05627-6

184. Johnson RB, Schoonenboom J. Adding Qualitative and Mixed Methods Research to Health Intervention Studies: Interacting With Differences. Qual Health Res. 2016;26(5):587-602. mhttps://doi.org/10.1177/1049732315617479

185. Malterud K. Systematic Text Condensation: A strategy for qualitative analysis. Scand J Public Health. 2012;40(8):795-805. https://doi.org/10.1177/1403494812465030

186. Curry LA, Nembhard IM, Bradley EH. Qualitative and mixed methods provide unique contributions to outcomes research. Circulation. 2009;119(10):1442-1452. https://doi.org/10.1161/circulationaha.107.742775

187. Plano Clark VL, Creswell J.W. *Understanding Research: A consumer's Guide.* 2 eds. Boston: Pearson education Inc; 2015. 432 pp.

188. Teddlie C, Tashakkori A. *The foundations of mixed methods research: Integrating quantitative and qualitative techniques in the social and behavioral Sciences.* Thousand Oaks, CA: SAGE; 2009. 472 pp.

189. Johnson RB, Onwuegbuzie AJ, Turner LA. Toward a Definition of Mixed Methods Research. J Mixed Methods Research. 2007;1(2):112-133. https://doi.org/11177/1558689806298224

190. Östlund U, Kidd L, Wengström Y, Rowa-Dewar N. Combining qualitative and quantitative research within mixed method research designs: a methodological review. Int J Nurs Stud. 2011;48(3):369-383. https://doi.org/10.1016/j.ijnurstu.2010.10.005

191. Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. Köln Z Soziol. 2017;69(2):107-131. https://doi.org/10.1007/s11577-017-0454-1

192. Ivankova NV, Creswell JW, Stick SL. Using mixed-methods sequential explanatory design: From theory to practice. Field methods. 2006;18(1):3-20. https://doi.org/10.1177/1525822X05282260

193. Leavy P. Research Design: *Quantitative, Qualitative, Mixed Methods, Arts-Based, and Community-Based Participatory Research Approaches.* New York: Guilford Publications; 2017. 300 pp.

194. Glasziou P, Heneghan C. A spotter's guide to study designs. Evid Based Med. 2009; 14(2):37. https://doi.org/10.1136/ebm.14.2.37-a

195. Muse A. Baldwin JM. Quasi-Experimental Research Design. In: Barnes C, Forde DR. *The Encyclopedia of Research Methods in Criminology and Criminal Justice.* Chicago: Wiley-Blackwell 2021;1:307-310.

196. Price PC, Jhangiani RS, Chiang I-CA. Quasi-experimental research. *Research Methods in Psychology.* 2015. [Accessed 14. February 2022] Available from: Quasi-Experimental Research – Research Methods in Psychology (pressbooks.pub)

197. Giorgi A. The theory, practice, and evaluation of the phenomenological method as a qualitative research procedure. Journal of phenomenological psychology. 1997;28(2):235-260.

198. Lindseth A, Norberg A. Elucidating the meaning of life world phenomena. A phenomenological hermeneutical method for researching lived experience. Scand J Caring Sci. 2004;18(2):145-53. https://doi.org/10.1111/scs.13039

199. Gadamer H-G, Weinsheimer J, Marshall DG. *Truth and method.* London, England: Bloomsbury Academic; 2013. 640 pp.

200. Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. Seizures during hyperbaric oxygen therapy: retrospective analysis of 62,614 treatment sessions. Undersea Hyperb Med. 2016;43(1):21-28.

201. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56(6):899-905. https://doi.org/10.1016/s0090-4295(00)00858-x

202. Wei JT. Scoring Instructions for the Expanded Prostate cancer Index Composite (EPIC). Ann Arbor. 2002;1001:48109-0330. [Accessed 23 Nov. 2021] Available at: Scoring Instructions for the (umich.edu)

203. Umbehr MH, Bachmann LM, Poyet C, Hammerer P, Steurer J, Puhan MA, et al. The German version of the Expanded Prostate Cancer Index Composite (EPIC): translation, validation and minimal important difference estimation. Health Qual Life Outcomes. 2018;16(1):36. https://doi.org/10.1186/s12955-018-0859-1

204. Gil KM, Pugh SL, Klopp AH, Yeung AR, Wenzel L, Westin SN, et al. Expanded validation of the EPIC bowel and urinary domains for use in women with gynecologic cancer undergoing postoperative radiotherapy. Gynecol Oncol. 2019;154(1):183-188. https://doi.org/10.1016/j.ygyno.2019.04.682

205. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30 reference values manual (ed. 3) 2008. [Accessed 24. November 2021] Available at: Introduction (eortc.org)

206. Fayers P, Bottomley A. Quality of life research within the EORTC - the EORTC QLQ-C30. Eur J Cancer. 2002;38:S125-S133. https://doi.org/10.1016/s0959-8049(01)00448-8

207. Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). 1998:16(3);p.1188-1196. https://doi.org/10.1200/jco.1998.16.3.1188

208. Goldberg DP. *User's guide to the General Health Questionnaire.* Windsor; NFER-NELSON 1988. 129 pp.

209. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med. 1997;27(1):191-7. https://doi.org/10.1017/s0033291796004242

210. Kvale S. *Doing Interviews.* London: SAGE Publications; 2008. 208 pp.

211. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant. 2018;52(4):1893-1907. https://doi.org/10.1007/s11135-017-0574-8

212. George D, Mallery P. *IBM SPSS Statistics 26 step by step: A simple guide and reference.* New York, NY: Routledge; 2019. 402 pp.

213. Mulhern G, Greer B. *Making sense of data and statistics in psychology.* 2 ed. London; Springer Nature Limited: 2011. 416 pp.

214. Akoglu H. User's guide to correlation coefficients. Turk J Emerg Med. 2018;18(3):91-93. https://doi.org/10.1016/j.tjem.2018.08.001

215. Sullivan GM, Feinn R. Using Effect Size—or Why the P Value Is Not Enough. J Grad Med Educ. 2012;4(3):279-282. https://doi.org/10.4300/JGME-D-12-00156.1

216. Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3 ed. Brussels, Belgium. EORTC publications; 2001. [Accessed 24. November 2021] Available from: Microsoft Word - SCmanual.doc (eortc.org)

217. Veierød MB, Lydersen S, Laake P (eds.). *Medical statistics: in clinical and epidemiological research.* Oslo: Gyldendal akademisk; 2012. 707 pp.

218. Hayes AF. *Introduction to mediation, moderation, and conditional process analysis: a regression-based approach.* 3 ed. New York: The Guilford Press; 2017. 683 pp.

219. Wei JT, Dunn RL, Sandler HM, McLaughlin PW, Montie JE, Litwin MS, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol. 2002;20(2):557-566. https://doi.org/10.1200/jco.2002.20.2.557

220. Expanded Prostate Index Composite, Characteristics of EPIC domain-specific summary and subscale scores for 112 controls without prostate cancer. [Accessed 21 Mar. 2021]. Available from: Characteristics of EPIC domain-specific summary and subscale scores on controls without prostate cancer (umich.edu)

221. Nerdrum P, Rustøen T, Rønnestad MH. Student Psychological Distress: A psychometric study of 1750 Norwegian 1st-year undergraduate students. Scandinavian journal of educational research. 2006;50(1):95-109. https://doi.org/10.1080/00313830500372075

222. Hedges LV. Estimation of effect size from a series of independent experiments. Psychol Bull. 1982;92(2):490-499.

223. Malterud K. *Kvalitative forskningsmetoder for medisin og helsefag.* 4. utg. Oslo: Universitetsforl.; 2017. 254 pp.
224. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-357. https://doi.org/10.1093/intqhc/mzm042
225. Gray DE. Doing research in the real world. 4 ed. London: Sage Publications Ltd; 2017. 824 pp.
226. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. [Accessed 18. January 2021] Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki--ethical-principles-for-medical-research-involving-human-subjects
227. Chassang G. The impact of the EU general data protection regulation on scientific research. Ecancermedicalscience. 2017;11:709. https://doi.org/10.3332/ecancer.2017.709
228. Qu SQ, Dumay J. The qualitative research interview. Qualitative research in accounting & management. 2011;8(3):238-264. https://doi.org/10.1108/11766091111162070
229. Patton MQ. *Qualitative research & evaluation methods: Integrating theory and practice.* 4 ed. Saint Paul, MN: Sage publications; 2014. 832 pp.
230. Morris KA, Haboubi NY. Pelvic radiation therapy: Between delight and disaster. World J Gastrointest Surg. 2015;7(11):279-288. https://doi.org/10.4240/wjgs.v7.i11.279
231. Yavas G, Yavas C, Dogan NU, Ilhan TT, Dogan S, Karabagli P, et al. Pelvic radiotherapy does not deteriorate the quality of life of women with gynecologic cancers in long-term follow-up: A 2 years prospective single-center study. J Cancer Res Ther. 2017;13(3):524-532. https://doi.org/10.4103/0973-1482.187243
232. Posternak V, Dunn LB, Dhruva A, Paul SM, Luce J, Mastick J, et al. Differences in demographic, clinical, and symptom characteristics and quality of life outcomes among oncology patients with different types of pain. Pain. 2016;157(4):892. https://doi.org/10.1097/j.pain.0000000000000456
233. Shao Y-J, Ji K, Hao J-L, Cheng X-J, Guan B-Q, Liu W-S, et al. Nonpain symptom prevalence and intensity of inpatients with moderate to severe cancer pain in China. American Journal of Hospice and Palliative Medicine®. 2016;33(5):448-455. https://doi.org/10.1177/1049909114565109
234. Wang XS, Zhao F, Fisch MJ, O'Mara AM, Cella D, Mendoza TR, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. Cancer. 2014;120(3):425-432. https://doi.org/10.1002/cncr.28434
235. Zeng L, Koo K, Zhang L, Jon F, Dennis K, Holden L, et al. Fatigue in advanced cancer patients attending an outpatient palliative radiotherapy clinic as screened by the Edmonton

Symptom Assessment System. Support Care Cancer. 2012;20(5):1037-1042. https://doi.org/10.1007/s00520-011-1179-8

236. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain. 2015;16(8):769-780. https://doi.org/10.1016/j.jpain.2015.05.002

237. Steen R, Dahl AA, Hess SL, Kiserud CE. A study of chronic fatigue in Norwegian cervical cancer survivors. Gynecol Oncol. 2017;146(3):630-635. https://doi.org/10.1016/j.ygyno.2017.05.028

238. Vistad I, Fosså S, Kristensen G, Dahl A. Chronic fatigue and its correlates in long-term survivors of cervical cancer treated with radiotherapy. BJOG. 2007;114(9):1150-1158. https://doi.org/10.1111/j.1471-0528.2007.01445.x

239. Strollo SE, Fallon EA, Gapstur SM, Smith TG. Cancer-related problems, sleep quality, and sleep disturbance among long-term cancer survivors at 9-years post diagnosis. Sleep Med. 2020;65:177-185. https://doi.org/10.1016/j.sleep.2019.10.008

240. Grov EK, Fosså SD, Dahl AA. Activity of daily living problems in older cancer survivors: A population-based controlled study. Health Soc Care Community. 2010;18(4):396-406. https://doi.org/10.1111/j.1365-2524.2010.00912.x

241. Agasi-Idenburg SC, Thong MSY, Punt CJA, Stuiver MM, Aaronson NK. Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. Support Care Cancer. 2017;25(2):625-632. https://doi.org/10.1007/s00520-016-3451-4

242. Kim Y, Shaffer KM, Carver CS, Cannady RS. Prevalence and predictors of depressive symptoms among cancer caregivers 5 years after the relative's cancer diagnosis. J Consult Clin Psychol. 2014;82(1):1-8. https://doi.org/10.1037/a0035116

243. Utne I, Miaskowski C, Bjordal K, Paul SM, Rustoen T. The relationships between mood disturbances and pain, hope, and quality of life in hospitalized cancer patients with pain on regularly scheduled opioid analgesic. J Palliat Med. 2010;13(3):311-318. https://doi.org/10.1089/jpm.2009.0294

244. Ilie G, Bradfield J, Moodie L, Lawen T, Ilie A, Lawen Z, et al. The Role of Response-Shift in Studies Assessing Quality of Life Outcomes Among Cancer Patients: A Systematic Review. Front Oncol. 2019;20(9):783. https://doi.org/10.3389/fonc.2019.00783

245. Paiva C, Faria C, Nascimento M, Dos Santos R, Scapulatempo H, Costa E, et al. Effectiveness of a palliative care outpatient programme in improving cancer-related symptoms among ambulatory Brazilian patients. Eur J Cancer Care. 2012;21(1):124-130. https://doi.org/10.1111/j.1365-2354.2011.01298.x

246. Shi R-C, Meng A-F, Zhou W-L, Yu X-Y, Huang X-E, Ji A-J, et al. Effects of home nursing intervention on the quality of life of patients with nasopharyngeal carcinoma after

radiotherapy and chemotherapy. Asian Pac J Cancer Prev. 2015;16(16):7117-7121. https://doi.org/10.7314/apjcp.2015.16.16.7117

247. Jacobs LA, Shulman LN. Follow-up care of cancer survivors: challenges and solutions. Lancet Oncol. 2017;18(1):e19-e29. https://doi.org/10.1016/s1470-2045(16)30386-2

248. Dalton SO, Johansen C. New paradigms in planning cancer rehabilitation and survivorship. Acta Oncol. 2013;52(2):191-194. https://doi.org/10.3109/0284186x.2012.748216

249. Cureton A, Pritham W, Royce M, Zahn K. Nurse practitioner-led breast cancer survivorship clinic. J Clin Oncol. 2009;27(15_suppl):e20723-e20723.

250. Nasjonal behandlingstjeneste for elektiv hyperbar oksygenbehandling [Internet]. [Accessed 21. March 2022] Available from: https://helse-bergen.no/avdelinger/yrkesmedisinsk-avdeling/nasjonal-behandlingsteneste-for-elektiv-hyperbar-oksygenbehandling

251. Hellbom M, Bergelt C, Bergenmar M, Gijsen B, Loge JH, Rautalathi M, et al. Cancer rehabilitation: A Nordic and European perspective. Acta Oncol. 2011;50(2):179-186. https://doi.org/10.3109/0284186x.2010.533194

252. Morris BA, Lepore SJ, Wilson B, Lieberman MA, Dunn J, Chambers SK. Adopting a survivor identity after cancer in a peer support context. J Cancer Surviv. 2014;8(3):427-436. https://doi.org/10.1007/s11764-014-0355-5

253. Dunn J, Ralph N, Green A, Frydenberg M, Chambers SK. Contemporary consumer perspectives on prostate cancer survivorship: Fifty voices. Psychooncology. 2020;29(3):557-563. https://doi.org/10.1002/pon.5306

254. Pistrang N, Jay Z, Gessler S, Barker C. Telephone peer support for women with gynaecological cancer: benefits and challenges for supporters. Psychooncology. 2013;22(4):886-894. https://doi.org/10.1002/pon.3080

255. Dellis A, Papatsoris A, Kalentzos V, Deliveliotis C, Skolarikos A. Hyberbaric oxygen as sole treatment for severe radiation induced haemorrhagic cystitis. Int Braz J Urol. 2017;43(3):489-495. https://doi.org/10.1590/s1677-5538.ibju.2016.0451

256. Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al. Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form. Urology. 2015;85(1):101-105. https://doi.org/10.1016/j.urology.2014.08.044

257. Potter PA, Hall AM, Stockert PA. Fundamentals of Nursing. 10 ed. WR O, editor. Missouri, USA: Elsevier; 2020. 1440 pp.

258. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Development of fatigue in cancer survivors: a prospective follow-up study from diagnosis into the year after treatment. J Pain Symptom Manage. 2013;45(2):213-222. https://doi.org/10.1016/j.jpainsymman.2012.02.009

259. Ebede CC, Jang Y, Escalante CP. Cancer-related fatigue in cancer survivorship. Medical Clinics. 2017;101(6):1085-1097. https://doi.org/10.1016/j.mcna.2017.06.007

260. Ferrell B, Paice J, Koczywas M. New standards and implications for improving the quality of supportive oncology practice. J Clin Oncol. 2008;26(23):3824-3831. https://doi.org/10.1200/jco.2007.15.7552

261. Skinner EA, Edge K, Altman J, Sherwood H. Searching for the structure of coping: a review and critique of category systems for classifying ways of coping. Psychol Bull. 2003;129(2):216-269. https://doi.org/10.1037/0033-2909.129.2.216

262. Zimmerman MA, Warschausky S. Empowerment theory for rehabilitation research: Conceptual and methodological issues. Rehabil Psychol. 1998;43(1):3. https://psycnet.apa.org/doi/10.1037/0090-5550.43.1.3

263. Abowitz DA, Toole TM. Mixed method research: Fundamental issues of design, validity, and reliability in construction research. Journal of construction engineering and management. 2010;136(1):108-116. https://doi.org/10.1061/(ASCE)CO.1943-7862.0000026

264. Mohajan HK. Two criteria for good measurements in research: Validity and reliability. Annals of Spiru Haret University Economic Series. 2017;17(4):59-82.

265. Lin H-Y, Lai H-L, Chen C-I, Huang C-Y. Depression and health-related quality of life and their association with resourcefulness in survivors of prostate cancer. Arch Psychiatr Nurs. 2017;31(4):407-413. https://doi.org/10.1016/j.apnu.2017.04.014

266. Skolarus TA, Wolf AM, Erb NL, Brooks DD, Rivers BM, Underwood W, et al. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J Clin. 2014;64(4):225-249. https://doi.org/10.3322/caac.21234

267. Hauken MA, Larsen TMB, Holsen I. "Back on Track" A Longitudinal Mixed Methods Study on the Rehabilitation of Young Adult Cancer Survivors. J Mixed Methods Research 2017:13(3);339-360.

268. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Stuart JP et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. PLoS. 2007;4(10):e297. https://doi.org/10.1371/journal.pmed.0040297

269. Boddy CR. Sample size for qualitative research. Qualitative Market Research: An International Journal. 2016;19(4):426-432. https://psycnet.apa.org/doi/10.1108/QMR-06-2016-0053

270. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health. 2010;25(10):1229-1245. https://doi.org/10.1080/08870440903194015

271. Mitchell J, Boettcher-Sheard N, Duque C, Lashewicz B. Who do we think we are? Disrupting notions of quality in qualitative research. Qual Health Res. 2018;28(4):673-680. https://doi.org/10.1177/1049732317748896

272. Berger R. Now I see it, now I don't: Researcher's position and reflexivity in qualitative research. Qualitative research. 2015;15(2):219-234. https://doi.org/10.1177/1468794112468475

273. Dodgson JE. Reflexivity in qualitative research. J Hum Lact. 2019;35(2):220-222. https://doi.org/10.1177/0890334419830990

274. Grove J. Researching a marginalised group: Reflections on being an outsider. Counselling and Psychotherapy Research. 2017;17(3):176-180. http://dx.doi.org/10.1002/capr.12120

275. Tashakkori A, Creswell JW. The new era of mixed methods. Sage Publications; 2007:1(1);3-7.

ARTICLE 1

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ORIGINAL ARTICLE

Symptom burden, psychological distress, and health-related quality of life in cancer survivors with pelvic late radiation tissue injuries

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Abstract

Purpose Curative radiotherapy for cancer may lead to severe late radiation tissue injuries (LRTIs). However, limited knowledge exists about pelvic cancer survivors' LRTI symptoms, distress, and health-related quality of life (HRQOL). We sought to assess the symptom burden, distress, and HRQOL in survivors with established pelvic LRTIs compared to norm populations and to investigate the relation between these factors.

Methods Cancer survivors referred for treatment of established pelvic LRTIs were recruited nationwide. LTRIs were assessed with the Expanded Prostate Cancer Index Composite (EPIC), psychological distress was assessed with the General Health Questionnaire (GHQ-12), and HRQOL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORCT-QLQ-C30).

Results A total of 107 participants (mean age 64, 53% men) were included. Compared to norms, participants reported more urinary (mean 68.7 vs. 89.5; $p=0.00$; $d=1.4$) and bowel symptoms (mean 62.5 vs. 92.4; $p=0.00$; $d=2.7$), increased psychological distress (mean 13.4 vs. 10.3; $p=0.00$; $d=0.6$), and overall poorer HRQOL (mean 54.9 vs. 71.2; $p=0.00$; $d=0.7$). Higher symptom burden and higher levels of psychological distress were associated with lower HRQOL ($r^2=46\%$), but psychological distress did not moderate the influence of symptoms on HRQOL.

Conclusion Cancer survivors with established pelvic LRTIs are highly burdened compared to norms. The association of the LRTI-related symptom burden with HRQOL is independent of the level of psychological distress. Both coping and treatment interventions are crucial to promoting long-term health and HRQOL.

Trial registration NCT03570229.

Keywords Late effects · Long-term survivors · Pelvic malignancies · Pelvic radiotherapy · Psychological distress · Quality of life

Introduction

Annually, more than 34,000 Norwegians are diagnosed with cancer, where pelvic malignancies—including prostate, urological, bowel, and gynaecological malignancies—account for approximately 35% of all cases [1]. Radiotherapy is an important part of the multimodal curative treatment for pelvic cancers. However, as radiation also affects normal tissue, it may lead to radiation tissue injuries that can increase or persist for a long time and are often severe [2–6]. Adverse effects of radiotherapy on normal tissue leave approximately 5–15% of patients with late radiation tissue injuries (LRTIs) [7]. Pelvic LRTIs are characterized by tissue damage, fibrosis, hypoxia, and poor microcirculation affecting the bowel, urinary tract, genitalia, and pelvic bones [7]. Symptoms such as diarrhoea, faecal leakage, incontinence, haematuria, increased urinary/ bowel frequency, increased urinary/ bowel urgency, and sexual dysfunction are documented in survivors of rectal, anal, urological, prostate, and gynaecological malignancies [8–10]. These cancer survivors experience severe symptom burden, especially related to bowel symptoms, although symptoms often decrease over time [10, 11]. On the other hand, pelvic LRTI symptoms are often underdiagnosed and are often interpreted as symptoms

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related to aging, and thus, only a minority are referred to follow-up and treatment [2, 7]. Furthermore, the treatment options for pelvic LRTIs are limited and mostly focused on symptom relief [12].

Late effects from cancer and cancer treatment, especially radiotherapy, are associated with psychological distress. This includes emotional symptoms such as worry, sorrow, anxiety, and depression, where higher symptom burden predicts higher levels of distress across cancer diagnoses [13–16]. In addition to the symptom burden, it is crucial to have a focus on psychological distress because this may also impair health-related quality of life (HRQOL) and increase poor health behaviours, consumption of medical resources, and mortality [17, 18]. However, studies of psychological distress in survivors with pelvic LRTIs are very limited. Bergerot et al. [19] showed that patients with gynaecological and gastrointestinal cancers are in general at higher risk of psychological distress. Adams et al. [2] found that more severe pelvic LRTI symptoms across cancer types were associated with higher rates of depression but not with higher rates of anxiety.

It is well-established that late effects from cancer may affect all areas of cancer survivors' lives [20]. Based on a bio-psychological view of health, HRQOL is defined as an individual, subjective, multidimensional, and dynamic concept and is reckoned as an important outcome of cancer survivors' perceived health and well-being after cancer treatment [21, 22]. HRQOL theory posits that challenges and strengths within each dimension will contribute to the individuals' overall HRQOL [23]. This implies that distress from pelvic LRTI symptoms may negatively influence the different dimensions of the cancer survivors' HRQOL and overall HRQOL. Consequently, improvements in LRTI symptoms or any other HRQOL dimension may positively influence HRQOL. Thus, HRQOL may give a holistic picture of the cancer survivors' perceived health and overall well-being. Previous studies indicate that pelvic LRTIs across cancer types may severely impair the survivors' HRQOL, where higher treatment toxicity and comorbidity after radiation as well as combinations of chemotherapy and radiotherapy seem to be important risk factors [24–26]. Nevertheless, there is a lack of studies focusing on the influence of pelvic LRTI symptoms on HRQOL.

Based on the outlined research and the theoretical framework, we have limited knowledge about the levels of symptom burden, distress, and HRQOL in cancer survivors with pelvic LRTI symptoms compared to norms. Furthermore, the relationship between pelvic LRTIs, psychological distress, and HRQOL remains unclear, including with respect to whether the degree of experienced psychological distress influences the symptoms' relation with HRQOL.

This is important knowledge in planning effective treatment interventions, following up on survivorship, and promoting long-term health and HRQOL for survivors with pelvic LRTIs.

Study aims

The overall aim of this study was to explore symptoms, psychological distress, and HRQOL in cancer survivors with pelvic LRTIs and the relationship between these outcome variables. The conceptual framework is outlined in Fig. 1. More specifically, we aimed to:

1. Investigate pelvic LRTI symptoms, psychological distress, and HRQOL in cancer survivors compared to norm populations.
2. Study the influence of pelvic LRTI symptoms and psychological distress on HRQOL and investigate whether the relation between LRTI symptoms and HRQOL is moderated by psychological distress.

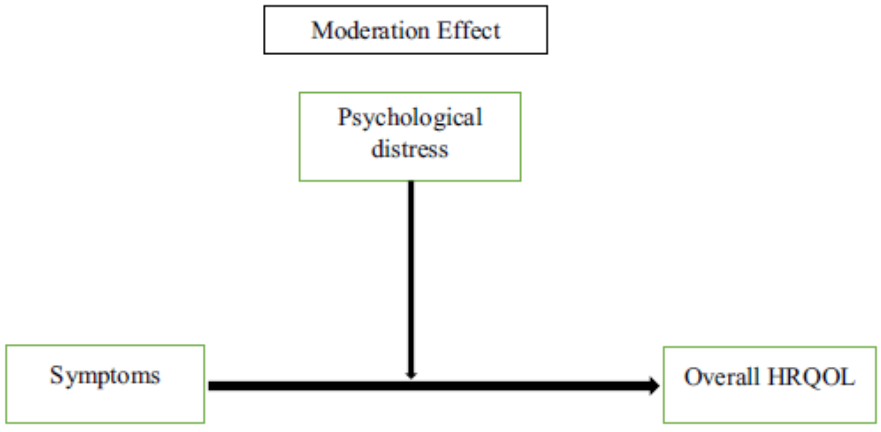

Fig. 1 Conceptual framework. Abbreviations: HRQOL, health-related quality of life

The EPIC mean scores (urinary/bowel total scores) were compared with controls without prostate cancer ($N=112$) [37]. The GHQ-12 mean scores were compared with a sample consisting of married/cohabiting students ($N=1750$), published by Nerdrum et al. [38]. Mean scores of HRQOL were compared to the EORTC reference values of a general European population ($N=7802$) [33]. The manual suggests changes of clinical significance to be 8 endpoints in overall HRQOL as a primary outcome [33]. Using the 'true value' (mean score = 61.4/SD = 24.7) on overall HRQOL, the estimated mean will be 68.3 for the participants. Based on a two-sided significance level of $\alpha=0.05$ and a power of 80% ($\beta=0.20$), we needed a sample size of 81. With estimated 20% dropout, the warranted samples were 101 participants.

Background variables as age, gender, type of cancer treatment, and radiation-related variables were regarded as important variables, and all outcome variables were controlled against these using the independent-samples *t*-test. Regression analysis was used to assess the influence of age and clinical variables (cancer site, time since treatment, and radiation dose) [39]. Correlation analysis, using Pearson's *r* and explained variance (r^2), was performed between pelvic LRTI symptoms, psychological distress, and overall HRQOL. Multiple linear regression analysis was carried out to explore the relationship between pelvic LRTI symptoms, psychological distress, and overall HRQOL (model 1) [40]. A moderation analysis was conducted to examine the influence of psychological distress (the moderator) on the association of pelvic LRTI symptoms with overall HRQOL, by adding the product of psychological distress and pelvic LRTI symptoms to the multiple regression analyses (model 2) [40]. For all analyses, a two-tailed *P*-value < 0.05 was set as the significance level.

Ethical considerations

The study was approved by the Regional Committee of Medical and Health Research Ethics, Northern Norway. (ID-number: 2018/706) and was conducted in compliance with the Declaration of Helsinki and the requirement for data processing and handling of the data [41]. The participants received written information about the study that participation in the study was voluntary, that all data would be treated confidentially, that they could withdraw from the study at any time, and that data could be deleted on request. All participants gave written consent.

Results

Study population

In total, 129 survivors met the eligibility criteria, and 107 participants were included in the study. Non-participation was related to declining to participate ($n=11$), withdrawal from treatment ($n=6$), and previous hyperbaric oxygen therapy ($n=5$). The participants' mean age was 64 years, slightly more were men (53.3%), and the majority were married/cohabiting (72%). Most participants had a college or university education, but only a few worked full or part time. The majority had pelvic LRTI injuries from prostate or gynaecological cancers (88%), and the mean time since radiation was 70.5 months. Demographic and medical characteristics are outlined further in Table 1.

Pelvic LRTI symptoms, psychological distress, and HRQOL

Addressing our first study aim, we found that cancer survivors with pelvic LRTIs experienced considerably more symptoms, psychological distress, and impaired overall HRQOL than norms. Mean scores for LRTI symptoms, psychological distress, and HRQOL, as well as comparison with the respective norms, are presented in Table 2.

Compared to norms, the participants reported a higher symptom burden on EPIC bowel and urinary total scales and on all subscales, mostly with very large effect sizes. Women reported more bowel total symptoms than men (mean 58.6 vs. 65.7, $P=0.00$). Participants treated with both chemotherapy and radiation reported more total bowel symptoms than participants treated with radiation only (mean 58.8 vs. 65.0, $P=0.02$). The participants also scored higher on psychological distress than the norm, with a medium-size difference ($P=0.00$).

The participants scored lower than the general population on overall HRQOL and on all of the subdimensions, except for emotional function. The largest differences were observed for social function, physical function, and role function with large or very large effect sizes. The participants scored significantly higher than the norm on all symptom scales, with very large or large effect sizes for diarrhoea, constipation, fatigue, and insomnia as illustrated in Fig. 2. Participants working full or part time scored higher on overall HRQOL than those not working ($F=11,50/P=0.00$).

Regression analysis showed no association between EPIC urinary/ bowel symptoms, psychological distress, or overall HRQOL and age, cancer site, time since treatment, or radiation dose.

The influence of pelvic LRTI symptoms and psychological distress on HRQOL

Addressing the first part of our second study aim, we tested the influence of pelvic LRTI symptoms and psychological distress on HRQOL. LRTI symptoms were positively correlated with HRQOL, meaning that a higher symptom burden is associated with lower HRQOL. The strongest negative

Table 1 Demographic and medical variables

	n (%)
Gender	
Female	50 (46.7)
Male	57 (53.3)
Age, years [mean (SD, range)]	64 (12, 32–84)
Education	
Primary/high school	22 (20.5)
College/university	85 (79.5)
Work status	
Full time/part time employment	19 (17.7)
Sick leave/disability pension/retired	88 (82.3)
Civil status	
Single	30 (28.0)
Married/cohabiting	77 (72.0)
Children under 18 years of age	
Yes	13 (12.1)
No	94 (87.9)
Medical characteristics	
Cancer site	
Rectum/anus	13 (12.1)
Prostate	56 (52.4)
Gynaecological	38 (35.5)
Referral diagnosis	
Proctitis	45 (42.1)
Cystitis	39 (36.4)
Proctitis and cystitis	9 (9.4)
Osteoradionecrosis pelvis	11 (10.3)
Wound/fistula	3 (2.8)
Type of cancer treatment	
Chemotherapy and radiation	39 (36.4)
Radiation only	68 (63.6)
Types of radiation	
External only	77 (72.0)
External and internal	30 (28.0)
Radiation dose, Gy [range]	
External	35.0–100.0
Internal	7.0–75.0
Months since radiation [mean (SD, range)]	70.48 (78.32, 11–511)

Abbreviations: *Gy*, Gray; *SD*, standard deviation. Numbers are number of participants (% of total) if not specified otherwise

correlation was found between psychological distress and HRQOL, predicting that a higher level of distress is associated with a lower level of HRQOL. Urinary and bowel symptoms were also negatively correlated with psychological distress (Table 3).

The multiple linear regression analysis (model 1) showed that LRTI symptoms and psychological distress together explained 46.8% of the variance of overall HRQOL. Addressing the second part of our second study aim, we tested the moderation effect of psychological distress. Despite the high correlation of psychological distress with overall HRQOL, the moderation analysis (model 2) showed that psychological distress did not moderate the association of the severity of LRTI symptoms with HRQOL. This means that the influence of LRTI symptoms on HRQOL is independent of the level of distress (Table 4).

Discussion

To our knowledge, this is the first study to focus on the level of symptom burden, distress, and HRQOL compared to norm as well as the interaction between these variables in cancer survivors with pelvic LRTIs.

It is well-known that radiotherapy to the pelvic area may cause severe side effects [3, 8, 9]. However, studies on long-term pelvic LRTIs are sparse, and thus, the present study contributes to improve this knowledge. At a mean time of nearly 6 years from the end of radiotherapy, the participants reported significantly higher levels of LRTI symptoms compared to a norm population. Similar results have been shown in previous studies [25, 42]. No differences in the symptom profile across cancer types, age, or time since treatment were found, except that women had higher bowel impairment. This aligns with other studies indicating that survivors after gynaecological cancer are especially affected by bowel symptoms [3, 10]. This may be explained by an objective increased affection of bowel function based on anatomic gender differences, or the more frequent application of brachytherapy and multimodal treatment in women compared to men [11]. Furthermore, bowel symptoms such as faecal urgency or leakage may be particular embarrassing and might poorly correspond with feelings of femininity in terms of body image, attractiveness, and sexuality [3].

The participants reported moderately more psychological distress than norms. This supports earlier findings of high levels of anxiety, depression, and impaired mental health among survivors treated for different pelvic malignancies [2, 26]. To the best of our knowledge, this is the first study reporting psychological distress and the effect sizes of differences in cancer survivors with established pelvic LRTIs compared to norms. Unlike other studies, no interaction between age and psychological distress was found [26, 43]. Compared to norms, the participants reported a large impairment in overall HRQOL and in all the functional subdimensions, except for emotional function, as well as a high symptom burden for fatigue, insomnia, and pain. Corresponding studies on the long-term HRQOL of survivors with pelvic malignancies report slightly better overall HRQOL [9, 25], mainly explained by complete disease remission and the decline of symptoms over time [11, 24]. Here, an obvious explanation may be that our participants represent a selected

Table 2 Symptoms, psychological distress, and health-related quality of life compared to norm populations

EPIC	Study population $N = 107$	Controls without cancer[a] $N = 112$	Study population vs. controls		
	Mean (SD)	Mean (SD)	Diff	*z*/*P*	*d*
Urinary total	68.7 (18.0)	89.5 (11.2)	−20.8	−10.4/0.00	1.4
Urinary function	68.1 (27.9)	95.5 (9.5)	−27.3	−9.3/0.00	1.5
Urinary bother	69.0 (17.0)	85.2 (14.1)	−16.2	−7.7/0.00	1.0
Bowel total	62.5 (13.6)	92.4 (8.7)	−29.9	−19.0/0.00	2.7
Bowel function	60.3 (18.0)	92.1 (8.5)	−31.8	−17.7/0.00	2.4
Bowel bother	64.5 (15.5)	92.8 (11.1)	−28.3	−15.7/0.00	2.1
GHQ-12		Cohabiting/married adults[b] $N = 1750$	Study population vs. healthy adults		
Psychological distress	13.4 (5.5)	10.3 (4.9)	3.1	6.2/0.00	0.6
EORTC-QLQ-C30		General population[c] $N = 7802$	Study population vs. general population		
Overall HRQOL	54.9 (22.6)	71.2 (22.4)	−16.3	−7.4/0.00	0.7
Physical function	69.1 (23.7)	89.8 (16.2)	−20.7	−9.0/0.00	1.2
Role function	59.9 (35.7)	84.7 (25.4)	−24.8	−7.2/0.00	0.9
Emotional function	73.6 (23.8)	76.3 (22.8)	−2.7	−1.2/0.22	0.1
Cognitive function	72.0 (27.5)	86.1 (20.0)	−14.1	−5.2/0.00	0.7
Social function	48.3 (32.1)	87.5 (22.9)	−39.2	−12/0.00	1.7
Fatigue	49.8 (28.5)	24.1 (24.0)	−25.7	9.2/0.00	1.1
Nausea and vomiting	9.7 (16.0)	3.7 (11.7)	6.0	4.0/0.00	0.5
Pain	39.6 (32.6)	20.9 (27.6)	18.7	5.8/0.00	0.7
Dyspnoea	26.5 (29.3)	11.8 (22.8)	14.7	5.3/0.00	0.6
Insomnia	47.1 (32.7)	21.8 (29.7)	25.3	7.9/0.00	0.9
Appetite loss	16.0 (25.0)	6.7 (18.3)	9.5	4.0/0.00	0.5
Constipation	28.6 (32.7)	6.7 (18.4)	21.9	7.1/0.00	1.2
Diarrhoea	50.5 (35.5)	7.0 (18.0)	43.5	12.8/0.00	2.3
Financial difficulties	20.6 (32.9)	9.5 (23.3)	11.1	3.5/0.00	0.5

Abbreviations: *d*, effect size, judged as small ($d \geq 0.2$), medium ($d \geq 0.5$), large ($d \geq 0.8$) or very large ($d \geq 1.3$); *EORTC-QLQ-C30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *EPIC*, The Expanded Prostate Cancer Index Composite; *GHQ-12*, General Health Questionnaire; *Overall HRQOL*, overall health-related quality of life; *P*, statistically significance difference < 0.05; *SD*, standard deviation; *z score*, provided by *z* test

Norm populations: [a]EPIC, control population [37]; [b]GHQ-12, studied by Nerdrum et al. [38]; [c]EORTC-QLQ-C30, reference value manual [33]

sample with established LRTIs where the symptoms had not declined over time. Overall, these findings indicate that all areas of the participants' lives are negatively affected. However, an interesting finding is that their emotional function was comparable to the norm population. One explanation may be that the participants have adapted and developed several coping strategies related to their pelvic LRTIs. Another explanation may be that they were about to start hyperbaric oxygen therapy and consequently had hope for a positive outcome, which is an important factor for coping and for HRQOL [44].

