Palliative pelvic radiotherapy of symptomatic prostate and rectal cancers

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”There seems to be a need for some consensus.
With such wide differences in treatment techniques and conflicting results
everybody cannot be right. Maybe everybody is wrong.
One cannot build another level of useful information
without having a solid ground to build on.”

– Gilbert Fletcher (1)

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1. PREFACE

1.1 Acknowledgements

The work for this thesis was carried out at the Center for Cancer Treatment in Kristiansand from 2009 to 2016 and was made possible by a generous grant from the South-Eastern Norway Regional Health Authority. In addition, the research department at Sørlandet Hospital supported me with much-needed extended funding, coffee, and encouragement, even as the years dragged on and on and on.

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I have been fortunate from the start. I met the right people in the right place at the right time. Thank you all for your kindness. Enjoy the book. I was assured that no one would actually read it.

Kristiansand, September 1, 2016
Marte Grønlie Cameron

1.2 Abbreviations

3D	Three-dimensional
5-FU	Fluourouracil
BPI	Brief Pain Inventory (short form)
CER	Comparative effectiveness research
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBM	Evidence-based medicine
EBRT	External beam radiotherapy
ECOG-PS	Eastern Cooperative Oncology Group performance status
EORTC	European Organisation for Research and Treatment of Cancer
GTV	Gross tumor volume
Gy	Gray
HRQOL	Health-related quality of life
IMRT	Intensity-modulated radiotherapy
LUTS	Lower urinary tract symptoms
PICO	Participants, interventions, comparisons, outcomes
PRO	Patient-reported outcome
PTV	Planning target volume
QLQ	Quality of life questionnaire
QLQ-C30	Quality of life questionnaire – Core 30
QLQ-CR29	Quality of life questionnaire – Colorectal 29
QLQ-PR25	Quality of life questionnaire – Prostate 25

1.3 List of papers

Paper 1:

Cameron MG, Kersten C, Guren MG, Fosså SD, Vistad I. **Palliative pelvic radiotherapy of symptomatic incurable prostate cancer - a systematic review.** Radiotherapy and Oncology. 2014 Jan; 110(1): 55–60.

Paper 2:

Cameron MG, Kersten C, Vistad I, Fosså S, Guren MG. **Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review.** Acta Oncologica. 2014 Feb; 53(2): 164–73.

Paper 3:

Cameron MG, Kersten C, van Helvoirt R, Rohde G, Fosså SD, Vistad I. **Patient reported outcomes of symptoms and quality of life among cancer patients treated with palliative pelvic radiation: a pilot study.** BMC Research Notes. 2011 Jul 21; 4:252.

Paper 4:

Cameron MG, Kersten C, Vistad I, van Helvoirt R, Weyde K, Undseth C, Mjaaland I, Skovlund E, Fosså SD, Guren MG. **Palliative pelvic radiotherapy for symptomatic incurable prostate cancer – A prospective multicenter study.** Radiotherapy and Oncology. 2015 Jun; 115(3): 314–20.

Paper 5:

Cameron MG, Kersten C, Vistad I, van Helvoirt R, Weyde K, Undseth C, Mjaaland I, Skovlund E, Fosså SD, Guren MG. **Palliative pelvic radiotherapy for symptomatic incurable rectal cancer – A prospective multicenter study.** Acta Oncol. 2016 Jun 22; 1–8.

2. INTRODUCTION

2.1 The impact of cancer

The incidence and prevalence of cancer are rising globally, primarily due to the world's aging population (2). In addition, the developing world has adopted some of the unfavorable, cancer-promoting lifestyles of the developed world, thereby further increasing the scope of the problem (3). Prostate and rectal cancers are among the most common cancers in Norway (4). Improved treatment in recent decades has led to increased numbers of patients both surviving and living with these cancers (5, 6). As a consequence, their prevalence, particularly among the elderly, is likely to continue to rise in years to come (4).

2.2 Incurable cancer

Despite significant advances in treatment, roughly half of all patients in industrialized countries who are diagnosed with cancer will ultimately succumb to the disease (2). Cancer is often deemed incurable due to the presence of locally advanced or metastatic disease, but major comorbidity may also prohibit a curative treatment approach.

Patients in whom a malignancy cannot be completely eradicated may receive treatments intended to prolong life, delay the onset of symptoms, relieve established symptoms, or achieve a combination of these. In such contexts, chemotherapy, hormonal manipulation, radiotherapy, and surgery are the commonly used tumor-targeted measures. In addition, an array of symptomatic interventions that do not inhibit tumor growth are available. These include surgical interventions such as diverting colostomies and lesser interventions such as ureteric stent placement as well as analgesic, anti-emetic, anti-inflammatory and other medications.

Although the potential for cure may not exist, systemic cancer therapies may induce remissions or temporarily halt cancer progression and thus slow clinical decline. In some scenarios, a clear distinction between therapeutic objectives of cure, prolonged survival, local control and symptomatic relief may be difficult to establish and treatment indications may overlap. This is not uncommon in cases of androgen deprivation therapy in which patients with incurable prostate cancer can live for many years with their malignancy (7).

As improved multimodal oncologic management continues to push the boundaries of curative treatment, grey zones develop in the transition from curative to palliative treatment intent. This is exemplified by the case of oligometastatic rectal cancer where patients previously considered incurable, may now be cured by modern, aggressive approaches such as resection of liver metastases (8). As a consequence, the precise definition of incurable cancer and the palliative context is increasingly ambiguous (9).

Clinicians' sound prognostication and understanding of therapeutic options within a palliative approach are necessary to optimally and realistically tailor treatment to each unique clinical scenario. As malignancy progresses, functional status declines and prognosis worsens, aims of palliative interventions change accordingly. Treatments that are appropriate for patients with life-expectancies of months to years may not be appropriate for those who are only expected to live for weeks (Figure 1).