More than just the single variables of symptom burden, distress, and HRQOL, the interactions found between these variables are important. First, the results revealed a strong correlation between LRTI symptoms and HRQOL, confirming previous research on symptom burden as a risk factor for impaired HRQOL [6, 11, 24–26]. It is worrisome that these patients often are underdiagnosed and undertreated, although the symptom burden severely impairs HRQOL [2, 7].

Second, the participants' elevated levels of psychological distress also impaired their HRQOL negatively. This may be interpreted as a normal reaction to the everyday burden of living with LRTIs. However, an interesting finding is that the pelvic LRTI symptoms affected HRQOL regardless of the level of psychological distress. This indicates that the symptom burden is a strong predictor for impaired HRQOL in cancer survivors with pelvic LRTIs, which aligns with previous research suggesting that more cancer survivors have reduced HRQOL as a result of physical impairments rather than psychological impairments [18]. Third, the fact that psychological distress did not moderate the connection between symptom burden and HRQOL might have several relevant explanations, such

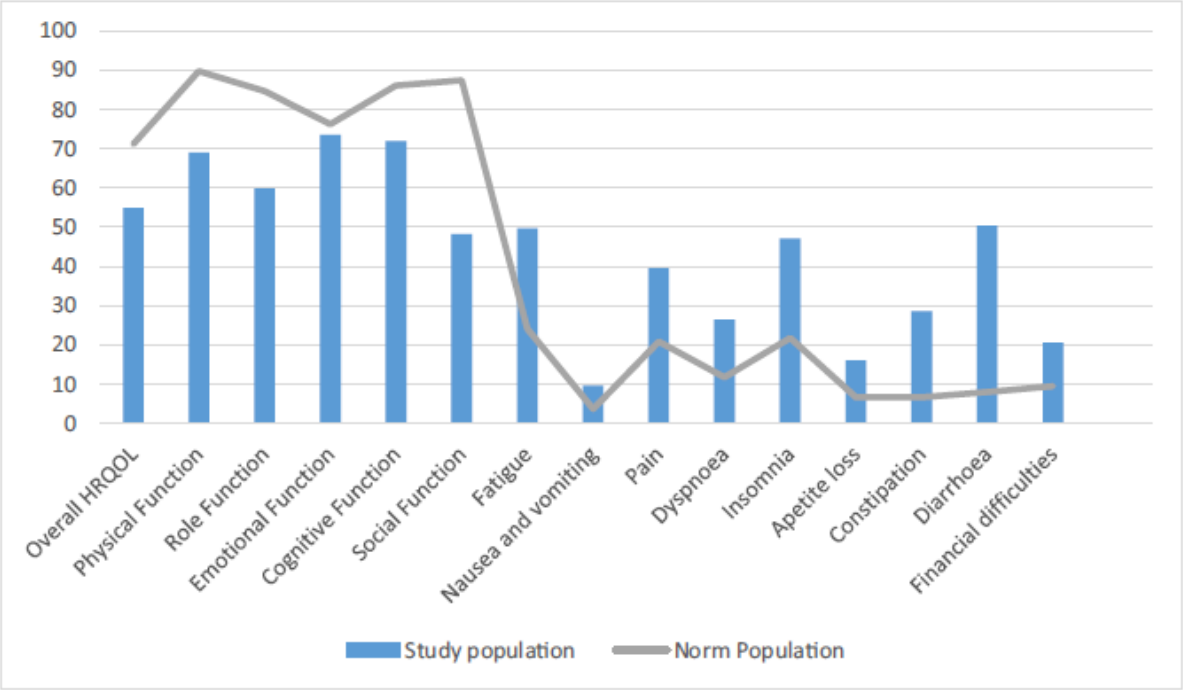

Fig. 2 EORTC-QLQ-C30 mean scores compared to norm population[a]. Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HRQOL, health-related quality of life. For functional scales and overall HRQOL, a high score reflects a high level of functional capacity. High scores on the symptom scales represent a high symptom burden associated with poor HRQOL. Norm population: [a]EORTC-QLQ-C30, reference values manual [33]

Table 3 Correlation analysis between HRQOL, symptoms, and distress

Dependent variable	Correlation	Urinary total	Bowel total	Psychological distress
Overall HRQOL	Pearson *r*	0.7	0.28	− 0.55
	P	0.00	0.00	0.00
Psychological distress	Pearson *r*	− 0.19	− 0.24	
	P	0.03	0.01	

Abbreviations: *HRQOL*, health-related quality of life; *P*, statistical significance

as elevated levels of psychological distress before cancer treatment, going through a life-threatening diagnosis and treatment, or anxiety about cancer recurrence [16, 45]. Another explanation for the elevated distress may be related to hyperbaric oxygen therapy the participants were about to start, as this represents a new, highly technological, and unknown treatment for most patients. On the other hand, the significant association between HRQOL and psychological distress, as well as the symptoms' significant correlation with psychological distress, indicate the importance of screening and identifying survivors in need of psychological distress interventions in addition to pelvic LRTI symptom management.

Overall, this study's results underline the complexity and interactions between LTRI symptoms, psychological distress, and HRQOL and the importance of a bio-psychological or holistic view in screening, survivorship follow-up, and interventions.

Clinical implications

The results documenting a high symptom burden, elevated distress, and impaired HRQOL raise several implications for clinical practice and further research. First, the results indicate that several cancer survivors with pelvic LRTIs have significantly impaired HRQOL and debilitating symptoms

Table 4 Multiple regression models for overall health-related quality of life scores

Overall HRQOL[a]	*B*	SE *B*	*β*/(*P*)	Multicollinearity	r^2
Model 1					
Constant	51.30	11.92			0.468
Urinary total	0.30	0.09	0.24 (0.00)	0.95	
Bowel total	0.19	0.13	0.12/(0.13)	0.93	
Psychological distress	− 2.20	0.31	− 0.55/(0.00)	0.91	
Model 2					
Constant	28.55	25.70			0.473
Urinary total	0.45	0.26	0.36/(0.08)	0.13	
Bowel total	0.40	0.33	0.24/(0.23)	0.14	
Psychological distress	− 0.44	1.80	− 0.11/(0.80)	0.03	
Psychological distress × urinary total	− 0.01	0.02	− 0.21/(0.53)	0.05	
Psychological distress × bowel total	− 0.02	0.03	− 0.25/(0.50)	0.04	

Abbreviations: *B*, unstandardized regression coefficient; *HRQOL*, health-related quality of life; *Model*, 'enter' method in SPSS statistics; *Multicolinearity*, tolerance factor; *P*, significance level; r^2, explained variance; SE *B*, standard error of the coefficient; *β*, standardized coefficient. [a]Dependent variable

several years after radiation. Consequently, there seems to be a need for increased competence and education of healthcare professionals about LRTIs. Second, cancer survivors with pelvic cancers should be informed about LRTIs as a possible late effect from radiation, and which symptoms to be aware of. Third, systematic assessment of pelvic LRTI symptoms and HRQOL after radiation should be part of routine follow-up, whereby impairment should be addressed with proper symptom management and educating survivors in adequate coping skills (e.g. hyperbaric oxygen therapy, rehabilitation programme). Fourth, with persisting symptoms, early diagnosis of established pelvic LRTIs should be confirmed by objective measures and available treatment options as, for example, hyperbaric oxygen therapy should be considered. Finally, overall, nurses play a crucial role in supporting cancer survivors with pelvic LRTIs in all these means, especially by encouraging them to express their needs, screening for LTRI symptoms, and promoting coping and effective treatment interventions to decrease the symptom burden. Furthermore, nurses should have a holistic approach and screen for impaired HRQOL, acknowledging that other factors than the LRTI symptoms may be a source of increased distress. More research in this field is highly needed, especially related to the survivorship follow-up, effects of available treatment options, and rehabilitation programmes.

Strengths

Study strengths are the inclusion of a relatively large and national cohort of both men and women with a range of clinically significant and objectively verified pelvic LRTIs.

Symptoms, distress, and HRQOL were evaluated with validated, well-recognized instruments, and the outcomes were compared to established norms. Furthermore, high survey completion rates strengthen the study. However, the focus on a selective population referred to hyperbaric oxygen therapy may limit the generalization of the findings.

Conclusion

Cancer survivors with established LRTIs reported a severe symptom burden, moderate levels of psychological distress, and highly impaired HRQOL compared to norms several years after radiation. To improve HRQOL, treatment of pelvic LRTI symptoms and interventions related to coping are of great importance.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Grete K. Velure, Bernd Müller, and May Aa. Hauken. The first draft of the manuscript was written by Grete K. Velure, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability De-identified data will be available from the study leader on reasonable request after the end of the project.

Code availability Not applicable.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Committee of Medical and Health Research Ethics, Northern Norway, ID2018/706.

Consent to participate Participants signed informed consent regarding publishing their data.

Conflict of interest The authors declare no competing interests.

References

1. Larsen IK (2018) Cancer in Norway 2018 - cancer incidence, mortality, survival and prevalence in Norway, Cancer Registry of Norway, 2019. https://cin2018.pdf (kreftregisteret.no) Assessed 31 Mar 2021
2. Adams E, Boulton MG, Horne A, Rose PW, Durrant L, Collingwood M, Oskrochi R, Davidson SE, Watson EK (2014) The effects of pelvic radiotherapy on cancer survivors: symptom profile, psychological morbidity and quality of life. Clin Oncol 26:10–17. https://doi.org/10.1016/j.clon.2013.08.003
3. Bradley KA, McHaffie DR (2020) Treatment-related toxicity from the use of radiation therapy for gynecologic malignancies. UpToDate. Assessed 29 Oct 2020
4. Lawrie TA, Green JT, Beresford M (2018) Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev. Lawrie, TA - 2018 | Cochrane Library Assessed 20 Oct 2021
5. Holch P, Henry AM, Davidson S, Gilbert A, Routledge J, Shearsmith L, Franks K, Ingleson E, Albutt A, Velikova G (2017) Acute and late adverse events associated with radical radiation therapy prostate cancer treatment: a systematic review of clinician and patient toxicity reporting in randomized controlled trials. Int J Radiat Oncol Biol Phys 97:495510. https://doi.org/10.1016/j.ijrobp.2016.11.008
6. Sipaviciute A, Sileika E, Burneckis A, Dulskas A (2020) Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review". Int J Colorectal Dis 35:977–983. https://doi.org/10.1007/s00384-020-03595-x
7. Andreyev HJN, Wotherspoon A, Denham JW, Hauer-Jensen M (2010) Defining pelvic-radiation disease for the survivorship era. Lancet Oncol 11:310–312. https://doi.org/10.1016/S1470-2045(10)70026-7
8. Oscarsson N, Müller B, Rosén A, Lodding P, Mölne J, Giglio D, Hjelle KM, Vaagbø G, Hyldegaard O, Vangedal M, Salling L, Kjellberg A, Lind F, Ettala O, Arola O, Seeman-Lodding H (2019) Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. Lancet Oncol 20:1602–1614. https://doi.org/10.1016/s1470-2045(19)30494-2
9. Knowles G, Haigh R, McLean C, Phillips H (2015) Late effects and quality of life after chemo-radiation for the treatment of anal cancer. Eur J Oncol Nurs 19:479–485. https://doi.org/10.1016/j.ejon.2015.02.007
10. Kamga AM, Dumas A, Joly F, Billa O, Simon J, Poillot ML, Darut-Jouve A, Coutant C, Fumoleau P, Arveux P, Dabakuyo-Yonli TS (2019) Long-term gynecological cancer survivors in Côte d'Or: health-related quality of life and living conditions. Oncologist 24:e490–e500. https://doi.org/10.1634/theoncologist.2018-0347
11. Yavas G, Yavas C, Dogan NU, Ilhan TT, Dogan S, Karabagli P, Ata O, Yuce E, Celik (2017) Pelvic radiotherapy does not deteriorate the quality of life of women with gynecologic cancers in long-term follow-up: a 2 years prospective single-center study. J Cancer Res Ther 13:524–532. https://doi.org/10.4103/0973-1482.187243
12. Andreyev HJN, Davidson SE, Gillespie C, Allum WH, Swarbrick E (2012) Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut 61:179–192. https://doi.org/10.1136/gutjnl-2011-300563
13. Carlson LE, Waller A, Groff SL, Giese-Davis J, Bultz BD (2013) What goes up does not always come down: patterns of distress, physical and psychosocial morbidity in people with cancer over a one year period. Psychooncology 22:168–176. https://doi.org/10.1002/pon.2068
14. Han CJ, Gigic B, Schneider M, Kulu Y, Peoples AR, Ose J, Kölsch T, Jacobsen PB, Colditz GA, Figueiredo JC, Grady WM, Li C, Shibata D, Siegel EM, Toriola T, Ulrich AB, Syrjala KL, Ulrich CM (2020) Risk factors for cancer-related distress in colorectal cancer survivors: one year post surgery. J Cancer Surviv 14:305–315. https://doi.org/10.1007/s11764-019-00845-y
15. Joshy G, Thandrayen J, Koczwara B, Butow P, Laidsaar-Powell R, Rankin N, Canfell K, Stubbs J, Grogan P, Bailey L, Yazidjoglou A, Banks E (2020) Disability, psychological distress and quality of life in relation to cancer diagnosis and cancer type: population-based Australian study of 22,505 cancer survivors and 244,000 people without cancer. BMC Med 18:372–372. https://doi.org/10.1186/s12916-020-01830-4
16. Lotfi-Jam K, Gough K, Schofield P, Aranda S, Jefford M (2019) A longitudinal study of four unique trajectories of psychological distress in cancer survivors after completing potentially curative treatment. Acta Oncol 58:782–789. https://doi.org/10.1080/0284186X.2018.1562209
17. Hulbert-Williams N, Neal R, Morrison V, Hood K, Wilkinson C (2012) Anxiety, depression and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? Psychooncology 21:857–867. https://doi.org/10.1002/pon.1980
18. Silver JK, Baima J, Mayer RS (2013) Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. CA Cancer J Clin 63:295. https://doi.org/10.3322/caac.21186
19. Bergerot CD, Razavi M, Clark KL, Philip EJ, Pal SK, Loscalzo M, Dale W (2021) Emotional problem-related distress screening and its prevalence by cancer type: assessment by patients' characteristics and level of assistance requested. Psychooncology 30:1332–1338. https://doi.org/10.1002/pon.5685

20. Brearley SG, Stamataki Z, Addington-Hall J, Foster C, Hodges L, Jarrett N, Richardson A, Scott I, Sharpe M, Stark D, Siller C, Ziegler L, Amir Z (2011) The physical and practical problems experienced by cancer survivors: a rapid review and synthesis of the literature. Eur J Oncol Nurs 15:204–212. https://doi.org/10.1016/j.ejon.2011.02.005
21. Ferrell B, Paice J, Kozywas M (2008) New standards and implications for improving the quality of supportive oncology practice. J Clin Oncol 26:3824–3831. https://doi.org/10.1200/JCO.2007.15.7552
22. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Dehaes JCJM, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F (1993) The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a quality-of-life instrument for use in international clinical-trials in oncology. J Natl Cancer Inst 85:365–376. https://doi.org/10.1093/jnci/85.5.365
23. Corner L (2004) Quality of life. In: Carr I, Higginson J, Robinson PG (eds) Alison J. BMJ Publishing, London, pp 636–637
24. Pate A, Lowery J, Kilbourn K, Blatchford PJ, McNulty M, Risendal B (2020) Quality of life and the negative impact of comorbidities in long-term colorectal cancer survivors: a population-based comparison. J Cancer Surviv 14:653–659. https://doi.org/10.1007/s11764-020-00876-w
25. Bentzen AG, Balteskard L, Wanderås EH, Frykholm G, Wilsgaard T, Dahl O, Guren MG (2013) Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. Acta Oncol 52:736–744. https://doi.org/10.3109/0284186X.2013.770599
26. Chambers SK, Ng SK, Baade P, Aitken JF, Hyde MK, Wittert G, Frydenberg M, Dunn J (2017) Trajectories of quality of life, life satisfaction, and psychological adjustment after prostate cancer. Psychooncology 26:1576–1585. https://doi.org/10.1002/pon.4342
27. Glasziou P, Heneghan C (2009) A spotter's guide to study designs. Evid based Nurs 12:71–71. https://doi.org/10.1136/ebn.12.3.71
28. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 56:899–905. https://doi.org/10.1016/s0090-4295(00)00858-x
29. Gil KM, Pugh SL, Klopp AH, Yeung AR, Wenzel L, Westin SN, Gaffney DK, Small W, Thompson S, Doncals DE, Cantuaria GHC, Yaremko BP, Chang A, Kundapur V, Mohan DS, Haas ML, Kim YB, Ferguson CL, Deshmukh S, Kachnic LA, Bruner DW Expanded validation of the EPIC bowel and urinary domains for use in women with gynecologic cancer undergoing postoperative radiotherapy. Gynecol. Oncol.154:183–188. https://doi.org/10.1016/j.ygyno.2019.04.682
30. Goldberg DP (1988) User's guide to the General Health Questionnaire. NFER-NELSON, Windsor, Berkshire
31. Goldberg P, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, Rutter C (1997) The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med 27:191–197. https://doi.org/10.1017/S0033291796004242
32. Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A (2001) EORTC QLQ-C30 scoring manual (ed 3). EORTC publications, Brussels
33. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, Gundy C, Koller M, Petersen MA, Sprangers MA (2008) EORTC QLQ-C30 reference values manual. https://Introductioneortc.org). Assessed 31 Mar 2021
34. George D, Mallery P (2019) IBM SPSS Statistics 26 step by step: a simple guide and reference. Routledge, New York
35. Wei JT (2002) Scoring Instructions for the Expanded Prostate cancer Index Composite (EPIC). Ann Arbor 1001:48109–40330
36. Sullivan GM, Feinn R (2012) Using effect size—or why the P value is not enough. J Grad Med Educ 4:279–282. https://doi.org/10.4300/jgme-d-12-00156.1
37. Expanded Prostate Index Composite (2015) Characteristics of EPIC domain-specific summary and subscale scores for 112 controls without prostate cancer. http://www.med.umich.edu/urology/research/EPIC/norms.pdf. Assessed 31 Mar 2021
38. Nerdrum P, Rustøen T, Rønnestad MH (2006) Student psychological distress: a psychometric study of 1750 Norwegian 1st-year undergraduate students. Scand J Educ Res 50:95–109. https://doi.org/10.1080/00313830500372075
39. Rayat CS (2018) Statistical Methods in Medical Research. Springer, Singapore
40. Hayes AF (2017) Introduction to mediation, moderation, and conditional process analysis: a regression-based approach, 2nd edn. The Guilford Press, New York
41. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki--ethical-principles-for-medical-research-involving-human-subjects Assessed 18 Jan 2021
42. Welzel G, Hägele V, Wenz F, Mai S (2011) Quality of life outcomes in patients with anal cancer after combined radiochemotherapy. Strahlenther Onkol 187:175–182. https://doi.org/10.1007/s00066-010-2175-5
43. Adams SV, Ceballos R, Newcomb PA (2016) Quality of life and mortality of long-term colorectal cancer survivors in the Seattle Colorectal Cancer Family Registry". PLoS ONE 11:e0156534. https://doi.org/10.1371/journal.pone.0156534
44. Rustoen T (1998) Hope and quality of life in newly diagnosed cancer patients. Department of Public Health and Primary Health Care Division for Nursing Science, University of Bergen, Bergen
45. Cessna Palas JM, Hyland KA, Nelson AM, Small BJ, Jim HSL, Jacobsen PB (2021) An examination of the relationship of patient modifiable and non-modifiable characteristics with fear of cancer recurrence among colorectal cancer survivors. Support Care Cancer 29:869–876. https://doi.org/10.1007/s00520-020-05552-4

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Experiences of patients with pelvic radiation injuries after cancer treatment undergoing hyperbaric oxygen therapy: A phenomenological-hermeneutical study

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Abstract

Radiotherapy of pelvic cancers may cause severe tissue injuries, and hyperbaric oxygen therapy (HBOT) is one of few treatment alternatives. As part of a longitudinal, mixed-methods study, this study's aim was to explore pelvic cancer survivors' experiences of undergoing such treatment. Using a phenomenological-hermeneutical design, in-depth interviews of 20 cancer survivors were conducted and analysed using systematic text condensation. This study is reported in accordance with COREQ. The informants' experiences were identified as: *Approaching an unknown world*, *From feeling worried to becoming familiar*, *A long-lasting treatment course*, and *The treatment course went better than expected*. Despite information prior to the treatment, informants were worried about HBOT but were still motivated to try it. A combination of relevant information, clear routines, person-centred care, peer support, and limited side effects seem to be important factors for patients' experiences of safety from this treatment.

Keywords

experiences, high technology, patient perspective, qualitative study

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Introduction

Irradiation is an essential part of the curative treatment of pelvic malignancies, including gynaecological, prostate, and rectal cancers.[1] However, radiation may affect the surrounding healthy tissues and lead to acute or chronic injuries, and 5–15% of patients develop late radiation tissue injuries (LRTIs) months or years after radiation.[2,3] These injuries are characterised by poor microcirculation, hypoxia, tissue damage, and fibrosis,[3–6] causing symptoms such as increased frequency, urgency, and leakage of urine and faeces, diarrhoea, and pain, which diminish the individual's quality of life.[7–11] Treatment options are limited, but hyperbaric oxygen treatment (HBOT) has shown promising effects in treating pelvic LRTI.[1,2,12–14] The aim of this treatment is to increase tissue oxygen concentrations and stimulate neoangogenesis and cellular regeneration, thereby revitalising and healing the hypoxic tissue and alleviating the symptom burden.[6,15]

Hyperbaric oxygen treatment is a high-technology treatment where patients are enclosed in a pressurised chamber and breath pure oxygen at a pressure of 2 atmospheres absolute or more for 90–100 minutes once a day for 6–8 weeks.[1] Strict safety routines are applied because the ambient oxygen level increases the risk of fire and oxygen seizures.[16] Consequently, HBOT requires specific technical competence and constant and close observation of the patients during the treatment, and this is commonly provided by specialised trained nurses.

Physical side effects of HBOT are usually mild and temporary (e.g. barotrauma and visual changes).[16] Because HBOT is only administrated at relatively few specialised centres, most patients and healthcare professionals are unfamiliar with this treatment. The technical environment, the confining and uncomfortable space inside the chambers, and the exposure to noise and changing temperatures may induce or increase distress, anxiety, and claustrophobia and lead to termination or refusal of treatment.[17]

In addition, patients with pelvic LRTI often have substantial and complex symptoms in one or multiple organs (e.g. bladder, bowel, rectum, and genitalia),[2–5,10] and this may create concerns when enclosed in the chamber for two

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hours daily. The nurse's ability to provide person-centred care based on the individual patient's needs combined with their technical competence are of crucial importance to minimise the negative impacts of the treatment.[18] However, despite the patients' multiple challenges, no prior research that has explored how patients with pelvic LRTIs experience undergoing HBOT were identified. This is important knowledge to guide nurses in how to prepare patients for the treatment, to alleviate anxiety and distress, to meet the patients' needs, and to promote trust and coping ability throughout the treatment trajectory. This study therefore aimed to explore how cancer survivors with pelvic LRTIs experience undergoing HBOT.

Methods

The study was performed in line with the Consolidated Criteria for Reporting Qualitative Research checklist.[19] It was anchored in qualitative methods, using a phenomenological-hermeneutical approach.[20] This approach permits in-depth insights into individuals' experiences of a topic and provides an understanding of the essential meaning of individuals' lived experiences of a phenomenon, in this case the patients' experience of undergoing HBOT.[20] The researchers act as an instrument in a process in which the individuals' life-world experiences are transcribed into text (phenomenological) and subsequently interpreted (hermeneutical). This leads to a back-and-forth process between the informants' expressed experiences and letting the phenomenon speak for itself and the researchers' open-minded and dwelling approach with close awareness of their own preunderstanding and interpretation. This process, also referred to as the hermeneutic circle, generates new insights and understandings about a phenomenon.[20,21]

Recruitment and participants

This study is part of a longitudinal mixed-methods study of patients with pelvic LRTI undergoing HBOT in monoplace hyperbaric chambers at the Norwegian national centre for HBOT (trial registration: ClinicalTrials.gov. NCT03570229). Participants in the current study were recruited through purposive sampling[20] from the main study, for which the eligibility criteria were a) pelvic LRTI after intended curative radiation for pelvic cancer (prostate, gynaecological, urological, or bowel cancer), b) symptoms of radiation injury of the bowels, bladder or pelvic bones, objectively verified by endoscopy or radiology; c) $\geq$ 6 months from completing radiation; d) referred to The Norwegian National Unit for Planned Hyperbaric Oxygen Treatment; and e) age $\geq$ 18 years. Eligible participants were consecutively contacted by a study nurse who gave them written and verbal information about the study. Recruitment was continued until a sample of 20 participants was obtained. The sample reflected a broad variety of demographic and medical backgrounds as required for qualitative research.[20] The participants, 11 women and nine men with different civil status, were between 36 and 77 years of age when interviewed. They had been diagnosed with different pelvic cancers, had undergone pelvic radiation, and had developed different LRTIs (radiation cystitis and proctitis and osteoradionecrosis).

Data collection

To capture the lived experiences of undergoing HBOT, in-depth, individual, face-to-face interviews were conducted at the end of six weeks of HBOT between January and November 2019. The first and third authors performed the interviews in an office free from any disturbance at the HBOT location. The authors had not met any of the informants before the interviews. Before starting the interview, the interviewers introduced themselves and reminded participants of the purpose of the study and the interview, the voluntary nature of participation and their right to withdraw, protection of anonymity, permission to audiotape the interview, and the interviewers' status as researchers outside the HBOT centre, and they encouraged the participants to speak freely. To ensure that the two authors conducted the interviews in a reasonably similar manner, a brief interview guide with the information outlined above along with some broad topics (e.g. experiences related to information, procedures, follow-up) was developed, pilot-tested, and used without any revisions.[22] All interviews started with the opening question: 'Can you please describe how you have experienced undergoing HBOT'? The informants were encouraged to tell their own stories as freely as possible, and their stories led to new follow-up questions. The context allowed for an exploration of the individual participants' experiences where they could direct the course of the interview and identify and describe experiences that were not considered by the researchers. Each interview was audiotaped and lasted approximately one hour. After each interview, the informants had the opportunity to respond to the interview itself. Here, many found it positive to tell 'the whole story' to an interested listener, whereby some expressed that the interview clarified what they had gone through. After each interview, the two interviewers discussed their immediate reflections on special themes or nuances or important clues to be followed up on in forthcoming interviews. Data saturation was accomplished around the 15th interview, but we continued up to 20 interviews to make sure that no new topics emerged.[23] The interviews were transcribed verbatim, concealing any identifiable variables, and a pseudonym was given to each participant.[20] Transcripts were not returned to the participants for comments.

Data analysis

The analysis was performed in collaboration by all authors, emphasising the importance of working both systematically and creatively to capture the essence of the informants' experiences. Here, systematic text condensation was considered an appropriate method because it represents a descriptive and explorative method for thematic cross-case analysis, and is well suited for capturing informants' lived

experiences.[24] This four-step analysis starts with interviewing and then moves into analytic circles, aligning to the study's phenomenological–hermeneutical approach.[20] First, all authors read the interviews separately to obtain a general overview related to the study aim and then discussed their impressions until consensus was reached. Second, the interviews were re-read, and eight representative units of meaning were extracted. The units of meaning were transferred into NVivo12 software for further coding and sorting of the data (www.qsrinternational.com). All interviews were again re-read and coded in relation to the units of meaning. Third, the coded units of meaning were condensed into abstracted themes, engaging the researchers in an analytic circle between the identified themes, transcribed interviews, and discussions. At the conclusion of this process, four themes were agreed on, each having two subthemes. The analyses were discussed among the authors until all interpretations reached consensus.[20,24] With backgrounds in cancer care and qualitative research and experiences as a specialised HBOT trained nurse and a senior neurologist/HBOT physician, the authors' preconceptions of the topic were made explicit and were critically discussed during the research process.[24] To validate the analysis, the fourth step entailed comparing the findings with the transcribed interviews in order to ensure that we had captured the informants' expressed and intended meanings (Table 1). The findings were also unanimously validated by the study's advisory board, consisting of user representatives and healthcare providers with and without experience in HBOT.

Ethical considerations

Data in the present study were collected as an initial part of the longitudinal mixed methods study Hyperbaric Oxygenation Treatment and Quality of Life, approved by the Norwegian Regional Committee of Research and Ethics (2018/706) and registered at ClinicalTrials.gov (NCT03570229). The study was carried out in line with the Declaration of Helsinki[25] and in compliance with the General Data Protection Regulation (GDPR).[26] All informants agreed to participate voluntarily and gave written consent.

Findings

Four main themes emerged from the analysis of the participants' experiences of undergoing HBOT: a) *Approaching an unknown world*, b) *From feeling worried to becoming familiar*, c) *A long-lasting treatment course*, and d) *The treatment course went better than expected.*

Approaching an unknown world

Most participants reported that they knew very little of what to expect when arriving at the HBOT unit. They felt that they had entered a totally unknown and somewhat scary environment that was difficult to imagine prior to arriving at the treatment centre. The analysis showed that there were several facets underpinning this experience.

An important part of this experience was elaborated as 'I got information but I still felt unprepared'. There was considerable variation in how participants initially had been informed about HBOT as a treatment option for their LRTI symptoms. Most were informed about this option by a physician, but some had introduced this possibility themselves to their general practitioner because they had seen a programme about HBOT on TV or had been recommended to try it by others. Despite these variations, a common experience was that they had received very little information about HBOT from the referring physician. However, all reported that they had received written information about the treatment procedures from the HBOT unit prior to the treatment. Nevertheless, the participants still found it difficult to understand what it really was to undergo HBOT and felt insecure and unprepared for what to expect:

> I got just a little information (…) I was really tense when I started, because I didn't know what I should expect (…) when I first came here, I thought they were going to immerse me in water. (Maria)

As exemplified in Maria's quotation, and based on the experiences related to the information that was provided to them, the participants experienced anxiety and distress before coming to the unit. This was especially connected to how HBOT was performed, whereby informants described scary images, for example, of being 'immersed in water' or 'aliens growing in the chambers'. Specifically, the informants expressed concerns related to their LRTI symptoms, such as how to get in contact with the nurses for help or what to do if they had to go to the toilet during the treatment sessions.

Another important part of the informants' experiences of entering an unknown world was identified as 'HBOT may be my chance'. Even if HBOT was highly unknown and unfamiliar to them, the informants expressed that they were very eager to start the treatment. Prior to treatment, they described vast physical, emotional, and social implications of living with pelvic LRTI over time with limited treatment options. Consequently, they experienced that HBOT was a golden opportunity to finally ease their symptoms. Even if the informants experienced a common hope that the HBOT would decrease their LRTI symptoms, they were very realistic and welcomed any improvement – as illustrated by Julia:

> I hope this can alleviate some of the pain and nausea (…) Just a few per cent improvement would be better than it is now.

From feeling worried to becoming familiar

The informants described entering the HBOT unit with worries and about how different it was from earlier treatment experiences. In particular, they experienced the high focus on security, precautions, and technical equipment as

Table 1. The analysis process based on systematic text condensation.

STEP 1: Getting an overall impression	STEP 2: Identifying units of meaning			STEP 3: Abstracting the contents of individual units of meaning	STEP 4: Summarising the findings
Process: a) The authors read the transcribed interviews separately. b) They discussed their overall impression until reaching consensus.	*Process:* a) The authors coded the data separately. b) They discussed the codes until reaching consensus.			*Process:* a) The authors analysed the contents separately. b) They had several discussions until reaching consensus.	*Process:* a) The authors discussed the findings against the transcribed interviews. b) Each author identified direct statements to elucidate units of meaning and discussed these until reaching consensus.
Identified total impression:	***Identified units of meaning:***			***Abstracted contents and sub-contents:***	***Summarising:***
Varying degrees of preparation and nervous at start-up		***Source***	***References***	**Approaching an unknown world.** I got information but still I felt unprepared. Hyperbaric oxygen therapy may be my chance.	Summarised findings and presenting direct statements within the abstracted contents.
First 'dives' challenging	Approaching an unknown world	20	192		
Good individual care and safety	From scary to routine	20	238		
Time-consuming treatment	To be seen and heard, safety	20	231		
The importance of peer patients	Away from daily life	20	137		
Experienced side effects and initial symptom relief	The importance of peer patients	19	113	**From feeling worried to becoming familiar.** I had to learn to 'dive'. The nurses made me feel safe.	The findings were discussed and unanimously validated by user representatives and healthcare providers with and without experience in HBOT.
	Experienced side effects	20	104		
	Experienced initial effects	20	72		
	Hope for the future	20	154	**A long-lasting treatment course.** Being away from daily life. The importance of peer patients.	
				The treatment course went better than expected. Experiencing limited side effects. Experiencing the beginning symptom relief.	

Notes. HBOT: hyperbaric oxygen therapy; Source: number of participants who presented the theme; References: number of mentions in the interviews.

being unfamiliar and unexpected. Gradually, the informants' experiences went from feeling worry, towards HBOT becoming a familiar routine.

An essential part of this experience can be summed up as 'I had to learn to "dive"'. Here, the informants expressed that they had to learn and understand the safety procedures, that they had to wear suitable clothes, that they could not use any ointments, and that they had to go through safety checks before being allowed to enter the chamber. However, they expressed that the nurses' information about what was going to happen when inside the pressure chamber, how to manage challenges, for example, inner ear equalisation problems, were important in making them feel secure. Still, a common experience related to the first treatment sessions was initial problems with their ears, as expressed by Sarah:

> I wasn't prepared that I had to work that hard to equalise the pressure in my ears, I thought I could just relax (...). At first it was scary, because I didn't know what it was when I got pain in both my ears, it felt like my eardrum was going to burst. The nurse showed me how I could equalise the pressure by holding my nose and swallowing (...). I had to use this technique the first week (...), but now I can equalise just by swallowing, so it goes really well.

As illustrated by Sarah's quotation, 'learning by doing' was an important factor to decreasing the informants' anxiety and distress, and after a few sessions they grew accustomed to being inside the chamber and learned how to cope with the situation. Despite being enclosed in the chamber for approximately two hours daily, only one participant experienced having to interrupt some of the initial treatment sessions due to bladder and bowel urgency.

Another important facet of the informants' experiences from being worried to becoming familiar with the treatment was identified as 'The nurses made me feel safe'. Here, the informants described how the nurses handled their individual needs and arrangements in a caring and reassuring way, as illustrated by Anna:

> I have a lot of pain in the pelvic area and cramps over my bladder (...) the nurses noticed that, and they solved this issue by piling up pillows under my hips, and they took great care for me to be comfortable (...) I experienced that being in the pressure chamber went surprisingly well.

The informants expressed that the nurses' continuous presence outside the chamber and the ability to communicate with them during the treatment sessions was very comforting. Due to claustrophobia, a few informants needed anxiolytic medication before entering the chamber, but experiencing the nurses' safeguarding inside the chamber made all but one quit the medication after a few sessions. A common experience was that being able to watch a movie or TV during the treatment sessions was an important means of decreasing anxiety and distress, as well as making the time go by. Furthermore, the informants experienced that the daily chat with the nurses about, for example, their spare time, family, and other interests made them feel safe, remembered, and familiar.

A long-lasting treatment course

Overall, the informants experienced that the HBOT was a lengthy and time-consuming process because most of them had to stay at the hospital's patient hotel for the six weeks of treatment because the centre was so far from their homes. This experience had two main facets.

In 'Being away from daily life', the informants experienced that the daily treatments and their absence from home greatly affected their everyday life, and they found it difficult to be away from their spouses, families, friends, and pets. Participants who were caring for underage children, especially single parents, experienced concerns and challenges related to childcare and follow-up. Although the informants could travel home every weekend, a common experience was that these journeys were too exhausting or there were concerns related to their symptoms, as illustrated by Joe:

> I had planned to go home a couple of weekends during the treatment period (...) but I didn't dare because I was afraid, I would start bleeding from the urinary tract during the trip (...) now I haven't seen my wife for six weeks (...) it would have been hard without the telephone.