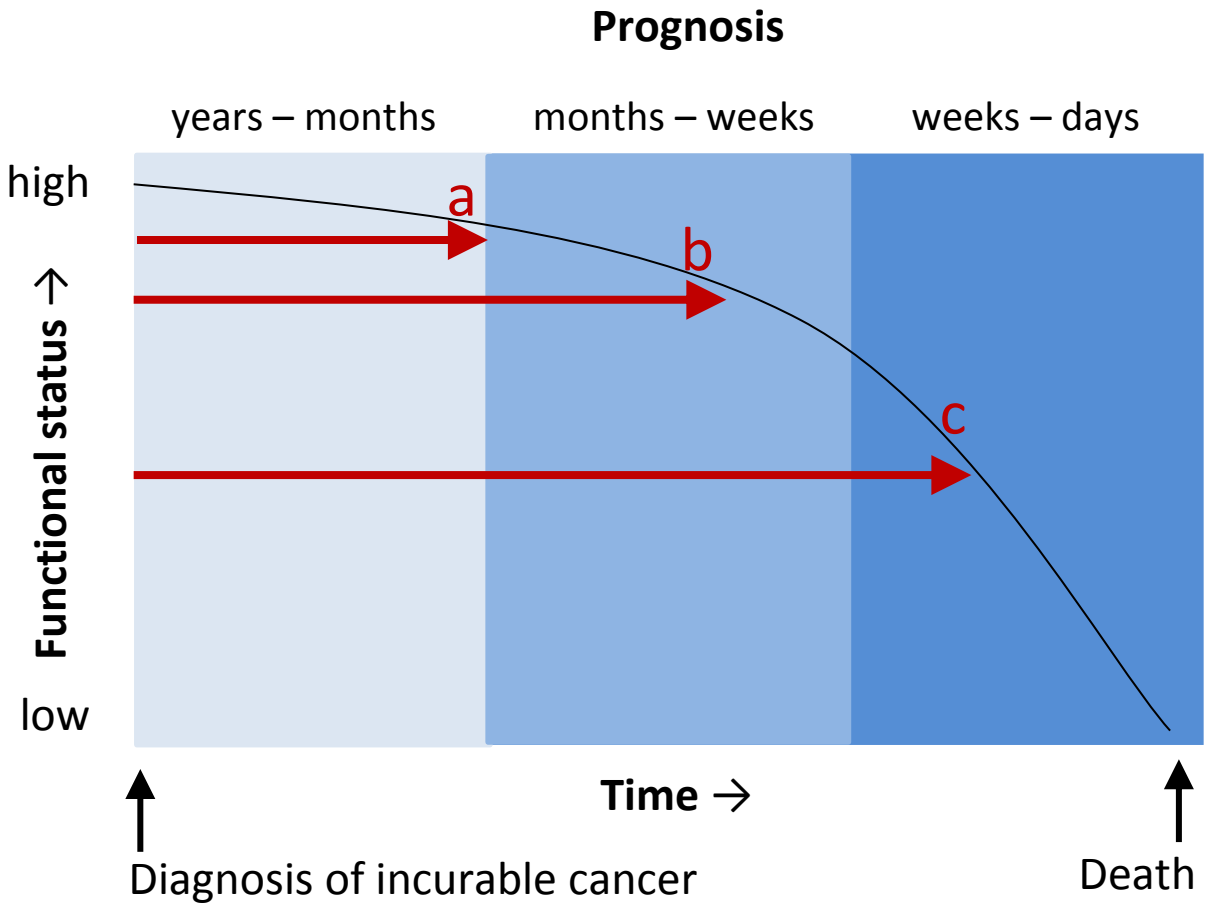

Figure 1: Illness trajectory for incurable cancer (*adapted from Lynn J, Adamson DM. Living well at the end of life. Adapting health care to serious chronic illness and old age. Washington: Rand Health 2003* (10)) divided into three hypothetical prognostic phases. Arrows roughly indicate which time-frames typically are appropriate for different palliative interventions, including therapies that aim to: a) alter the course of the disease, leading to prolonged survival and delayed onset of symptoms, b) palliate and delay the onset of cancer-related symptoms without affecting prognosis, and c) palliate symptoms without necessarily otherwise influencing the clinical course.

2.3 Pelvic tumors

Malignant pelvic tumors; most often prostate, rectal, bladder or gynecological cancers; may consist of primary tumors (Figure 2), local recurrences, and/or enlarged pelvic lymph nodes or tumor-deposits. With the many organs and traversing structures in the pelvic space, modest tumor growth may lead to clinically significant symptoms. Tumor progression may result in pain, bleeding, discharge, altered bowel and bladder function, visceral obstruction, sexual dysfunction, fistula formation, infection and lymphedema; all of which can worsen health-related quality of life (HRQOL) (11, 12). Constellations of pelvic symptoms often present together because the enlarging cancerous mass invades and disturbs the function of several structures simultaneously (Figure 2).

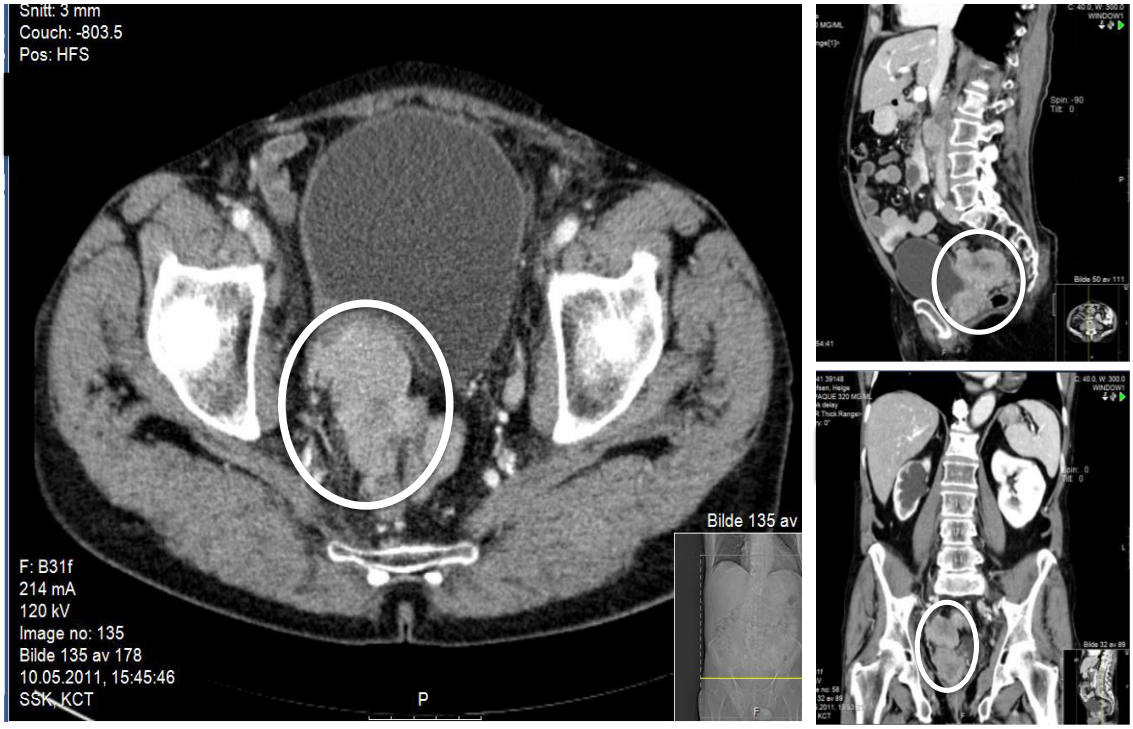

Figure 2: Computerized tomography scan of a study patient (PallRad1 study) with a large prostate tumor affecting neighboring structures including bladder and rectum.

2.4 Prostate cancer

Prostate cancer is the second most common cancer among men world-wide, ranking first in developed countries (2). 4889 new cases of prostate cancer were diagnosed and 1093 men died of the disease in Norway in 2014. The relative 5-year survival for Norwegian men with prostate cancer reached 91% in the period 2010–2014 (Figure 3). However, patients with metastatic prostate cancer at the time of diagnosis had a 5-year relative survival rate of only 34% (4).

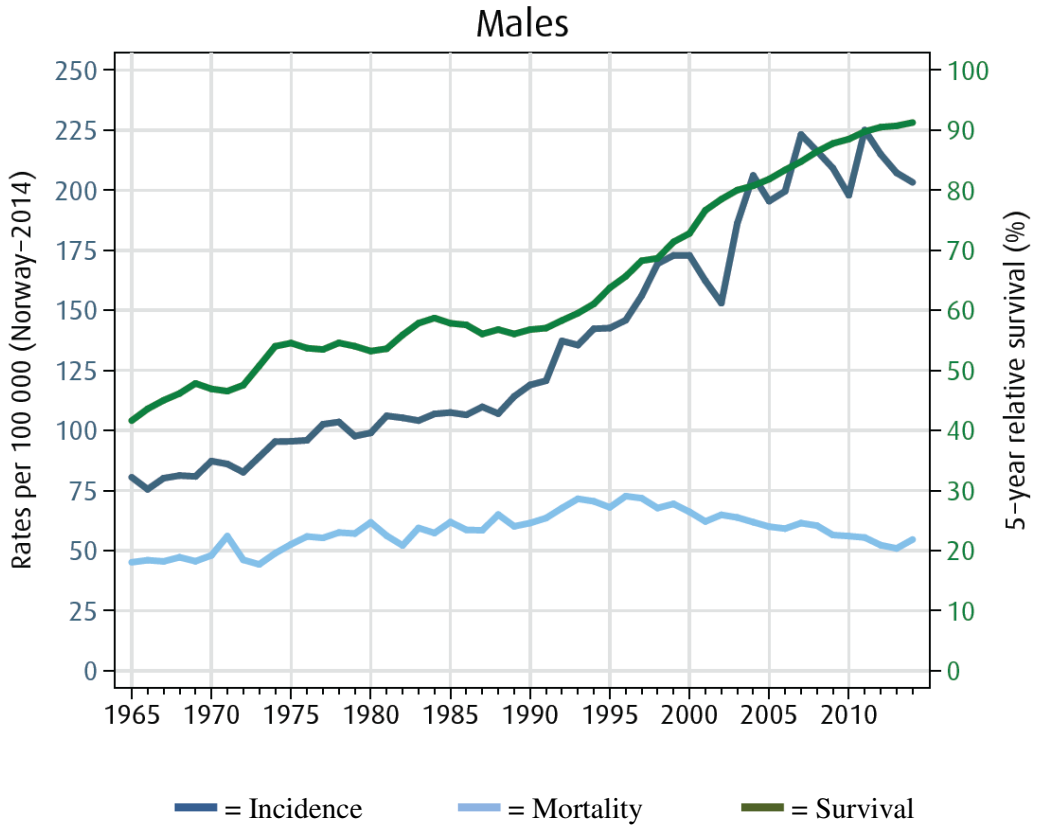

Figure 3: Trends in incidence and mortality rates and 5-year relative survival proportions for prostate cancer in Norway (4).

Curative treatment of prostate cancer consists of both surgical and radiotherapeutic approaches. Radiotherapy may be delivered externally, internally, or in combination, with or without hormonal manipulation. Prostate cancer may behave relatively indolently and in many men with advanced age, is unlikely to cause symptoms during their lifetime. Risking side-effects of immediate curative treatment may not always be judicious, and active surveillance may be preferred in order to delay or avoid the burdens associated with curative treatments (13).

First line palliative systemic treatment of prostate cancer most often consists of androgen deprivation therapy using either surgical (bilateral orchiectomy) or medical approaches. Medicines used include anti-androgens (flutamide, bicalutamide) and gonadotropin releasing hormone agonists (leuprolide, goserelin, buserelin, triptorelin), either alone or in combination. In most cases, androgen deprivation and ultimately castration can halt prostate cancer progression for several years. Once castration alone fails to control the prostate cancer (usually after 2–3 years), it is said to be castration-resistant, and additional therapeutic approaches are required for tumor-control (14).

Chemotherapy (docetaxel, cabazitaxel), more advanced hormonal manipulation (abiraterone, enzalutamide), and/or bone-targeted agents (zolendronic acid, denosumab, radium 223) may then be recommended for systemic control (6).

Palliative systemic treatment of castration resistant prostate cancer (CRPC) is indicated to improve survival and HRQOL (15-17). The majority of studies on which these treatment recommendations are based focus on survival time and time to objectively measurable (by laboratory test or radiologic imaging) tumor progression in patients with metastatic disease. Although many major trials have evaluated symptoms and HRQOL secondarily, effect on the primary tumor and its resultant pelvic symptoms cannot be specifically extrapolated from the reported results (6).

The prevailing clinical manifestation of CRPC in most patients who have metastatic disease is painful skeletal metastases (11), for which systemic therapy and/or palliative radiotherapy are often indicated (18). Systemic treatments have not been shown to have a positive impact on locally advanced CRPC. However, patients with CRPC who have only pelvic tumor manifestations may be good candidates for relatively high doses of non-curative radiotherapy (in the range of 40–60 Gray (Gy)). In selected patients, this has demonstrated prolonged local control with acceptable toxicity and should be considered in patients with little or no extra-pelvic manifestations of prostate cancer, independent of the presence of symptoms (19-21).

However, in approximately 15% of patients with CRPC, symptoms from a soft-tissue pelvic tumor dominate the clinical picture (22). It is these patients, along with a similar group of patients with rectal cancer that are the focus of the palliative pelvic radiotherapy described in this thesis.