Another facet of experiencing the HBOT as lengthy included a more positive experience, identified as 'The importance of peer patients'. The informants experienced that one of the main advantages of the lengthy HBOT course was that they met other patients with pelvic LRTI symptoms. Here, they experienced that they could share common experiences, as well as spare time, such as common meals, going for walks, shopping, or visiting a cafe. The participants experienced that this fellowship provided them with positive relations and a sense of being part of a community, as expressed by Lily:

> It was first when I came here and met the others that I realized I actually have radiation injuries (...) I'm not the only one who has such damage (...) it is a relief to meet others in the same situation and to share experiences.

In contrast, a few participants expressed that the community of peer patients was too overwhelming for them or was focused too much on illness, and they withdrew from the peer patients.

The treatment course went better than expected

Overall, the informants expressed that even if the treatment course was experienced as lengthy, it went far better than they had expected it to in advance. This experience was based on two main features, identified as 'Experiencing limited side effects' and 'Experiencing the beginning of symptom relief'.

The first facet of the positive experience of the treatment course was that the informants experienced limited side effects of the HBOT. Most common was barotrauma, whereby most handled this by learning how to equalise the inner ear pressure just by swallowing. A few informants needed treatment with nasal spray or tablets, and one needed a surgical intervention with paracenteses.

Several informants experienced significant fatigue both during and between the treatment sessions, and this was especially significant for informants already diagnosed with fatigue:

> I have fatigue and it is just as it became worse (…), I don't remember which day it is, I don't remember if I have talked to those at home today (…) it'll be tough when I get home again. (Susan)

Another commonly experienced side effect was visual changes at the end of the treatment period, causing problems with their ordinary glasses, orientation, watching TV, reading, or driving. In contrast, others experienced the visual changes as a benefit, with some becoming able to read without glasses. A few participants experienced dizziness for a short while when coming out of the chamber.

Although all informants experienced some side effects, these were commonly expressed as tolerable. However, those who experienced adverse events stated that they were quickly seen by a HBOT physician for diagnosis and management.

The second facet of the positive experience was that the informants articulated that they experienced an improvement of their pelvic LRTI symptoms during the treatment course, outlined as pain relief and less bleedings, as well as less urge and frequency of urine and faeces and consequently fewer toilet visits during both the day and night, as illustrated by Eric:

> The last nights I have only been up once or twice (…) that's a record (…) usually, I'm up to the toilet at least ten times a night.

However, the participants expressed concerns that the experienced improvement might be short-term. Despite this, the informants underlined that they would appreciate only a few per cent symptom improvement compared to their initial symptom burden.

Discussion

Although HBOT is an approved indication for several conditions, for example, LRTI, it is not widely established or studied, and it is relatively unknown among both healthcare professionals and patients.[1,27] To our knowledge, this is the first study focusing on patients' experiences of undergoing HBOT. The findings illuminate important aspects of the patients' own experiences that may provide nurses with important understanding and knowledge in caring for patients undergoing HBOT and other high-technology treatments.

First, the findings showed that even if the patients got information about HBOT and the routines before entering the unit, they experienced mixed feelings of distress and hope. In line with our findings, previous research shows that entering a high-technology treatment may increase the level of distress and anxiety.[28] Because information and knowledge have been documented to be important in decreasing treatment-related distress,[29] our findings highlight the importance of increasing knowledge of HBOT among healthcare professionals in preparing patients for such treatment. However, even though our participants received written information and a link to a video, they still found it difficult to comprehend what HBOT was like in advance. Comparable to our findings, patients with other conditions have described HBOT as 'a new world' and call for more information to be provided in advance.[30,31] To alleviate distress, in addition to the written information, a phone call from the HBOT unit before attendance may be helpful where patients can air their concerns and clear up remaining questions and misunderstandings. Furthermore, it is important that nurses at the unit are aware of the patient's level of distress when entering the unit, let them know that this is normal, address the patient's individual needs, and repeat the information.[28] Even though feeling distressed and anxious, the patients were very motivated and hopeful regarding the treatment. This is an important resource in treatment because hope and outcome expectations play a predominant role in mediating distress and promoting health-related quality of life.[7,27]

Second, our findings showed that although the patients experienced initial distress and anxiety, they became accustomed to the HBOT after a few sessions. Building on previous research,[28–30,32] the combination of psychoeducation, entertainment distraction, and the close follow-up from the nurses seem to be important factors in making the patients feel comfortable and safe. Patients have previously reported discomfort related to the chamber environment[30,31] but this was not supported by our informants. This may be due to the use of monochambers in this study, as well as our informants' indications of the nurses' ability to make individual arrangements, e.g. with additional pillows, thus making the patients feel as comfortable as possible. An important finding is that the patients' high symptom burden and concerns related to urgency and leakage of urine and faeces only appeared to be a minor problem. This may be explained by consistent information, clear routines, daily contact with specialised nurses, and the nurses' constant follow-up and responding to the patients' individual needs, which are known to be important factors for acceptance and coping during HBOT.[30,31,33] Another important factor seems to be that that the patients found relief in distraction, such as watching a movie during treatment. This aligns with earlier findings that patients who are distracted by entertainment during treatment show less anxiety.[29] The development of a trustful relationship, meeting individual needs, and mastering 'learning by doing' seem to have facilitated the patients' coping abilities and a feeling

of safety. These findings highlight the importance of predictability and patient-centred care as being essential for positive coping experiences, in addition to specific professional nursing competence as a safeguard for patients in a HBOT environment.

Third, the findings showed that even if the patients experienced the treatment course as long lasting and did not enjoy being away from their everyday lives and loved ones, the absence from home and social relations was acceptable. An important reason for this was the opportunity for patients to socialise, share symptom burdens, and support each other. In Norway, rehabilitation is not an integrated part of the cancer treatment trajectory. Research has shown that patients often feel left alone with their latent affects and cancer-related challenges, and in addition to professional follow-up they often request peer support.[34,35] It seems that the opportunity for the informants to share time with other patients with similar challenges allowed for a unique community to develop, and this to a certain degree compensated for being away from family and friends. Peer support is shown to be important for promoting positive changes and improving psychosocial function, empowerment, and quality of life.[36] Consequently, nurses should facilitate and promote peer support as an important part of the treatment course.

Fourth, the findings indicated that the majority of participants had only minor, temporary, and highly tolerable side effects of HBOT, such as mild barotrauma, visual changes, tiredness, and claustrophobia. Most of these are well known and temporary.[16] However, a new finding not previously documented was that most patients reported high levels of fatigue, both during and after treatment. This may be another aspect of oxygen toxicity, and preexisting fatigue after cancer treatment may be a predisposing factor. More attention and research should be directed to this issue. No participants dropped out, and only one needed anxiolytic medication for more than a few days. In contrast, a study by London et al.[37] reported that nearly one third of patients treated in monoplace chambers required sedative premedication due to claustrophobia. This may again be explained by the specialised nurses' knowledge of the side effects of HBOT and their ability to perform the high technology treatment procedures while at the same time attending to the patients' individual needs and thereby preventing serious side effects. An interesting finding is that most participants described initial symptom relief during the treatment course, while symptom effects often do not occur until several weeks after completing an HBOT session.[14] Although a placebo effect cannot be excluded, participants reported rather specific and objective symptom relief, such as fewer toilet visits, which may indicate structural improvement. This beginning of symptom relief promoted the informants' hope for further symptom relief even if they were very realistic and expressed that they appreciated any improvements of their symptom burden, no matter how small. Experiencing initial symptom relief, having hope, and positive outcome expectancy for further improvements have been shown to be important factors for cancer survivors' coping and health-related quality of life.[7,38,39] This has also been documented in patients undergoing elective HBOT for other conditions, for example, osteoradionecrosis of the head and neck or diabetic foot ulcers.[31,33]

Strengths and limitations

This study has several strengths. It is the first study that provides insights into how cancer survivors with pelvic LRTIs experience the HBOT trajectory. Another significant strength is the enrolment of a diverse sample from across the country, with varying backgrounds, cancer diagnoses, pelvic LRTI injuries, gender, and age. Furthermore, data saturation, defined as no new lived experiences being outlined,[23] was achieved in the interviews. The study's analysis process was transparent, performed and validated by all authors, discussed in relation to the authors' preunderstandings, and validated by illustrative quotations. The elaborated themes were consistent, suggesting that we captured a valid sample of the participants' lived experiences, thus making the findings valid and transferable to other LRTI patients.[20,24] However, the qualitative design and the single-centre approach limit the generalisability of the findings.[20] Furthermore, the sample did not include participants refusing HBOT or study participation, meaning that we captured a sample that was highly motivated for HBOT and positive towards our research. Because we only included participants treated in monoplace chambers, the patients' experiences may differ in some aspects from treatment in multiplace chambers.

Conclusion

Starting HBOT was experienced as *Approaching an unknown world* for many patients, and detailed information was needed to prevent distress and anxiety. Clear routines, highly specialised personnel with a reassuring attitude, person-centred care, and distraction during treatment seemed to be important factors to make the patients feel safe and to promote their coping abilities during treatment. The downside of the HBOT course being long seemed to be outweighed by the benefits of meeting peer patients. Overall, HBOT was experienced as a safe treatment with limited side effects, where many patients noticed a beginning of symptom relief. Our findings indicate that HBOT is feasible for patients with pelvic LRTI. More research within this field is warranted, especially longitudinal studies of the development of pelvic symptom burden, late side effects from radiation, and quality of life.

Trial registration

This study is part of a longitudinal mixed-methods study of cancer survivors with pelvic radiation injuries undergoing hyperbaric oxygen therapy and the main study was registered in ClinicalTrials.gov (NCT03570229).

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Declaration of conflicting interests

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References

1. Moon R. *Hyperbaric oxygen therapy indications*. 14th ed. North Palm Beach, FL: Best Publishing Company, 2019.
2. Bennett MH, Feldmeier J, Hampson NB, et al. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2016; 4(4): 43–54.
3. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer* 2014; 120(24): 3870–3883.
4. Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract* 2011; 2011: 917–941.
5. Niezgoda JA, Serena TE, Carter MJ. Outcomes of radiation injuries using hyperbaric oxygen therapy: an observational cohort study. *Adv Skin Wound Care* 2016; 29(1): 12–19.
6. Weir G. Hyperbaric oxygen therapy for complications of radiotherapy: general review. *Wound Healing Southern Africa* 2009; 2(2): 60–62.
7. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol* 2003; 56(5): 395–407.
8. Ferrell B, Paice J, Koczywas M. New standards and implications for improving the quality of supportive oncology practice. *J Clin Oncol* 2008; 26(23): 3824–3831.
9. Hewitt M, Greenfield S, Stovall E. *From cancer patient to cancer survivor: lost in transition*. Washington, DC: National Academies Press, 2005.
10. Widmark A, Fransson P. Prospective follow-up of self-assessed late side effects fifteen years after external beam radiotherapy for localized prostate cancer: a comparison with age-matched controls. *Int J Radiat Oncol Biol Phys* 2004; 60(1): 452–452.
11. Fransson P, Widmark A. Late side effects unchanged 4–8 years after radiotherapy for prostate carcinoma: a comparison with age-matched controls. *Cancer* 1999; 85(3): 678–688.
12. Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; 72(1): 134–143.
13. Dellis A, Papatsoris A, Kalentzos V, et al. Hyberbaric oxygen as sole treatment for severe radiation induced haemorrhagic cystitis. *International Braz J Urol* 2017; 43(3): 489–495.
14. Oscarsson N, Müller B, Rosén A, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. *Lancet Oncol* 2019; 20(11): 1602–1614.
15. Macdonald HM. Hyperbaric oxygenation in the patient with malignancy: friend or foe? *Diving Hyperb Med* 2007; 37(3): 133–138.
16. Camporesi EM. Side effects of hyperbaric oxygen therapy. *Undersea Hyperb Med* 2014; 41(3): 253–257.
17. Barnard A, Sandelowski M. Technology and humane nursing care: (ir)reconcilable or invented difference? *J Adv Nurs* 2001; 34(3): 367–375.
18. Sandelowski M. Toward a theory of technology dependency. *Nurs Outlook* 1993; 41(1): 36–42.
19. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007; 19(6): 349–357.
20. Creswell JW, Poth CN. *Qualitative inquiry and research design: choosing among five approaches*. 4th ed. Thousand Oaks, CA: SAGE Publications, 2017.
21. Gadamer HG, Weinsheimer J, Marshall DG. *Truth and method*. 1st paperback ed. London: Bloomsbury Academic, 2013.
22. Kvale S. *Doing interviews*. London: SAGE Publications, 2008.
23. Saunders B, Sim J, Kingstone T, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Quality & Quantity* 2018; 52(4): 1893–1907.
24. Malterud K. Systematic text condensation: a strategy for qualitative analysis. *Scand J Public Health* 2012; 40(8): 795–805.
25. World Medical Association. *Declaration of Helsinki: ethical principles for medical research involving human subjects*. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (2018, accessed 19 January 2021).
26. Chassang G. The impact of the EU general data protection regulation on scientific research. *ecancermedicalscience* 2017; 11: 709–709.
27. Rustøen T, Cooper BA, Miaskowski C. The importance of hope as a mediator of psychological distress and life satisfaction in a community sample of cancer patients. *Cancer Nurs* 2010; 33(4): 258–267.
28. Clark C, Rock D, Tackett K. Assessment of the magnitude of anxiety in adults undergoing first oxygen treatment in a hyperbaric chamber. *Mil Med* 1994; 159(5): 412–415.
29. Allen KD, Danforth JS, Drabman RS. Videotaped modeling and film distraction for fear reduction in adults undergoing hyperbaric oxygen therapy. *J Consult Clin Psychol* 1989; 57(4): 554–558.
30. Chalmers A, Mitchell C, Rosenthal M, et al. An exploration of patients' memories and experiences of hyperbaric oxygen therapy in a multiplace chamber. *J Clin Nurs* 2007; 16(8): 1454–1459.
31. Lee A, Forner L, Jansen EC. Patient's perspective on hyperbaric oxygen treatment of osteoradionecrosis. *Int J Technol Assess Health Care* 2014; 30(2): 188–193.
32. Sandelowski M. Troubling distinctions: a semiotics of the nursing/technology relationship. *Nurs Inq* 1999; 6(3): 198–207.

33. Hjelm K, Löndal M, Katzman P, et al. Diabetic persons with foot ulcers and their perceptions of hyperbaric oxygen chamber therapy. *J Clin Nurs* 2009; 18(14): 1975–1985.
34. Hellbom M, Bergelt C, Bergenmar M, et al. Cancer rehabilitation: a Nordic and European perspective. *Acta Oncol* 2011; 50(2): 179–186.
35. Nilsen J, Jensen L, Bohn N, et al. *To live with and after cancer. Report.* Oslo: The Norwegian Cancer Society, April 2019.
36. Kowitt SD, Ellis KR, Carlisle V, et al. Peer support opportunities across the cancer care continuum: a systematic scoping review of recent peer-reviewed literature. *Support Care Cancer* 2019; 27(1): 97–108.
37. London SD, Park SS, Gampper TJ, et al. Hyperbaric oxygen for the management of radionecrosis of bone and cartilage. *Laryngoscope* 1998; 108(9): 1291–1296.
38. Davis S. *Rehabilitation: the use of theories and models in practice.* London: Elsevier Limited, 2006.
39. Rustoen T. Hope and quality of life, two central issues for cancer patients: a theoretical analysis. *Cancer Nurs* 1995; 18(5): 355–361.

ARTICLE 3

Supportive Care in Cancer
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ORIGINAL ARTICLE

Symptom burden and health-related quality of life six months after hyperbaric oxygen therapy in cancer survivors with pelvic radiation injuries

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Abstract

Purpose Late radiation tissue injuries (LRTIs) after treatment for pelvic cancer may impair health related quality of life (HRQoL). Hyperbaric oxygen therapy is an adjuvant therapy for LRTIs, but limited studied. The aim of this study was to explore the development and association between symptoms of LRTI and HRQoL following hyperbaric oxygen treatment.

Methods A pretest–posttest design was used to evaluate the changes in pelvic LRTIs and HRQoL from baseline (T1), immediately after treatment (T2) and at six-month follow-up (T3). EPIC and EORTC-QLQ-C30 were used to assess LRTIs and HRQoL. Changes were analysed with *t*-tests, and associations with Pearson's correlation and multiple regression analyses.

Results Ninety-five participants (mean age 65 years, 52.6% men) were included. Scores for urinary and bowel symptoms, overall HRQoL, all function scales and the symptoms scales sleep, diarrhoea, pain and fatigue were significantly improved six months after treatment (*P*-range = 0.00–0.04). Changes were present already at T2 and maintained or further improved to T3. Only a weak significant correlation between changes in symptoms and overall HRQoL was found (Pearson *r*-range 0.20–0.27).

Conclusion The results indicate improvement of pelvic LRTIs and HRQoL following hyperbaric oxygen therapy, corresponding to minimal or moderate important changes. Cancer survivors with pelvic LRTIs and impaired HRQoL may benefit from undergoing hyperbaric oxygen therapy. Especially the reduced symptom-severity and improved social- and role function can influence daily living positively.

Trial registration ClinicalTrials.gov: NCT03570229. Released 2. May 2018.

Keywords Hyperbaric oxygen treatment · Pelvic malignancies · Pelvic radiotherapy · Quality of life · Side effects

Introduction

Radiotherapy is an important part of the multimodal curative treatment for pelvic cancers (e.g. urological, bowel and gynaecological cancers), but late radiation tissue injuries (LRTIs) may develop months or years later [1–3]. This includes cystitis, proctitis/enteritis, soft tissue necrosis, osteoporosis and fistulas, with symptoms including increased frequency, urgency and leakage of urine and faeces, diarrhoea, haematuria, osteoradionecrosis and pain [4, 5]. Treatment options for LRTIs are limited and consist mainly of prophylactic measures and symptomatic treatment (e.g. local or systemic pharmacological, surgical, physiotherapeutic training and behavioural adaptions) [6, 7]. However, hyperbaric oxygen therapy has shown positive effects on a range of LRTIs, including soft tissue necrosis, cystitis and proctitis, based on its ability to increase tissue oxygenation, stimulate angiogenesis and cellular regeneration and thereby induce revitalising and healing of damaged tissue [8–10].

As late effects from cancer treatment may affect all parts of cancer survivors' life, HRQoL has emerged as an important indicator of healthcare outcomes [11]. HRQoL is commonly defined as an individual, subjective, multidimensional, dynamic and interrelated concept consisting of physiological, psychological and social aspects of well-being

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[12, 13]. Distress from LRTI symptoms is therefore likely to influence the different dimensions and overall HRQoL negatively, while improvements in symptoms or any other dimension may promote HRQoL positively. Previous studies, including research from our group, show that pelvic LRTIs across cancer types impair cancer survivors HRQoL, with higher radiation-toxicity, combinations of chemotherapy and radiotherapy and higher symptom burden as risk factors [2, 14, 15]. Especially gastrointestinal symptoms seem to severely impair HRQoL [16]. Although some studies have demonstrated positive associations between symptom improvement and HRQoL after hyperbaric oxygen therapy, results are conflicting and more research is needed [8, 17, 18]. The goal of this study was to explore the development of symptom severity and HRQoL following hyperbaric oxygen therapy, as well as the associations between these over times.

Methods

Study design, recruitment and eligibility criteria

This study is part of a prospective longitudinal study with an overarching aim to increase the understanding of pelvic LRTIs in cancer survivors undergoing hyperbaric oxygen therapy (trial registration: ClinicalTrials.gov. NCT03570229). In the study at hand, we used a pretest–posttest design in order to assess changes in the development of pelvic LRTI symptoms and HRQoL after hyperbaric oxygen therapy.

The study sample was recruited from all cancer survivors with pelvic LRTIs (proctitis, cystitis, osteoradionecrosis, wounds and fistulas) assigned to hyperbaric oxygen therapy at The Norwegian National Unit for Planned Hyperbaric Oxygen Therapy between August 2018 and March 2021. Inclusion criteria were as follows: (a) pelvic radiation injury after intended curative radiation for pelvic cancer (prostate, gynaecological, urological, bowel and bone cancers); (b) LRTI symptoms from bowel, bladder or pelvic area, with signs of radiation injury verified by endoscopy or radiology; (c) $\geq$ 6 months from finished radiation; (d) aged $\geq$ 18 years. Exclusion criteria were as follows: (a) severe physical and/or mental comorbidity representing a contraindication for hyperbaric oxygen therapy including signs of active cancer; (b) insufficient language skills to complete study questionnaires; (c) previously treated with hyperbaric oxygen.

Hyperbaric oxygen therapy

During hyperbaric oxygen therapy, patients are placed in a pressure chamber and breathe 100% oxygen while exposed to elevated ambient pressure [9]. The side effects of hyperbaric oxygen therapy are usually minimal and temporary, limited mostly to mild middle ear barotrauma and transient visual disturbance [19]. In the present study, the participants received hyperbaric oxygen therapy in a monoplace chamber, breathing pure oxygen at a pressure of 2.4 atmosphere absolute for 90 min once a day (Monday–Friday) for six weeks.

Data collection

Data were collected by self-report questionnaires at baseline (T1), at the end of the six-week hyperbaric oxygen therapy course (T2), and at follow-up six months after treatment (T3).

Pelvic LRTI symptoms were measured with the Expanded Prostate Cancer Index Composite (EPIC), urinary and bowel domain [20]. This is a self-report questionnaire on urinary and bowel symptoms based on the past four weeks [21, 22]. Items are scored on Likert scales, with different response categories (0–4, 1–3, 1–4 and 1–5), and transformed to a 0–100 score [23]. A total score for each domain, as well as urinary sub scores (function, bother, incontinence, irritation/obstruction) and bowel subscales (function, bother), is calculated by the mean of all included items. A lower score indicates more severe symptoms. The instrument has shown to be valid, reliable and sensitive to assess urinary and bowel toxicity and complications from radiotherapy for prostate cancer and gynaecological malignancies (Cronbach's alpha range between 0.82 and 0.86) [20, 21]. The minimal clinically important changes in the EPIC urinary domain are stated to be between 6 and 9 points and between 4 and 6 points in the bowel domain [24]. In healthy controls, mean urinary scores of 89.5 (SD 11.2) and bowel scores of 92.5 (SD 8.7) have been reported [25].

HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30, version 3.0) [26]. This is a self-report questionnaire consisting of 30 questions. Items are scored on Likert scales with different response categories (1–4, 1–7) and transformed into a 0–100 score. The scores are combined into five functional scales (physical, role, emotional, cognitive and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, sleep, appetite loss, constipation, diarrhoea and financial difficulties) and one overall HRQoL scale [27]. A high score reflects a high level of function or overall HRQoL, while high scores on the symptom scales represent a high symptom burden associated with poor HRQoL. This instrument is widely used with documented robust psychometric properties (Cronbach's alpha range between 0.80 and 0.90 for most multi-item scales and single items) [28]. Changes are categorised as minimal clinically important if 5–10 points, moderate if 10–20 points and very much if > 20 points [27, 29]. Overall HRQoL scores

of the general population have been reported to be at mean 71.2 (SD 22.4) [28].

To ensure an acceptable study participation burden and that the questions were comprehendible and perceived relevant, the questionnaires were tested with four cancer survivors with pelvic LRTIs who were previously treated with hyperbaric oxygen and not participating in the study. They provided positive feedback on the relevance, content, comprehensibility and length of the questionnaires, and did not offer any suggestions for improvements.

Statistics

Descriptive continuous data are presented as means and categorical data as frequencies. All variables were normally distributed and determined by histograms and skewness. Cronbach's alpha was high for both instruments ($\alpha = 0.80–0.89$). The few missing data were not replaced.

Differences in pelvic LRTI symptoms and HRQoL between the time points T1, T2 and T3 were analysed by paired-samples *t*-test [30]. As a value of less than 80 points in the urinary and bowel domain of the EPIC indicates a significant symptom burden, separate analyses were performed for the respective subgroups (EPIC < 80 at T1) [31]. Development over time is presented as mean change of scores, with 95% confidence intervals.

To assess the correlation of the development in pelvic LRTI symptoms with overall HRQoL, Pearson's correlation analysis was used [32]. Multiple linear regression analysis was carried out to explore the relationship between changes in overall HRQoL as dependent variable and changes in pelvic LRTI symptoms as independent variables. *P*-values ≤ 0.05 indicate statistically significant findings. All analyses were performed using IBM SPSS Statistics for Windows version 26 [33].

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics, (Nothern Norway) (2018/706) and was conducted in compliance with the Declaration of Helsinki and the requirement for data processing and handling [34]. The participants received written information about the study, and all gave written consent.

Results

Sample characteristics

In total, 125 participants met the eligibility criteria, and 95 consented to participate in the study. Non-participation was related to decline ($n = 11$), withdrawal from treatment ($n = 8$), previous hyperbaric oxygen therapy ($n = 5$) and loss to follow-up ($n = 6$; one died, two did not return questionnaires and three discontinued treatment due to other illness). Sample characteristics are outlined in Table 1. All participants completed the six-week hyperbaric oxygen therapy course.

Pelvic LRTI symptoms

LRTI symptom scores during the study period are presented in Table 2.

At baseline, mean urinary and bowel total scores were clearly below the threshold generally regarded as

Table 1 Sample characteristics ($N = 95$)

	n (%)
Gender	
Male	50 (52.6)
Female	45 (47.4)
Age, years (mean (SD, range))	65 (11.6, 32–84)
Work status	
Sick leave/disability pension/retired	78 (82.1)
Full time/part time employment	17 (17.9)
Civil status	
Married/cohabiting	67 (70.5)
Single	28 (29.5)
Children under 18 years of age	
No	84 (88.4)
Yes	11 (11.6)
Medical characteristics	
Cancer site	
Prostate	49 (51.6)
Gynaecological	34 (36.0)
Rectum/anus	12 (12.4)
Referral diagnosis	
Cystitis and proctitis	54 (56.84)
Proctitis	25 (26.32)
Cystitis	11 (11.58)
Osteoradionecrosis pelvis	5 (5.26)
Type of cancer treatment	
Radiation only	61 (64.2)
Chemotherapy and radiation	34 (35.8)
Types of radiation	
External only	66 (69.5)
External and internal	29 (30.5)
Radiation dose, Gy (range)	
External	35.0–100.0
Internal	7.0–75.0
Months since radiation (median (range))	47.0 (7–511)

Abbreviations: *Gy*, Gray; *n*, total number of participants; *n*, number of participants; *SD*, standard deviation

Table 2 Urinary and bowel symptom scores and health-related quality of life scores at baseline and after hyperbaric oxygen therapy ($N = 95$)

HRQoL		Mean (SD) values			Mean (SD) values norm populations	Mean change from T1 to T3 (95% CI) *P*	
EPIC total urinary/bowel [a]		Baseline (T1)	Six weeks (T2)	Six months (T3)	Controls without cancer[c]	T1–T3	*P*
Urinary		70.0 (17.2)	72.9 (18.5)**	75.3 (17.3)	89.5 (11.2)	5.3 (2.3; 8.3)	< 0.00
Bowel		63.4 (13.4)	67.4 (14.7)**	70.0 (16.6)	95.5 (9.5)	6.7 (3.7; 9.6)	< 0.00
Urinary score < 80 at T1 ($n = 65$)		60.4 (11.8)	65.3 (17.0)***	70.5 (17.8)***		10.1 (6.4; 13.7)	< 0.00
Bowel score < 80 at T1 ($n = 79$)		60.1 (10.9)	64.9 (13.6)***	67.5 (16.0)		7.4 (4.1; 10.7)	< 0.00
EORTC QLQ-C30[b]					General population[d]		
Overall HRQoL		54.7 (21.7)	61.3 (19.9)**	61.8 (20.0)	71.2 (22.4)	7.1 (2.5; 11.7)	< 0.00
Function	Physical	69.3 (23.7)	71.9 (24.2)	72.8 (24.2)	89.8 (16.2)	3.5 (0.3; 6.7)	0.03
	Role	60.8 (35.1)	65.9 (28.7)*	67.2 (28.4)	84.7 (25.4)	6.4 (0.4; 12.4)	0.04
	Emotional	73.3 (24.6)	81.1 (21.3)***	77.4 (23.5)*	76.3 (22.8)	4.1 (0.1; 8.2)	0.04
	Cognitive	73.3 (27.0)	75.4 (23.7)	78.1 (23.6)	86.1 (20.0)	4.8 (0.5; 9.2)	0.02
	Social	48.8 (31.8)	62.2 (32.2)***	63.4 (31.7)	87.5 (22.9)	14.6 (8.4; 20.6)	< 0.00
Symptoms	Fatigue	49.1 (28.4)	46.8 (26.9)	40.1 (27.1)***	24.1 (24.0)	−9.0 (−4.1; −13.9)	< 0.00
	Pain	40.3 (32.2)	31.6 (29.7)**	31.1 (29.8)	20.9 (27.6)	−9.2 (−3.6; −14.9)	< 0.00
	Nausea/vomiting	9.4 (16.1)	5.4 (9.65)**	5.1 (11.3)	3.7 (11.7)	−4.3 (−1.1; −7.5)	< 0.00
	Dyspnoea	28.1 (29.1)	27.4 (27.6)	22.2 (27.4)*	11.8 (22.8)	−5.9 (−0.6; −11.2)	0.03
	Sleep disturbance	49.3 (3.3)	39.5 (32.0)***	36.2 (32.7)	21.8 (29.7)	−13.1 (−6.8; −19.3)	< 0.00
	Appetite loss	13.7(21.6)	13.4 (23.2)	10.1 (20.8)	6.7 (18.3)	−3.6 (−0.9; −8.1)	0.11
	Constipation	27.7 (32.1)	29.2 (44.4)	24.1 (28.7)	6.7 (18.4)	−3.6 (−10.4; 3.0)	0.27
	Diarrhoea	52.7 (35.3)	38.3 (31.8)***	40.9 (34.2)	7.0 (18.0)	−11.8 (−5.2; −18.3)	< 0.00
	Financial impact	19.3 (32.6)	14.7 (30.3)*	16.9 (32.8)	9.5 (23.3)	−2.6 (−7.6; 2.4)	0.31

Mean (SD) values derived from descriptive statistics. Mean change scores over time (95% CI, *P*) derived from *t*-tests

Abbreviations: *Bowel score < 80*, scoring less than 80 points at baseline in the bowel domain of the Expanded Prostate Index Composite; *CI*, confidence intervals; *EORTC QLQ-C30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *EPIC*, the Expanded Prostate Index Composite (scores 0–100); *HRQoL*, health-related quality of life (scores 0–100); *P*, the mean difference is significant at the 0.05 level; *SD*, standard deviation; *Urinary score < 80*, scoring less than 80 points at baseline in the urinary domain of the Expanded Prostate Index Composite

[a]EPIC, minimal clinically important change; urinary total, range 6–9 points; bowel total, range 4–6 points [24]

[b]EORTC QLQ-C30, minimal clinically important change, range 5–10 points; moderate change, range 10–20 points; very much change, range > 20 points [28]

[c]EPIC, control population [25]

[d]EORTC-QLQ C30, reference values manual [28]

*$p < 0.05$; **$p < 0.01$; *** $p < 0.001$ for significance level of differences between T1 and T2 and between T2 and T3

significant symptomatic [31]. At six-month follow-up, urinary and bowel symptom scores had increased with 5.3 and 6.7 points, respectively, which is within the range of minimal clinically important changes.

Participants scoring less than 80 points in the EPIC urinary or bowel domain at baseline scored approximately 20–30 points below this threshold, indicating the more severe symptom burden. In these groups, the urinary and

bowel symptoms improved with 10.1 and 7.4 points, respectively, an improvement above the minimal clinically important change. A statistically significant, but less pronounced improvement of urinary and bowel symptoms was found already at T2, at the end of hyperbaric oxygen therapy.

HRQoL

The changes in HRQoL scores are presented in Table 2. The participants reported severely impaired overall HRQoL at baseline compared to the general population (mean 54.7 vs. 71.2). Overall HRQoL scores increased with 7.1 points from baseline to six-month follow-up corresponding to a minimal clinically important change. Interestingly, this increase was present already at the end of the hyperbaric oxygen therapy period.

At baseline, all function scale scores were below the scores of the general population, which indicates clinically important impairments. All these scores improved significantly at six-month follow-up. The increase in social function of 14.5 points corresponds to a moderate change, and the increase in role function of 6.4 points corresponds to a minimal clinically important change.

All HRQoL symptom scale scores at baseline were above the scores of the general population, indicating more symptoms, but most scores improved significantly after treatment. At six-month follow-up, scores for sleep disturbance and diarrhoea had decreased with − 13.1 and − 11.8, respectively, which corresponds to a moderate change. Pain and fatigue scores decreased with − 9.3 and − 9.0, which corresponds to a minimal clinically important change.

The largest improvements within all functional dimensions and most symptom scales were observed at the end of the treatment and were maintained at six-month follow-up. Emotional function scores decreased between the end of the treatment to six-month follow-up at T3. However, the scores at T3 were still statistically significantly higher than the baseline scores; i.e. an improvement was maintained.

Associations between changes in LRTI symptoms and overall HRQoL

Associations between changes in LRTI symptoms and overall HRQOL are presented in Table 3.

Overall, the observed changes in urinary and bowel symptoms and overall HRQoL showed a significant, but weak positive correlation. In the multiple linear regression analysis, changes in urinary and bowel symptoms from baseline (T1) to six-month (T3) follow-up explained only 10% of the variance of overall HRQoL.

Discussion

The development of symptom severity and HRQoL following hyperbaric oxygen therapy and the associations between these have been subject to limited research. This study adds to this knowledge base, and the main findings are discussed below.

At a median time of nearly four years following radiotherapy, the participants reported severe urinary and bowel symptoms compared to healthy controls [25]. Six months after hyperbaric oxygen therapy, symptom severity was significantly improved. Similar results have been shown in previous studies [8, 17], although the changes shown in the present study were less pronounced than the changes found in the RICH-ART study by Oscarsson et.al [8]. This may be explained by the fact that the RICH-ART study included cancer survivors with radiation cystitis with more pronounced urinary symptoms, while our study included

Table 3 Multiple regression analysis of changes in EPIC urinary and bowel symptom scores and overall HRQoL from baseline (T1) to six-month follow-up (T3)

Change Overall HRQoL[a] from T1 to T3	Pearson *r* (*P*)	B (SE B)	*β* (*P*)	Multicol- linearity	r^2
Multiple regression					0.10
Change EPIC urinary total from T1 to T3	0.27 (0.00)	0.37 (0.2)	0.22 (0.07)	0.83	
Change EPIC bowel total from T1 to T3	0.20 (0.04)	0.17 (0.19)	0.11 (0.37)	0.83	
Correlation only:					
Change EPIC urinary score < 80 at BL from T1 to T3	0.24 (0.03)				
Change EPIC bowel score < 80 at BL from T1 to T3	0.23 (0.02)				

Abbreviations: *B*, unstandardised regression coefficient; *BL*, baseline; *EPIC*, Expanded Prostate Cancer Index Composite; *HRQoL*, health-related quality of life; *Multicollinearity*, tolerance factor; *P*, significance level; r^2, explained variance; *SE B*, standard error of the coefficient; *β*, standardised coefficient

[a]Dependent variable

individuals with a broader range of pelvic LRTI symptoms and consequently less severe urinary symptoms. Despite relatively small changes in urinary and bowel symptoms in our sample, the changes were noticeable (both clinically and statistically significant) to the participants. Previous research has shown that patients with pelvic LRTIs appreciate and welcome any improvements in symptom severity, even if small [35].

An interesting finding was that more than half of the participants (56.8%) scored less than 80 points on both urinary and bowel symptoms at baseline. This supports the notion that pelvic LRTIs may be part of a pelvic syndrome with simultaneous affection of multiple organs. Not unexpectedly, participants with the most severe symptoms (urinary or bowel < 80) at baseline reported a larger symptom improvement after treatment. This aligns to previous research [36], and may thus give an indication of which patients might benefit the most and should be referred to hyperbaric oxygen therapy. These findings are also important for healthcare professionals with respect to patient information and clarifying expectations of hyperbaric oxygen therapy.

At baseline, the participants reported severely impaired HRQoL parameters compared to the general population [28], suggesting that their daily life was highly compromised and that supporting interventions seemed needed. Six months after hyperbaric oxygen therapy, overall HRQoL, all function scales and most symptom scores were significantly improved and closer to those of the general population [28]. A noticeable (both clinically and statistically significant) improvement was particularly observed for social- and role function, which deals with severity and interference in daily life, for example related to being out of work, social activities and/or family life and household tasks [37]. It is likely that decreased symptom severity such as less diarrhoea, urge, pain and improved sleep quality increase the survivors' ability to be social active and increase their role participation. This is supported in literature stating that improvement in bodily and structural dimensions facilitates improvement in activity and participation [38]. However, despite a clinically significantly improvement in pain and diarrhoea, the scores were still high and clearly above the general population at six-month follow-up [28], underlining that the participants still experienced noticeable symptom burden.