2.5 Rectal cancer

Rectal (including rectosigmoid) cancer constitutes the 6th and 7th most common cancer types among Norwegian men and women, respectively. 1365 new cases of rectal or rectosigmoid cancers were diagnosed in Norway in 2014 and in the same year, 408 Norwegians died of the disease. The relative 5-year survival for rectal (including rectosigmoid) cancer in Norway was 66% in the period 2010–2014 (Figure 4). However, patients with metastatic disease at the time of diagnosis had a 5-year survival rate of only 18-19%. (4) The vast majority of these patients live with the burden of managing symptomatic incurable cancer from the time of diagnosis throughout the remainder of their lives. Approximately 40% of patients diagnosed with localized rectal cancer develop metastases at a later stage (23).

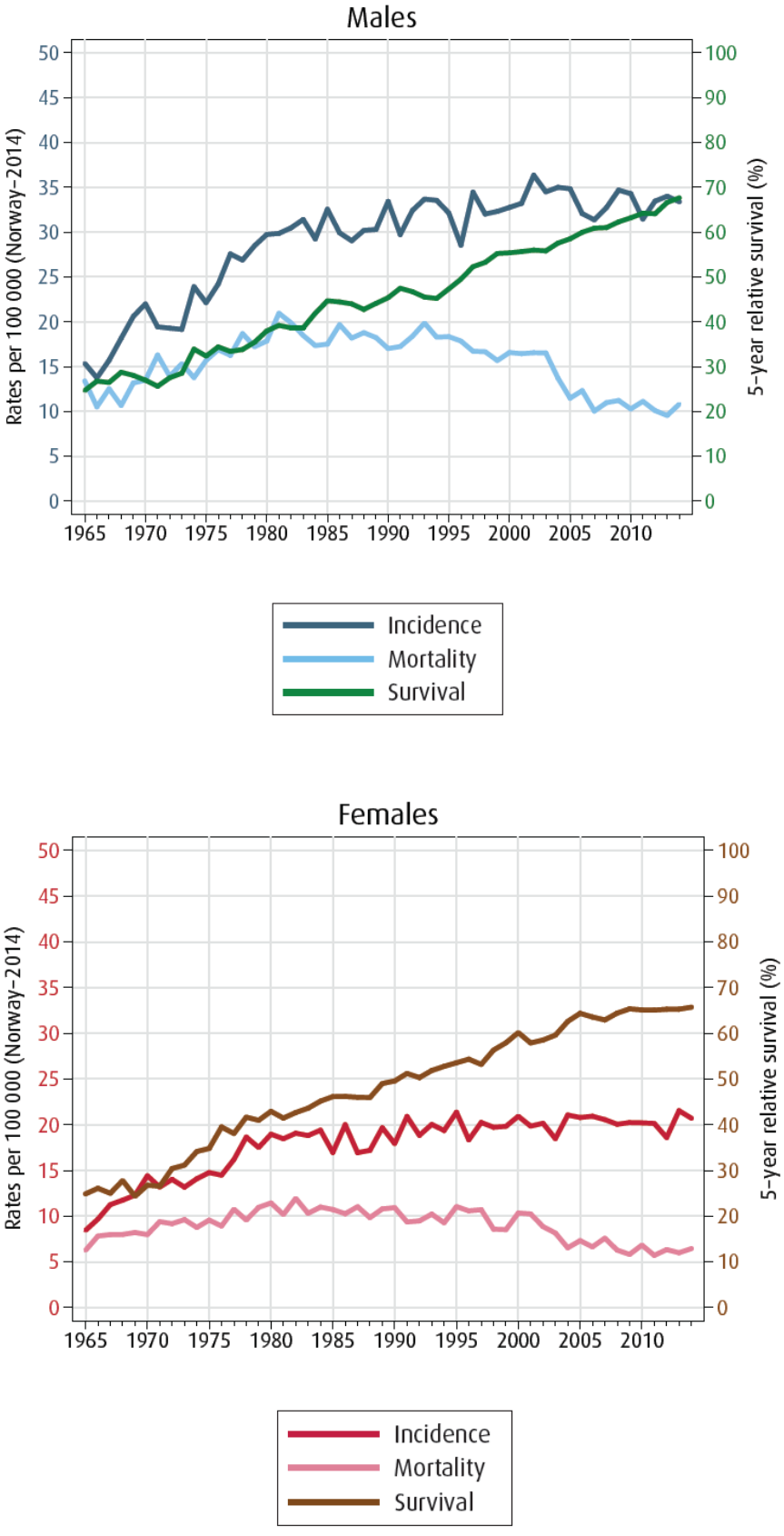

Figure 4: Trends in incidence and mortality rates and 5-year relative survival proportions for rectal (including rectosigmoid) cancer in Norway (4).

Surgery is the cornerstone of curative treatment of rectal cancer. Surgical procedures range from local excision in early stages to total pelvic exenteration combined with chemoradiotherapy in the most advanced cases.

Pelvic radiotherapy in combination with surgery has been widely studied with respect to curative treatment of rectal cancer (24). Currently, there are two principal approaches; one is a long-course of chemo-radiotherapy using a fluorouracil (5-FU) based regimen and daily fractions of up to 2 Gy to a total of approximately 50 Gy, the other consists of a short course of radiotherapy (without concomitant chemotherapy) delivering 5 consecutive daily fractions of 5 Gy to a total of 25 Gy. Both of these approaches are effective in reducing local recurrence rates and are considered to have an acceptable toxicity profile (25). Which approach to recommend in each clinical scenario should be decided by a multidisciplinary team, based on patient, tumor and treatment characteristics.

Although a primary tumor may be technically operable and even curable, the best course for a given patient may not involve its removal. Factors such as advanced age, significant comorbidity, risk of complications, the presence of metastatic disease, patient wishes and limited life-expectancy may preclude this approach. In some patients, the rectal tumor may remain relatively asymptomatic with systemic treatment and therefore does not require removal (26).

Chemotherapy (5-FU, capecitabine, oxaliplatin, irinotecan) and targeted therapies (the epithelial growth factor receptor inhibitors cetuximab and panitumumab and vascular endothelial growth factor receptor inhibitor bevacizumab) constitute standard palliative systemic treatment of rectal cancer in Norway today (27). These treatments generally demonstrate greater efficacy and tolerability when used early in the course of the disease (Figure 1). With improved systemic therapy and an increasingly aggressive approach to oligometastatic disease (surgery, local ablation), survival times among patients, even with metastases considered incurable, have increased to a median of 2 years in study patients (23). However, as new treatment options find their way into the increasingly complex armamentarium of cancer therapeutics, their prioritization and chronology within the management algorithm pose a challenge.

Palliative pelvic radiotherapy of rectal cancer to relieve or delay the onset of symptoms of a locally advanced rectal cancer or recurrence is a highly variable practice that is poorly researched and without established recommendations. Treatment strategies range from delivery of single fractions of 8 Gy to fractionated total doses over 50 Gy, sometimes in combination with radiosensitizing chemotherapy. Practices vary across different treatments centers based primarily on local traditions and extrapolation from evidence in similar clinical scenarios.

2.6 Radiotherapy

Radiotherapy for the treatment of cancer had its inception in the 1890's, and by 1913, routine delivery was possible. In the 1940's, megavolt radiotherapy became available, allowing deep tissue penetration, including delivery into the pelvis. Without technology for treatment planning, however, radiotherapy of deep structures such as the prostate gland and rectum was an imprecise practice with significant toxicity (28).

Initially, radiotherapy was primarily given with a single or a few large fractions (referred to today as hypofractionation), and was chiefly aimed at symptom palliation. In the 1930's, it became apparent that smaller doses given repeatedly to a higher total dose resulted in better tumor control and

decreased late toxicity. Consequently, practice trended toward longer courses and higher total doses, increasing the potential for cure. At roughly the same time, radiation treatment planning became feasible, making it possible to deliver maximal radiotherapy dose to a target while sparing organs at risk (28). This principle developed to encompass 3D treatment planning and intensity-modulated radiotherapy (IMRT), which are standard practice in much of the world today. These advanced planning systems are technically demanding, but allow for higher radiotherapy doses to be given with greater precision to the tumor while sparing normal tissues.

Roughly 50% of patients with cancer are estimated to benefit from radiotherapy at some point during the course of their disease (29). However, the number of patients who receive radiotherapy is considerably lower. This discrepancy is partly due to geographical and resource constraints and therefore varies between countries. There are also regional differences within countries due to the need for specialized equipment and staff (30). Although radiotherapy utilization rates in Norway increased when capacity increased in the 1990's, these rates are still considered suboptimal (31, 32).

2.7 Palliative radiotherapy

Nearly half of radiotherapy courses are given with palliative intent (33, 34). Palliative radiotherapy is often utilized when systemic treatments are not recommended, when these treatments have been exhausted, or in order to target an anatomically localized problem. External beam radiotherapy has been reported to palliate symptoms of advanced cancer in 50–90% of patients with relatively little toxicity and inconvenience (35). It is a cost-efficient procedure compared to many other palliative interventions (34).

In contrast to radiotherapy given with curative intent, palliative radiotherapy is generally given at a lower total dose and is often hypofractionated. In this case, the primary aim is to achieve relief or delayed onset of symptoms without burdening the patient with long treatment series and major side effects that accompany traditional higher-dose, long radiotherapy courses.

Palliative radiotherapy may make use of more limited treatment volumes than curative radiotherapy as areas at risk of micrometastases typically are not part of the target volume. When the aim of radiotherapy is maximal symptomatic improvement with the least possible toxicity, treatment fields can be limited to symptom-causing, tumor-containing tissue; thereby limiting margins, decreasing field size and consequently reducing toxicity.

Whereas there are no benchmarks for optimal rates of palliative radiotherapy, there are multiple reasons for its underuse, in addition to the barriers mentioned above. These include comorbidity, advanced age, and the perceived burden for patients (including travel and time spent away from home) (36). Uncertainty regarding the potential benefits of palliative radiotherapy also presents an important barrier to its use (37).

Patient selection and timing of radiotherapy are paramount. Palliative effects of radiotherapy become apparent at variable time points during or after treatment. These effects may be delayed by several weeks, depending on the target symptom, radiotherapy dose, and on biological characteristics of the tumor being irradiated. In this context, no efforts to lessen the burden of radiotherapy justify its use if the patient does not live long enough to benefit.

2.8 Toxicity of pelvic radiotherapy

In contrast to systemic tumor-targeted treatment, the majority of toxicity related to radiotherapy is localized to the anatomical region being treated. In cases of prostate and rectal cancers, tissues most at risk include the lower gastrointestinal and urinary tracts, reproductive organs, skin, nerves and the pelvic skeleton.

Damage to pelvic tissues may lead to acute toxicities including enteritis, proctitis, cystitis, vulvovaginitis and perineal dermatitis. Late toxicities(38), arbitrarily defined as appearing 90 or more days after radiotherapy start (39), are predominantly bladder and bowel dysfunction (including urinary and anal incontinence), infertility, sexual dysfunction (dyspareunia and both erectile and ejaculatory dysfunction), and pelvic pain due to nerve damage or microfractures. Existing reports of toxicity resulting from pelvic radiotherapy are based primarily on treatment given with curative intent (25, 40, 41). There is limited scientific data regarding the extent of toxicity after palliative pelvic radiotherapy.

In general, the higher the radiotherapy dose and shorter the delivery time of a radiotherapy course, the greater the potential for tissue damage. However, normal tissue injury after radiotherapy also depends on tissue characteristics. Tissues with rapid turnover (those of hematopoietic and epithelial origin) are prone to acute injury, often yielding symptoms within days to weeks, which in turn also usually resolve within weeks. Tissues with slow turnover are more prone to late injury that may become clinically apparent months to years after the radiotherapy (42). As such, many patients prescribed palliative radiotherapy do not live long enough to experience late toxicities and complications.

2.9 Evaluation of palliative treatment

Survival times and objective measures of tumor response are the customary outcome measures reported for oncologic trials. Objectives measures may include radiologically assessed tumor regression or surrogate markers thereof, such as prostate-specific antigen levels for prostate cancer and carcinoembryonic antigen levels for rectal cancer. These are important clinical outcomes and they have advantages in a research context, as they yield objectively measured data with limited room for misinterpretation or bias. Nonetheless, clinical practice is not as simple as these outcomes suggest. Patient well-being is highly subjective and of vital clinical importance, particularly in contexts where treatment is given without the possibility of cure. In many such cases, prolonged survival may not be possible and treatment intended to cause tumor shrinkage may not be justified without also improving patient well-being.

Patient well-being during and after oncologic treatment is a relevant research question in both curative and palliative contexts and it is more accurately and reliably assessed by the patient him or herself than by physicians or other third-parties (43). Patient-reported outcome (PRO) is the term used to describe “a measurement of any aspect of a patient's health status that comes directly from the patient” (44). PROs may examine various aspects of patient well-being and take different forms and have different levels of complexity, ranging from simple “yes/no” assessments to the use of complicated, multidimentional instruments. The unifying principle in the PRO term is that it is patients themselves that provide a direct assessment, without interpretation by intermediaries. This has become the preferred approach in oncology research (45).

HRQOL is one example of a complex PRO. It describes a multidimentional construct including physical and psychosocial domains and refers to the impact that illness and treatment have on these areas. HRQOL is an important outcome in both research and clinical practice because it describes patients' personal experiences of the effects of both disease and treatment; something that is difficult, if not impossible, for a third party to accurately assess and describe (43). However, HRQOL measurement and reporting have several limitations, not least of which is requiring sick patients to repeatedly report their state of health in a systematic, often complicated manner.

A multitude of tools have been developed for research using PROs, including several that examine HRQOL (46). The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30, v.3.0) core questionnaire has been developed and validated for use among cancer patients world-wide (47). It covers aspects of HRQOL considered to be relevant to most cancer patients, and includes five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain and nausea, and vomiting), a global HRQOL scale as well as five symptoms common among cancer patients (dyspnoea, anorexia, insomnia, constipation, and diarrhea) and perceived financial impact of the disease and treatment. This questionnaire has been specifically validated for use among Norwegian patients with heterogeneous cancer diagnoses (48) and among those receiving palliative radiotherapy (49).

The Brief Pain Inventory (BPI) is another PRO tool, which has robust psychometric properties (50, 51), and is recommended by the Working Group of the European Association of Palliative Care for the measurement of pain and pain-related problems (52). It provides information about the nature, location (using a body map), intensity and history of pain, the degree of pain relief offered by medications, as well as pain's interference with function and well-being.

2.10: Evaluation and synthesis of medical evidence

When looking to medical literature for guidance, clinicians are often confronted with overwhelming amounts of information in the form of heterogeneous primary studies. Medical literature reviews provide user-friendly syntheses of this primary research (Figure 5).

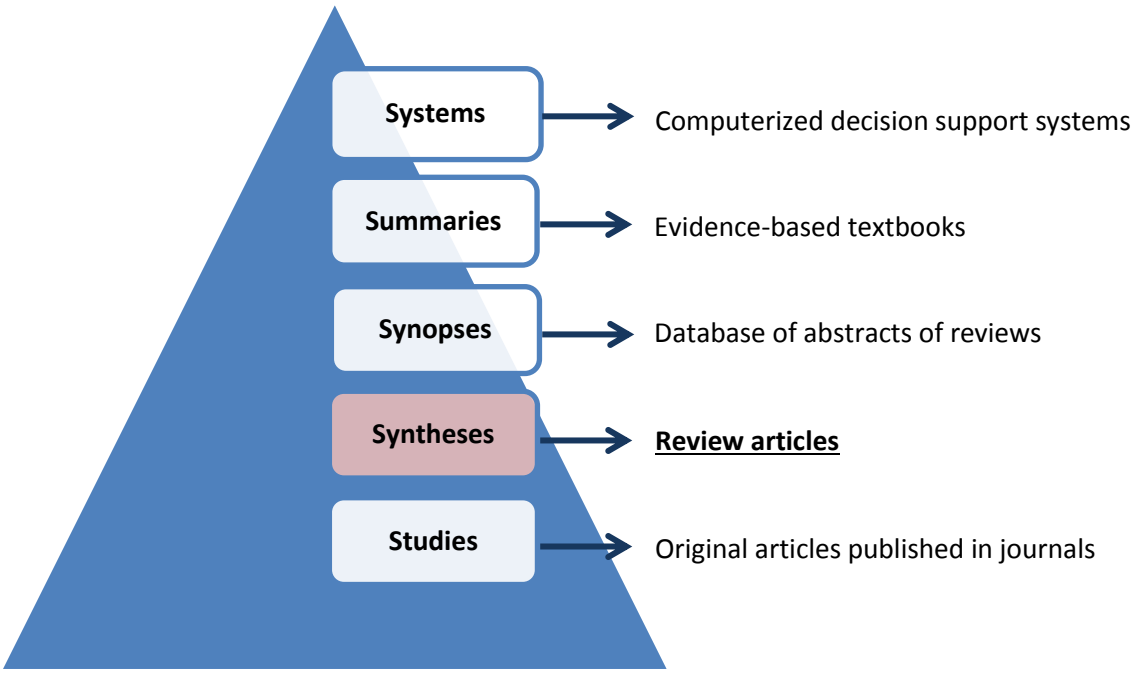

Figure 5: The "5S" levels of organisation of evidence from healthcare research (53).

Evidence-based medicine (EBM) is a paradigm of medical practice that "de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research" (54). EBM literature reviews tend to limit inclusion to what are generally considered "higher quality" trials such as randomized controlled trials (Figure 6).

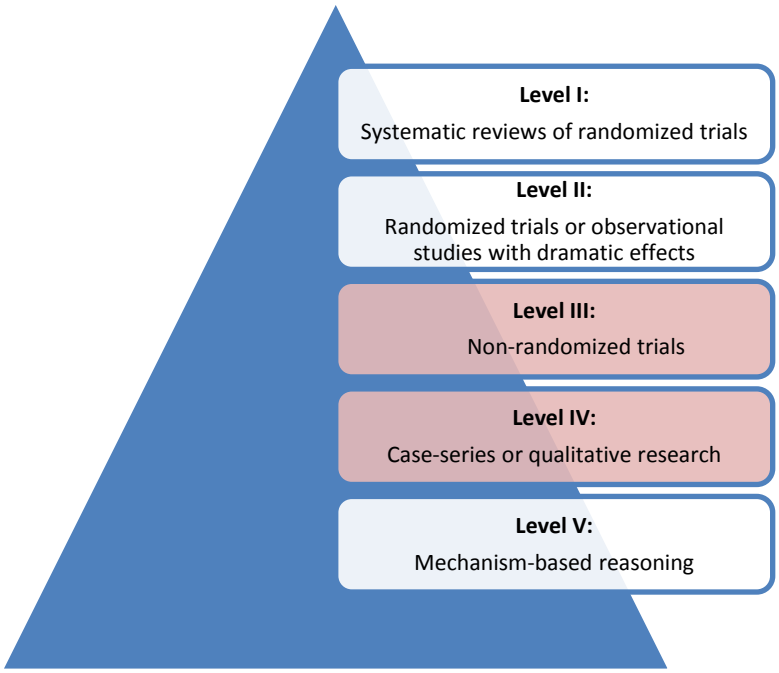

Figure 6: Hierarchy of medical evidence examining treatment benefits and harms (adapted from Oxford Centre for Evidence-Based Medicine) (55).

Strict rules governing EBM literature reviews limit the topics that can be studied. The capacity to reach clinically meaningful conclusions from the available research literature may also be precluded because EBM reviews do not have satisfactory procedures for dealing with small, non-randomized primary studies (56). Comparative effectiveness research (CER) has a different approach to medical evidence and its synthesis. The salient difference between EBM and CER is the latter's focus on assessments made within the framework of routine clinical practice. CER allows for a larger range of study designs than are commonly included in strict EBM syntheses (57), challenging the notion of hierarchy of evidence (Figure 6).

Considerable symptom-targeted research in the field of palliative oncology does not meet the standards set out by EBM guidelines and scoring systems (58, 59). A number of authors advocate changing the types of studies carried out among patients receiving palliative treatments so that they will meet the standards of EBM. Others argue that study of this patient group is a unique discipline and should instead consider alternative research designs that may be better suited for the particular population and context (60-63).

2.11 Status of evidence in palliative pelvic radiotherapy of prostate and rectal cancers

There are relatively few randomized studies of palliative interventions that document their efficacy in terms of symptom management (64, 65). This is partly due to the fact that researching such interventions is particularly challenging (Table 1). Target populations for palliative treatments are heterogeneous and have complex and fluctuating clinical pictures, making measurement and implementation of standardized study procedures difficult. In addition, advanced stage of disease

limits study compliance and follow-up (66). Table 1 summarizes the challenges of conducting research in palliative pelvic radiotherapy of prostate and rectal cancers.

Domain	Challenge
Patient	- Defining the palliative care patient (timing and terminology) - Heterogeneity of the population - Frailty - Unpredictable clinical course and declining health - Increased prevalence of cognitive impairment, particularly with advancing disease - Individual patient preferences to participate in disease-modifying research rather than symptom management research
System or organization	- Complicated or complex processes for obtaining ethical and administrative approval for research studies - Undeveloped research culture or lack of awareness of relevancy of research - Service delivery of palliative care services, which is not integrated or which has undergone substantial change - Funding challenges
Context or setting	- Gate keeping by clinicians or family members - Clinical practice does not align with protocols - Increased workload for clinicians - Lack of engagement by site investigators

Study design	- Patient eligibility and recruitment
	- High attrition rates because of progressive disease
	- Dealing with missing data
	- Randomization (patients' unwillingness to be part of a comparison group)
	- Blinding
	- Use of placebo may not be justified
	- Interventions
	  - Patients in control arm or comparison arm may perform better because of participation in the study or benefit of intervention
	  - Difficulty standardizing complex interventions, particularly psychosocial or spiritual interventions
	  - Difficulty controlling for nonspecific therapeutic factors, such as therapeutic relationship
	  - Difficulty designing appropriate interventions because of lack of understanding of complex pathophysiology
	- Selection of appropriate outcome measures that adequately capture complex concepts, such as psychosocial spiritual issues

Research team	- Recruitment, training and turnover of research staff - Lack of specific training of research staff in clinical trials
Ethics	- Obtaining patient consent and patient safety - Unable to withhold treatment

Table 1: Challenges of conducting research on palliative interventions (adapted from Aoun and Nekolaichuk) (61)

Patients considered for palliative pelvic radiotherapy of prostate and rectal cancers tend to be frail and elderly, unfit for surgery, or have incurable metastatic disease in addition to the localized pelvic tumor. Many have also exhausted other treatments and have short life-expectancies.

There is no consensus for the optimal radiotherapy doses or fractionation schedules for palliative pelvic radiotherapy of prostate or rectal cancers, yet as with other cancers, there is a trend toward using fewer fractions. Evidence supporting the different radiotherapy regimens commonly used in palliative pelvic radiotherapy of prostate and rectal cancers is sparse and there is no evidence that symptomatic response is dose-dependent (67-69). Clinical practice therefore varies greatly, often based on local tradition and extrapolation from other clinical scenarios. In addition, factors such as life expectancy, functional status, comorbidity, risk of short-term toxicity, previous radiotherapy, systemic treatment options and patient wishes, weigh differently from case to case in the decision-making process.

To illustrate, consider the different radiotherapeutic approaches exemplified in Figure 7. For patients with relatively long life-expectancies, delivery of for example 50 Gy in 25 fractions may be appropriate (19) given that such a dose may alter the course of the disease, leading to local control, delayed onset of symptoms, and possibly prolonged survival. Patients with relatively high functional status (Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2) and intermediate prognosis are most often given doses in the range of 20-39 Gy in 5-13 fractions, aiming to palliate cancer-related symptoms without significantly affecting survival time. Single fractions of 8–10 Gy may be suitable to target specific symptoms (such as bleeding) or in frail patients, without otherwise influencing the clinical course. Whereas higher doses (20–50 Gy) may be acceptable only when life-expectancy is relatively long, single fractions (8 Gy) may be justified throughout the course of the disease.

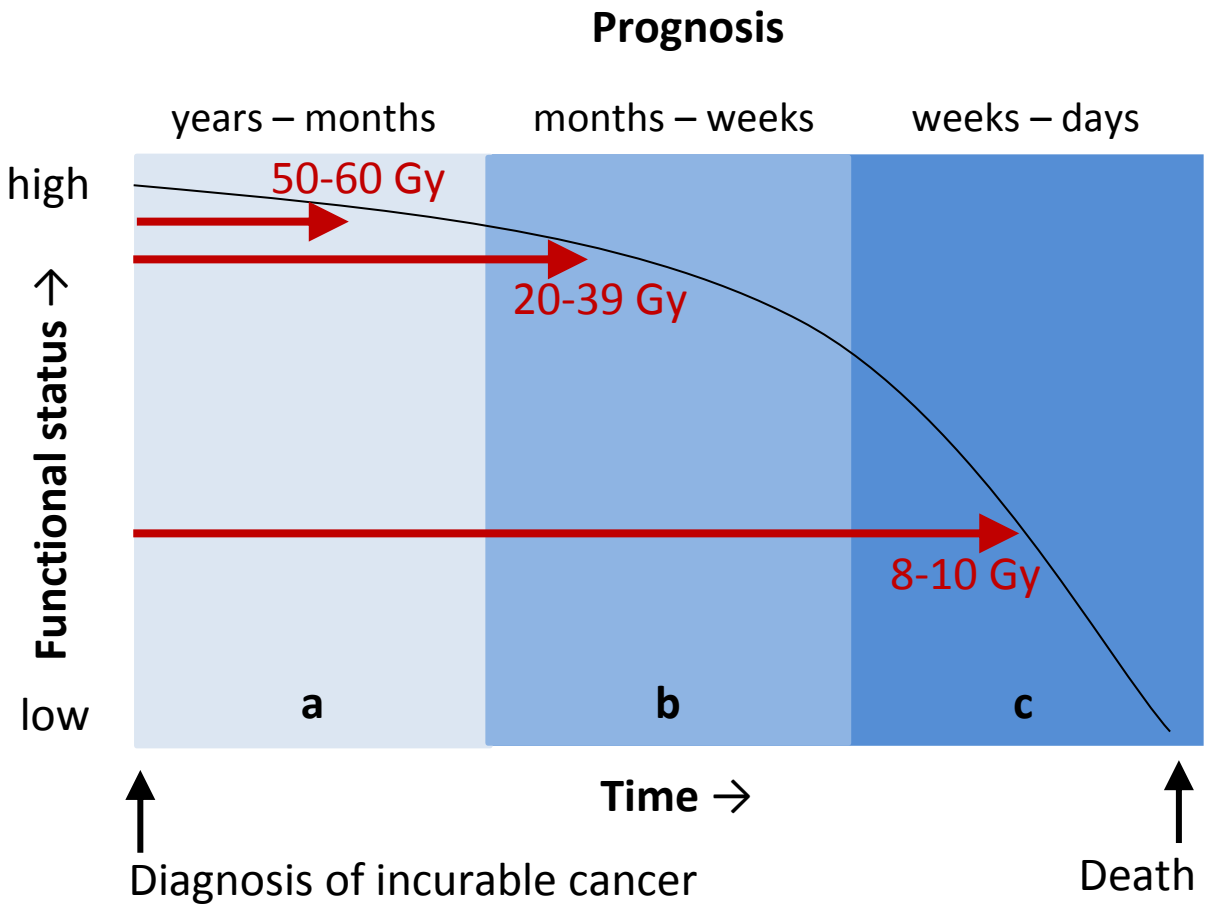

Figure 7: Illness trajectory for incurable cancer (10) divided into three hypothetical prognostic phases. Arrows roughly indicate time-frames most appropriate for different palliative radiotherapy doses in prostate and rectal cancers. a) Patients with relatively long life-expectancies (years to months) may be candidates for the full spectrum of doses (8–50 Gy). b) Patients with relatively high functional status and intermediate prognoses (months to weeks) are generally considered for moderate to low doses (8–39 Gy). c) In frail patients with short estimated survival, treatment options may be limited to only low dose radiotherapy (8–10 Gy).

When this thesis was being planned, several observational studies examining palliative pelvic radiotherapy of prostate and rectal cancers had been published, but no systematic summaries of the findings existed. Furthermore, there was a lack of prospective studies that used PRO-based measures as endpoints.

3. AIMS OF THE THESIS

3.1 Overall aim

The overarching aim of this thesis was to explore the role of pelvic radiotherapy in symptom management in the palliative treatment of patients with symptomatic incurable prostate and rectal cancers.

The thesis is built up of a series of studies including two systematic literature reviews, a feasibility study and a prospective multicenter study of patients with symptomatic prostate and rectal cancer receiving palliative pelvic radiotherapy. These three components all sought to address the overarching aim, although each methodological approach reflects the studies' specific, constituent objectives.

3.2 Aims of the systematic reviews

The aims of the two *systematic literature reviews* were to comprehensively synthesize and evaluate the current evidence regarding efficacy, toxicity and optimal delivery of palliative pelvic radiotherapy of prostate and rectal cancers. In addition, the reviews sought to elucidate potential research areas of value.

3.3 Aims of the feasibility study (SFK1)

The aim of the *feasibility study* was to determine whether prospective measurement of patient-reported symptoms and HRQOL in cancer patients treated with palliative pelvic radiotherapy was feasible and to explore potential barriers and possibilities related to such research.

3.4 Aims of the prospective multicenter study (PallRad1)

The aims of the *prospective multicenter study* was to:

- examine the extent to which patients treated with palliative pelvic radiotherapy of prostate and rectal cancers achieve symptomatic improvement.
- determine which pelvic symptoms are likely to improve after palliative pelvic radiotherapy of prostate and rectal cancers.
- assess the time course of symptom severity after palliative pelvic radiotherapy of prostate and rectal cancers.
- assess the extent of toxicity experienced after palliative pelvic radiotherapy of prostate and rectal cancers.
- examine the HRQOL of patients undergoing palliative pelvic radiotherapy of prostate and rectal cancers.

4. METHODS

4.1 Systematic reviews

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (The PRISMA statement) (70) was developed by a panel of international experts in the field of literature review in order to guide reviewers in the synthesis of medical research. These recommendations have been followed in the systematic reviews included in this thesis to the extent that this was possible.

Research protocols for the systematic reviews (Appendix i and ii) were written based on several of the Cochrane group recommendations (71). They include clearly formulated research questions and methods to identify and select studies, critically appraise them, and to extract and analyze their data.

Research questions were structured using the PICO (**P**articipants, **I**nterventions, **C**omparisons, **O**utcomes) approach, as recommended by the Cochrane Collaboration (Table 2) (71).

Participants	Patients with CRPC or incurable rectosigmoid cancer receiving palliative pelvic external beam radiotherapy (EBRT)
Interventions & **C**omparisons	- EBRT without comparison group - EBRT compared to no treatment - EBRT compared to medical treatment - EBRT compared to other type of radiotherapy - EBRT compared to combination treatment (EBRT + other) - Studies comparing different EBRT regimens (dose or fractionation)
Outcomes	- Symptoms - Health-related quality of life - Toxicity

Table 2: PICO structure of the systematic review research questions

The following is an example of the search strategy used in Medline: (radiotherapy OR radiation OR radiation oncology) AND (palliative care OR terminal care) AND prostatic/colorectal neoplasms. Corresponding searches were done in Embase and in the Cochrane library database. In addition, manual searches of the reference lists of relevant review articles and all articles reviewed in full-text were conducted.

The following additional eligibility criteria and clarifications were applied to the above PICO elements:

- Only studies of radiotherapy given with palliative intent were included
- Only studies of primary radiotherapy (not re-irradiation) were included
- Only studies of radiotherapy alone (not studies of co-interventions) were included
- Only studies reported in European languages were considered
- All study types, with the exception of case-reports