Socioeconomic factors such as unemployment are important social determinants in health, where research particularly indicates a relationship between urinary incontinence and work status [39]. In our study, only a minority of the participants worked part- or full time. This can partly be explained by the participants' age and retirement. However, most participants in working age were on sick leave or disability pension. Research shows that physical late effects and fatigue after cancer treatment continue to impair work ability among cancer survivors, affect career and increase economical stress [40]. Consequently, improvement in symptom severity, social- and role function seem to be important factors in considerations of return to work and work ability.

In addition, the findings revealed that emotional function improved significantly at the end of hyperbaric treatment. Already during the therapy course, the participants experienced improvement in symptoms (e.g. diarrhoea and pain) which may have contributed to reduced emotional distress. Furthermore, they met other patients in the same situation or with even more severe symptoms. Being in an environment with peers may itself have influenced emotional function positively, due to sharing of common experiences, socialising and supporting each other. Cancer survivors often feel left alone with their late effects and peer support has shown to be important for promoting positive changes, improving psychosocial function, empowerment and HRQoL [41–43]. Daily professional follow-up for several weeks during the therapy course may also have had a positive impact on the participants' emotional function [42]. The professionals' expertise, offering a combination of knowledge and opportunities for asking questions to medical professionals, is an essential factor in promoting emotional functioning and making patients feel comfortable and safe [35, 41]. These notions seem to be supported by the fact that emotional function scores decreased from the end of the treatment to six-month follow-up. It seems that returning to daily life after the treatment may have increased a feeling of being left alone and perhaps also increased emotional stress regarding remaining symptoms and concerns of daily life [44, 45]. This highlights the importance of support in coping with emotional issues, which has a documented impact on both physical and psychological well-being in cancer survivorship [38, 42].

It is interesting that the largest improvements also for overall HRQoL, all functional scales and most symptom scales were observed already at the end of hyperbaric oxygen therapy. This could have several explanations. First, experiences of symptom relief during treatment and the fact that the participants had just completed a six-week treatment course may have given hope for a more normalised everyday life. Hope and anticipations are known to play a predominant role in HRQoL [12, 46]. Second, getting a specific and causal explanation of their symptoms may have felt relieving, and research has shown that knowledge is an essential factor in coping [47, 48]. These factors, in addition to peer support and the professional follow-up, as mentioned above, may also be plausible in contributing to increased HRQoL immediately after treatment. In sum, the circumstances around the treatment with hyperbaric oxygen, the medical care, social aspects and close professional follow-up may all have contributed to improvement of HRQoL as well as the treatment itself [35].

The changes in symptom severity were significantly positively associated with changes in overall HRQoL, but the correlation was surprisingly weak. It may be questioned if the symptom burden has as much direct influence on overall HRQoL as previously expected. Here, both the amount of improvement and the severity of the remaining symptoms may be relevant. Furthermore, overall HRQoL had improved the most already at the end of the treatment, while the urinary and bowel symptoms improved through the whole course of the study. However, the overall improvement of HRQoL was maintained at six-month follow-up. An interesting question is therefore whether the improvement in overall HRQoL would have still been maintained at six-month follow-up if the symptoms had not improved, although no conclusion can be drawn here.

Clinical implications

The results demonstrate a high symptom severity and impaired HRQoL before hyperbaric oxygen therapy and an improvement after the treatment. This may have several implications for cancer survivors, clinical practice and further research. Systematic assessment of pelvic LRTI symptoms and HRQoL after radiation should be part of routine follow-up, whereby impairments should be addressed with appropriate symptom management and supporting interventions. Second, the clinically significant improvement in symptoms and HRQoL parameters after hyperbaric oxygen therapy indicate that this treatment can be relevant for cancer survivors with pelvic LRTIs. In particular decreased symptom severity and improvement in social and role function can influence survivors' day-to-day functioning positively. This is important knowledge for healthcare professionals, and may provide a basis for realistic information to patients, with the study suggesting that those with the most severe symptoms may benefit the most from hyperbaric oxygen therapy. Third, the improvement in HRQoL during the therapy course emphasises the importance of follow-up of cancer survivors in addition to appropriate pelvic LRTI symptom management. The benefits of meeting fellow patients, exchanging experiences and supporting each other seem to be important factors during the treatment course. Consequently, organising the hyperbaric oxygen therapy course in a way that enables peer support is of importance. Furthermore, the findings may also indicate that healthcare professionals' support and follow-up promoted HRQoL positively.

In general, there is limited evidence on the use of hyperbaric oxygen therapy in survivors of pelvic cancer with LRTI, and more research in this field is highly needed. Measurements over a longer period of time would be useful to gain increased knowledge about long-term changes in symptoms and HRQoL after hyperbaric oxygen therapy. Additionally, mixed methods studies would be valuable in adding to the knowledge base within this field of research. The combination of quantitative data examine outcome variables with qualitative data exploring participants' experiences would offer greater insight into the use of hyperbaric oxygen therapy in this group of patients.

Limitations and strengths

The focus on a selected population referred to hyperbaric oxygen therapy limits the generalisation of the findings, and the pretest–posttest design did not allow for assessment of causal relationships. However, the instruments used to evaluate symptom burden and HRQoL are well recognised, and the high survey completion rates also strengthen the study. The study revealed clinical important and potential explanatory variables for improved symptom severity and HRQoL parameters.

Conclusion

The results from this study indicate a beneficial outcome after hyperbaric oxygen therapy in patients with pelvic LRTIs concerning both pelvic symptoms and HRQoL. The observed changes were of small magnitudes but correspond to clinically significant improvements in both urinary and bowel symptoms after six months, with a noticeable improvement already at the end of hyperbaric treatment. The participants also reported an early positive influence on HRQoL after the treatment that was maintained six months later. Especially overall HRQoL, social- and role function, sleep disturbance, diarrhoea, pain and fatigue were improved after hyperbaric oxygen therapy, which is likely to lead to improvement in the daily life of the affected individuals. Changes in pelvic LRTIs were to a relatively small degree associated with changes in HRQoL.

Abbreviations EORTC: European Organization for Research and Treatment of Cancer EPICthe Expanded Prostate Cancer Index Composite; HRQoL: Health-related quality of life; LRTIs: Late radiation tissue injuries

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Data availability De-identified data will be available from the study leader on reasonable request after the end of the project.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Committee of Medical and Health Research Ethics, Northern Norway, Registration number: 2018/706.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All participants signed informed consent regarding publishing their data.

Conflict of interest The authors declare no competing interests.

Clinical trial registration ClinicalTrials.gov Identifier: NCT03570229. Released 2. May 2018.

Standards of reporting The researchers followed established guidelines in preserving anonymity and safe handling of the data as well as STROBE guidelines for reporting.

References

1. Lawrie TA, Green JT, Beresford M et al (2018) Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev 1:12529. https://doi.org/10.1002/14651858.CD012529
2. Sipaviciute A, Sileika E, Burneckis A et al (2020) Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review. Int J Colorectal Dis. https://doi.org/10.1007/s00384-020-03595-x
3. Holch P, Henry AM, Davidson S et al (2017) Acute and late adverse events associated with radical radiation therapy prostate cancer treatment: a systematic review of clinician and patient toxicity reporting in randomized controlled trials. Int J Radiat Oncol Biol Phys. https://doi.org/10.1016/j.ijrobp.2016.11.008
4. Mamguem Kamga A, Dumas A, Joly F et al (2019) Long-term gynecological cancer survivors in Côte d'Or: health-related quality of life and living conditions. Oncologist. https://doi.org/10.1634/theoncologist.2018-0347
5. Chung YK, Lee YK, Yoon BH et al (2021) Pelvic insufficiency fractures in cervical cancer after radiation therapy: a meta-analysis and review. In Vivo. https://doi.org/10.21873/invivo.12356
6. Paquette IM, Vogel JD, Abbas MA et al (2018) The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the treatment of chronic radiation proctitis. Dis Colon Rectum. https://doi.org/10.1097/dcr.0000000000001209
7. Pascoe C, Duncan C, Lamb BW et al (2019) Current management of radiation cystitis: a review and practical guide to clinical management. BJU Int. https://doi.org/10.1111/bju.14516
8. Oscarsson N, Müller B, Rosén A et al (2019) Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. Lancet Oncol. https://doi.org/10.1016/s1470-2045(19)30494-2
9. Moon R (ed) (2019) Hyperbaric oxygen therapy indications. Best Publishing Company, North Palm Beach
10. Clarke RE, Tenorio LM, Hussey JR et al (2008) Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. Int J Radiat Oncol Biol Phys. https://doi.org/10.1016/j.ijrobp.2007.12.048
11. Jacobsen PB, Jim HSL (2011) Consideration of quality of life in cancer survivorship research. Cancer Epidemiol Biomarkers Prev. https://doi.org/10.1158/1055-9965.EPI-11-0563
12. Crosby RD, Kolotkin RL, Williams GR (2003) Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol. https://doi.org/10.1016/s0895-4356(03)00044-1
13 Davis S (2006) Rehabilitation. The use of theories and models in practice. Elsevier Health Sciences, London
14. Chambers SK, Ng SK, Baade P et al (2017) Trajectories of quality of life, life satisfaction, and psychological adjustment after prostate cancer. Psychooncology. https://doi.org/10.1002/pon.4342
15. Velure GK, Müller B, and Hauken MA (2022) Symptom burden, psychological distress, and health-related quality of life in cancer survivors with pelvic late radiation tissue injuries. Supp Care in Cancer 30(3):2477–2486. https://doi.org/10.1007/s00520-021-06684-x
16. Pan YB, Maeda Y, Wilson A et al (2018) Late gastrointestinal toxicity after radiotherapy for anal cancer: a systematic literature review. Acta Oncol. https://doi.org/10.1080/0284186X.2018.1503713
17. Pereira D, Ferreira C, Catarino R et al (2020) Hyperbaric oxygen for radiation-induced cystitis: a long-term follow-up. Actas Urol Esp (Engl Ed) 44(8):561–567. https://doi.org/10.1016/j.acuro.2020.03.010
18. Lauvrak V, Frønsdal KB, Ormstad SS et al (2015) Effectiveness of hyperbaric oxygen therapy in patients with late radiation tissue injury or diabetic foot ulcer. Knowledge Centre for the Health Services at the Norwegian Institute of Public Health (NIPH). Effectiveness of Hyperbaric Oxygen Therapy in patients with Late Radiation Tissue Injury or Diabetic Foot Ulcer - NIPH (fhi.no). Accessed 20 Jan 2021
19. Camporesi EM (2014) Side effects of hyperbaric oxygen therapy. Undersea Hyperb Med 41(3):253–257
20. Wei JT, Dunn RL, Litwin MS et al (2000) Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. https://doi.org/10.1016/s0090-4295(00)00858-x
21 Gil KM, Pugh SL, Klopp AH et al (2019) Expanded validation of the EPIC bowel and urinary domains for use in women with gynecologic cancer undergoing postoperative radiotherapy. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2019.04.682

22. Umbehr MH, Bachmann LM, Poyet C et al (2018) The German version of the Expanded Prostate Cancer Index Composite (EPIC): translation, validation and minimal important difference estimation. Health Qual Life Outcomes. https://doi.org/10.1186/s12955-018-0859-1
23. Wei JT. Scoring instructions for the expanded prostate cancer index composite (EPIC), Scoring Instructions for the (umich.edu). Accessed 23 Nov 2021
24. Skolarus TA, Dunn RL, Sanda MG et al (2015) Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. Urology. https://doi.org/10.1016/j.urology.2014.08.044
25. Expanded Prostate Index Composite, Characteristics of EPIC domain-specific summary and subscale scores for 112 controls without prostate cancer. Characteristics of EPIC domain-specific summary and subscale scores on controls without prostate cancer (umich.edu). Accessed 31 March 2021
26. Aaronson NK, Ahmedzai S, Bergman B et al (1993) The European-Organization-for-Research-and-Treatment-of-Cancer Qlq-C30 - a quality-of-life instrument for use in international clinical-trials in oncology. J Natl Cancer Inst. https://doi.org/10.1093/jnci/85.5.365
27. Fayers P, Aaronson N, Bjordal K et al. EORTC QLQ-C30 scoring manual (ed 3). Brussels, Belgium; Microsoft Word - SCmanual.doc (eortc.org). Accessed 24 Nov 2021
28. Scott NW, Fayers P, Aaronson NK et al (2008) EORTC QLQ-C30 reference values manual. Introduction (eortc.org). Accessed 24 Nov 2021
29. Osoba D, Rodrigues G, Myles J et al (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. https://doi.org/10.1200/JCO.1998.16.1.139
30. Veierød MB, Lydersen S, Laake P (2012) Medical statistics : in clinical and epidemiological research. Gyldendal akademisk, Oslo
31. Wei JT, Dunn RL, Sandler HM et al (2002) Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol. https://doi.org/10.1200/JCO.2002.20.2.557
32. Akoglu H (2018) User's guide to correlation coefficients. Turk J Emerg Med. https://doi.org/10.1016/j.tjem.2018.08.001
33. George D, Mallery P (2019) IBM SPSS Statistics 26 step by step: a simple guide and reference. Routledge, New York
34. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki--ethical-principles-for-medical-research-involving-human-subjects. Accessed 18 Jan 2021
35 Velure G, Müller B, Hauken MA a (2021) Experiences of patients with pelvic radiation injuries after cancer treatment undergoing hyperbaric oxygen therapy: a phenomenological-hermeneutical study. Nordic J Nurs Res. https://doi.org/10.1177/2057158521994405
36. Waldauf P, Jiroutková K, Krajčová A et al (2020) Effects of rehabilitation interventions on clinical outcomes in critically ill patients: systematic review and meta-analysis of randomized controlled trials. Crit Care Med. https://doi.org/10.1097/CCM.0000000000004382
37. Giesinger JM, Loth FLC, Aaronson NK et al (2020) Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol. https://doi.org/10.1016/j.jclinepi.2019.10.003
38. Jette AM (2006) Toward a common language for function, disability and health. Phys Ther. https://doi.org/10.1093/ptj/86.5.726
39. Wellam F, Ko Y, Oliffe JL et al (2020) Prostate cancer treatment and work: a scoping review. Am J Mens Health. https://doi.org/10.1177/1557988320979257
40. Boelhouwer IG, Vermeer W, van Vuuren T (2021) The associations between late effects of cancer treatment, work ability and job resources: a systematic review. Int Arch Occup Environ Health. https://doi.org/10.1007/s00420-020-01567-w
41. Hellbom M, Bergelt C, Bergenmar M et al (2011) Cancer rehabilitation: a Nordic and European perspective. Acta Oncol. https://doi.org/10.3109/0284186X.2010.533194
42. Nilsen J, Jensen L, Bohn N et al (2019) Å leve med og etter kreft. En undersøkelse blant kreftpasienter og pårørende i Kreftforeingenes brukerpanel. [To live with and beyond cancer. A study among cancer patients and relatives in the Cancer Society's user panel]. The Norwegian Cancer Society. Rehabiliteringsrapporten-2018_web.pdf (kreftforeningen.no). Accessed 20 Jan 2021
43. Kowitt SD, Ellis KR, Carlisle V et al (2019) Peer support opportunities across the cancer care continuum: a systematic scoping review of recent peer-reviewed literature. Support Care Cancer. https://doi.org/10.1007/s00520-018-4479-4
44 Page AE, Adler NE (2008) Cancer care for the whole patient: meeting psychosocial health needs. The National Academies Collection, Washington. https://doi.org/10.17226/11993
45. Graells-Sans A, Serral G, Puigpinós-Riera R (2018) Social inequalities in quality of life in a cohort of women diagnosed with breast cancer in Barcelona (DAMA Cohort). Cancer Epidemiol. https://doi.org/10.1016/j.canep.2018.03.007
46 Rustøen T (1995) Hope and quality of life, two central issues for cancer patients: a theoretical analysis. Cancer Nurs 18(5):355–361. Hope and quality of life, two central issues for cancer patients: a theoretical analysis - PubMed (nih.gov). Accessed 10 Jan 2021
47. Korstjens I, Mesters I, Gijsen B et al (2008) Cancer patients' view on rehabilitation and quality of life: a programme audit. Eur J Cancer Care. https://doi.org/10.1111/j.1365-2354.2007.00864.x
48. Hersch J, Juraskova I, Price M et al (2009) Psychosocial interventions and quality of life in gynaecological cancer patients: a systematic review: psychosocial interventions in gynaeoncology. Psychooncology. https://doi.org/10.1002/pon.1443

APPENDIX 1

HELSE BERGEN
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Symptomer på stråleskade

I de neste spørsmålene vil vi gjerne få vite litt mer om symptomene dine på stråleskader tilknyttet blære og tarmfunksjon:

EPIC score (Blærefunksjon)

*Besvar spørsmålene ut i fra hvordan du har hatt det **DE SISTE FIRE UKER**.*

1. Hvor ofte har du hatt urinlekkasje?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

2. Hvor ofte har du hatt blod i urinen?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

3. Hvor ofte har du hatt smerter eller svie ved vannlating?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

4. Hvilken påstand beskriver best din kontroll over blærefunksjonen?

Ingen kontroll på blæren overhodet…….. 1

Hyppig lekkasje…….. 2 (sett ring rundt ett svar)

Lekkasje av og til…… 3

Full kontroll…….. 4

5. Hvor mange inkontinensbind/ bleier bruker du i gjennomsnitt hver dag?

Ingen…… 1

1 per dag …… 2 (sett ring rundt ett svar)

2 per dag …… 3

3 eller fler per dag …… 4

6. Hvor stort problem har følgende plager vært for deg de siste fire uker?

	Ikke noe problem	Veldig lite problem	Lite problem	Middels stort problem	Stort problem
a. Urinlekkasje	0	1	2	3	4
b. Svie/smerte ved vannlating	0	1	2	3	4
c. Blod i urinen	0	1	2	3	4
d. Svak stråle	0	1	2	3	4
e. Nattlig vannlating	0	1	2	3	4
f. Hyppig vannlating (dagtid)	0	1	2	3	4

7. Sett under ett, hvor stort problem har du hatt med vannlatingen siste fire uker?

Ikke noe problem.....	1	
Veldig lite problem	2	(sett ring rundt ett svar)
Lite problem.....	3	
Middels stort problem	4	
Stort problem	5	

EPIC score (Tarmfunksjon)

*Besvar spørsmålene ut i fra hvordan du har hatt det **DE SISTE FIRE UKER**:*

1. Hvor ofte har du følt avføringstrang uten at det har kommet avføring?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

2. Hvor ofte har du hatt lekkasje av avføring?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

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3. Hvor ofte har avføringen vært løs (diaré)?

Aldri	1	
Sjelden	2	
Omtrent halvparten av gangene	3	(sett ring rundt ett svar)
Vanligvis	4	
Alltid	5	

4. Hvor ofte har det vært synlig blod i avføringen på papiret eller i toalettskålen?

Aldri	1	
Sjelden	2	
Omtrent halvparten av gangene	3	(sett ring rundt ett svar)
Vanligvis	4	
Alltid	5	

5. Hvor ofte har du hatt smerter i forbindelse med avføring?

Aldri	1	
Sjelden	2	
Omtrent halvparten av gangene	3	(sett ring rundt ett svar)
Vanligvis	4	
Alltid	5	

6. Hvor mange tømminger med avføring har du hatt på en typisk dag?

2 eller færre	1	
3-4	2	(sett ring rundt ett svar)
5 eller mer	3	

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7. Hvor ofte har du hatt smerter i magen eller endetarmen?

Mer enn én gang om dagen.....	1	
Omtrent én gang om dagen.....	2	
Mer enn én gang i uken.....	3	(sett ring rundt ett svar)
Omtrent én gang i uken.....	4	
Sjelden eller aldri.....	5	

8. Hvor stort problem har følgende plager vært for deg de siste fire uker?

	Ikke noe problem	Veldig lite problem	Lite problem	Middels stort problem	Stort problem
a. Sterk avføringstrang (haster å nå toalettet)	0	1	2	3	4
b. Hyppig avføring	0	1	2	3	4
c. Løs avføring	0	1	2	3	4
d. Lekkasje av avføring	0	1	2	3	4
e. Blod i avføringen	0	1	2	3	4
f. Smerter i mage/endetarm	0	1	2	3	4

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9. Sett under ett, hvor stort problem har du hatt med tarmfunksjonen de siste fire uker?

Ikke noe problem	1	
Veldig lite problem	2	
Lite problem	3	(sett ring rundt ett svar)
Middels stort problem	4	
Stort problem	5	

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Livskvalitet: EORTC QLQ-C30 (Versjon 3.0)

*Vi er interessert i hvordan du selv opplever din livskvalitet på ulike områder i livet. Vær snill å besvare **ALLE** spørsmålene ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar.*

	SPØRSMÅL	Ikke i det hele tatt	Litt	En del	Svært mye
1.	Har du vanskeligheter med å utføre anstrengende aktiviteter slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2.	Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3.	Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4.	Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5.	Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

	I LØPET AV SISTE UKEN:	Ikke i det hele tatt	Litt	En del	Svært mye
6.	Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7.	Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8.	Har du vært tung i pusten?	☐	☐	☐	☐
9.	Har du hatt smerter?	☐	☐	☐	☐
10.	Har du hatt behov for å hvile?	☐	☐	☐	☐
11.	Har du hatt søvnproblemer?	☐	☐	☐	☐
12.	Har du følt deg slapp?	☐	☐	☐	☐
13.	Har du hatt dårlig matlyst?	☐	☐	☐	☐
14.	Har du vært kvalm?	☐	☐	☐	☐

	I LØPET AV SISTE UKEN:	Ikke i det hele tatt	Litt	En del	Svært mye
15.	Har du kastet opp?	☐	☐	☐	☐
16.	Har du hatt treg mage?	☐	☐	☐	☐
17.	Har du hatt løs mage?	☐	☐	☐	☐
18.	Har du følt deg trett?	☐	☐	☐	☐
19.	Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20.	Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21.	Har du følt deg anspent?	☐	☐	☐	☐
22.	Har du vært engstelig?	☐	☐	☐	☐
23.	Har du følt deg irritabel?	☐	☐	☐	☐
24.	Har du følt deg deprimert?	☐	☐	☐	☐
25.	Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26.	Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27.	Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28.	Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐
28. b	Har din fysiske tilstand eller medisinske behandling påvirket ditt seksualliv?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1(svært dårlig) til 7 (utmerket) som best beskriver din tilstand:

29. Hvordan har din helse vært i løpet av den siste uka?

	1	2	3	4	5	6	7	
Svært dårlig	☐	☐	☐	☐	☐	☐	☐	Utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

	1	2	3	4	5	6	7	
Svært dårlig	☐	☐	☐	☐	☐	☐	☐	Utmerket

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Haukeland universitetssjukehus

Generell helse

*Vi vil gjerne vite hvordan du opplever at din generelle helse har vært de **siste to ukene**. Vær vennlig å besvare ALLE spørsmålene ved å sette kryss i ruten ved det svaret som passer best for deg:*

Har du i løpet av de siste par ukene:		0	1	2	3
1.	Vært i stand til å konsentrere deg fullt ut om alt du har drevet med?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig
2.	Ligget våken på grunn av bekymringer?	□ Ikke i det hele tatt	□ Ikke mere enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
3.	Følt at du tar del i ting på en nyttig måte?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig
4.	Følt at du er i stand til å ta beslutninger?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig
5.	Følt deg stadig under press?	□ Ikke i det hele tatt	□ Ikke mere enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
6.	Følt deg ute av stand til å mestre vanskeligheter?	□ Ikke i det hele tatt	□ Ikke mere enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
7.	Vært i stand til å glede deg over dine daglige gjøremål?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig
8.	Vært i stand til å møte problemer?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig
9.	Følt deg ulykkelig eller nedtrykt?	□ Ikke i det hele tatt	□ Ikke mer enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
10.	Mistet troen på deg selv?	□ Ikke i det hele tatt	□ Ikke mer enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
11.	Tenkt på deg selv som en verdiløs person?	□ Ikke i det hele tatt	□ Ikke mer enn vanlig	□ Heller mer enn vanlig	□ Mye mer enn vanlig
12.	Stort sett følt deg tilfreds, alt tatt i betraktning?	□ Mer enn vanlig	□ Samme som vanlig	□ Mindre enn vanlig	□ Mye mindre enn vanlig

APPENDIX 2

Intervjuguide HBO studien etter endt HBO behandling

Hovedspørsmål	Periode	Oppfølgingstema hvis nødvendig
Kan du fortelle meg hvordan du har opplevd å gjennomgå hyperbar behandling?	Behandlingsperioden	- Informasjon i forkant - Selve dykket - Lengde på hver behandling - Antall uker - Bivirkninger (øredotter, klaustrofobi)
Kan du fortelle meg hvordan du har erfart oppfølgingen av helsepersonellet underveis gjennom behandlingen?		- Informasjon og kunnskap - Imøtekommenhet - Støtte underveis i dykket - Leger/sykepleiere - Noe som er savnet - Råd til helsepersonellet
Kan du fortelle meg om du har opplevd noen endringer i dine symptomer underveis i behandlingen?		- Cystitt, proctitt - Forverring/forbedring
Nå er du ferdig med behandlingen. Hvilke forventninger har du nå til tiden framover ift dine stråleskader og hvordan disse kommer til å påvirke hverdagslivet ditt?	Tiden etter behandling	

APPENDIX 3

Message generated by ClinicalTrials.gov Protocol Registration and Results System

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University of Bergen Protocol Record 01012018,
Hyperbaric Oxygenation Treatment and Quality of Life,
has been reviewed and will be made public on ClinicalTrials.gov.

RECORDS USUALLY APPEAR ON ClinicalTrials.gov WITHIN 2 BUSINESS DAYS
of the receipt of this message.

Reminder: Review Board approval is required by the time patient recruitment
begins. Update the Review Board information in this record when approval
has been granted.

QUESTIONS? Contact us at: register@clinicaltrials.gov

Thank you,

PRS Team
ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT03570229

APPENDIX 4

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			07.05.2018	2018/706/REK nord
			Deres dato:	Deres referanse:
			20.03.2018	

Vår referanse må oppgis ved alle henvendelser

May Aasebø Hauken
Senter for krisepsykologi/Psykologisk fakultet

2018/706 HBOT studien: En mixed metode studie av pasienter med stråleskade sine symtomer, livskvalitet og erfaringer før, under og etter hyperbar oksygen behanling (HBOT)

Forskningsansvarlig institusjon: Universitetet i Bergen, Helse Bergen HF - Haukeland universitetssykehus
Prosjektleder: May Aasebø Hauken

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 19.04.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektomtale
Bakgrunn: Hyperbaric oxygen behandling (HBOT) anvendes i økende grad som en effektiv behandling for ulike stråleskader, men lite forskning har fokusert på pasienter med stråleskade i bekkenområdet sine symptomer, livskvalitet (QOL) og erfaringer før, under og etter HBOT behandling. Mål: Økt forståelse og kunnskap om pasienter med stråleskade i bekkenområdet som gjennomgår HBOT med fokus på symptomer, livskvalitet og erfaringer før under og etter HBOT. Metode: Longitudinelt mixed metode der kvalitative dybdeintervju samles inn ved oppstart og avslutning av HBOT, og kvantitative spørreskjema om QOL symtomer, mental helse og tilfredshet med pleie fylles ut 8 ganger fra oppstart til 1 år etter HBOT. Det planlegges å inkludere ca 200 pasienter som gjennomgår HBOT på Haukeland Universitetssykehus.

Om prosjektet
Deltakerne skal fylle ut et spørreskjema 8 ganger i løpet av et år; ved oppstart, etter 3 uker (midt i behandlingen), etter 6 uker (ved avsluttet behandling), deretter hver sjette uke det første halve året etter endt behandling i tillegg til 1 år etter endt behandlingen.

I tillegg til dette vil ca. 15 tilfeldig utvalgte pasienter bli intervjuet ved oppstart av behandlingen for å få kunnskap om hvordan de opplever å leve med en stråleskade.

I sin vurdering tok komiteen stilling til om prosjektet var framleggingspliktig.
Prosjektet skal primært se på livskvalitet og velvære (quality of life/well-being). Dette er argumenter som taler for at prosjektet ligger utenfor helseforskingsloven. Imidlertid vil man også undersøke hvordan symptomer på stråleskader utvikler seg over tid, noe som peker i retning av at prosjektet ligger innfor helseforskningsloven. I tillegg nevnes det bruk av «psychological distress» som sekundære endepunkter, som da kan sies å gi potensiell ny kunnskap om mental helsestatus hos disse pasientene. Samlet sett har komiteen kommet til at prosjektet ligger innenfor helseforskinglovens rammer.

Vedtak
Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2025, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til:may.hauken@uib.no; grete.velure@helse-bergen.no;post@uib.no

APPENDIX 5

A Longitudinal Mixed Methods Study on Pelvic Radiation Injured Cancer Patients' Symptoms, Quality of Life and Experiences Before, Along and After the Hyperbaric Oxygenation Treatment Trajectory

31.05.2019. Versjon 2.

HELSE BERGEN
Haukeland universitetssjukehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

«En mixed metode studie av pasienter med stråleskade i bekkenområdet som gjennomgår hyperbar oksygenbehandling - med fokus på symptomer, livskvalitet og erfaringer», forkortet til HBOT studien

Dette er et spørsmål til deg om å delta i et forskningsprosjekt, ved Helse Bergen HF/ Haukeland universitetssykehus i samarbeid med Senter for krisepsykologi ved Universitetet i Bergen.

Du er en av dem som har fått tilbud om hyperbar oksygenbehandling (HBOT) for stråleskade etter kreftsykdom i bekkenregionen. Vi tar kontakt med deg fordi vi ønsker å spørre deg om du vil delta i et forskningsprosjekt der formålet er å få mer kunnskap om hvordan pasienter med din type stråleskade opplever sine symptomer og hvordan disse påvirker din livskvalitet, samt hvordan hyperbar oksygenbehandling påvirker stråleskadesymptomene og livskvalitet gjennom og etter behandlingsforløpet. Vi vil her komme med mer informasjon om prosjektet, hva det vil innebære å delta og hvordan du kan bli med.

Kreftbehandling kan være en stor påkjenning og stråleterapi er en vanlig behandlingsform for mange krefttyper. Denne behandlingen rammer ikke kun kreftcellene, men påvirker også friske celler i hud, slimhinner og knokler. Resultatet kan bli alvorlige og varige bivirkninger, stråleskader. Ved stråleskader er sirkulasjonen i de små blodkarene forstyrret, vevet blir oksygenfattig og dermed mindre i stand til å reparere seg selv. Hyperbarmedisinsk oksygenbehandling øker oksygenkonsentrasjonen i blodet og bidrar til dannelse av nye blodkar i oksygenfattig vev. Dette gjør at vevet som er stråleskadd i større grad blir i stand til å reparere seg selv. Det foreligger imidlertid svært lite forskning på hvordan den enkelte pasient opplever hvordan stråleskadene påvirker deres hverdagsliv, og hvorvidt hyperbar oksygenbehandling påvirker symptomer og pasientens livskvalitet gjennom og etter behandlingen.

Hensikten med denne studien er derfor å øke kunnskapen om hvordan pasienter med stråleskade etter kreftsykdom i bekkenområdet opplever å gjennomgå hyperbar oksygenbehandling, og hvordan denne behandlingen påvirker symptomer på stråleskaden og livskvalitet over tid.

HVA INNEBÆRER PROSJEKTET?

Alle pasienter med stråleskade etter kreftsykdom i bekkenområdet som skal gjennomgå planlagt hyperbar oksygenbehandling, er over 18 år, ikke har gjennomgått tilsvarende behandling tidligere og kan skrive og snakke norsk blir forespurt om å delta i studien. Forskningsprosjektet går ut på at deltakerne fyller ut et spørreskjema som omhandler ulike aspekter ved din helse og livskvalitet 8 ganger i løpet av et år; ved oppstart, etter 3 uker (midt i behandlingen), etter 6 uker (ved avsluttet behandling), deretter hver sjette uke det første halve året etter endt behandling, i tillegg til 1 år etter endt behandling.

Det tar omlag 15 minutter å fylle ut spørreskjemaet hver gang. Det første spørreskjemaet fyller får du tilsendt og tar det med deg ferdig utfylt når du kommer til din første behandling. De to neste fyller du ut på sykehuset under behandlingen. Etter at behandlingen er ferdig, får du tilsendt nye spørreskjema med ferdig frankert svarkonvolutt vedlagt som du fyller ut og returnerer til avtalt tidspunkt.

I tillegg til dette vil ca. 20 tilfeldig utvalgte pasienter bli intervjuet ved oppstart og avslutning av behandlingen. Dette for å få kunnskap om hvordan de opplever å leve med en stråleskade, og for at vi skal få mer kunnskap om hvordan de opplevde selve behandlingsforløpet. Hvert intervju vil vare ca. 45. – 60. minutter. Intervjuene vil bli tatt opp på lydbånd og lagret på sikker forskningsserver. Intervjuene skrives uten identifiserbare opplysninger (navn, stedsnavn mv.) og lydbåndet blir slettet når de er transkribert (nedskrevet ord for ord).

Medisinske opplysninger som diagnose, stråledose, tidspunkt for strålebehandling og medikamenter vil bli hentet fra din journal.

Prosjektet er underlagt strenge regler både for etikk og trygg oppbevaring av data. Informasjonen som registreres om deg kan derfor bare brukes slik som beskrevet i hensikten med studien. Samtlige opplysninger som kommer fram gjennom prosjektet vil bli behandlet konfidensielt, slik at det ikke skal gå an å spore svarene tilbake til den enkelte deltaker. Av denne grunn blir alle opplysningene behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Alle deltakerne i prosjektet får derfor en tallkode som knyttes til spørreskjemaene og intervjuene. Spørreskjemaene, intervjuene og navnelisten som identifiserer tallkodene vil oppbevares i separate og nedlåste skap som bare forskerne har tilgang til. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

MULIGE FORDELER OG ULEMPER

Siden denne studien går ut på at du skal fylle ut spørreskjema som omhandler hvordan du opplever din egen situasjon, kan vi ikke se at det skal være noen skade eller negative

konsekvenser av å delta i et slikt forskningsprosjekt. Forskerne har dessuten inngående kjennskap og erfaring på forskningsfeltet.

Fordelene ved deltakelse er at du bidrar til økt kunnskap om pasienter i din situasjon og denne behandlingsformen.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte:

Prosjektleder May Aasebø Hauken på telefon 55 58 46 82 eller e-post: may.hauken@uib.no

Stipendiat Grete Velure på telefon 55 97 39 01 eller e-post: grete.velure@helse-bergen.no

Overlege Bernd Mueller på telefon 55 97 73 75 eller e-post: bernd.mueller@helse-bergen.no

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun prosjektleder May Aasebø Hauken, stipendiat Grete Velure, overlege Bernd Mueller og vitenskapelige assistenter Tone Merete Jansen og Synnøve Andersen som har tilgang til denne listen.

Prosjektet avsluttes i desember 2024. Opplysningene om deg vil bli anonymisert eller slettet fem år etter prosjektslutt.

DELING AV DATA OG OVERFØRINGER TIL UTLANDET

Hyperbarmedisin er et relativt lite fag, og av den grunn er det etablert forskningssamarbeid med andre Skandinaviske land. Ved å delta i prosjektet, samtykker du også til at spørreskjemaopplysninger kan overføres til utlandet som ledd i forskningssamarbeid og publisering. Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte.

OPPFØLGINGSPROSJEKT

Dersom det blir aktuelt med en oppfølgingsstudie vil vi kontakte deg igjen og be om nytt samtykke til dette. Dersom du ikke har hørt fra oss innen desember 2024 vil datamaterialet anonymiseres.

ØKONOMI

Studien er et samarbeid mellom Senter for krisepsykologi ved Universitetet i Bergen og Yrkesmedisinsk avdeling, Haukeland universitetssykehus, Helse Bergen HF som begge går inn med midler i prosjektet. Extrastiftelsen i samarbeid med Gynkreftforeningen har bidratt med midler til stipendiatstilling.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning 2018/706. Prosjektet er også registrert i ClinicalTrials.com (ID: 01012018).

Etter ny personopplysningslov har behandlingsansvarlig Universitetet i Bergen, Psykologisk fakultet i samarbeid med Helse Bergen HF, Haukeland universitetssykehus og prosjektleder May Aasebø Hauken et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med:

Prosjektleder May Aasebø Hauken på telefon 55 58 46 82 eller e-post: may.hauken@uib.no
Stipendiat Grete Velure på telefon 55 97 39 01 eller e-post: grete.velure@helse-bergen.no
Overlege Bernd Mueller på telefon 55 97 73 75 eller e-post: bernd.mueller@helse-bergen.no

A Longitudinal Mixed Methods Study on Pelvic Radiation Injured Cancer Patients' Symptoms, Quality of Life and Experiences Before, Along and After the Hyperbaric Oxygenation Treatment Trajectory

31.05.2019. Versjon 2.

Personvernombud ved institusjonen kan kontaktes på e-post: personvernombudet@helse-bergen.no

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Prosjektnummer

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver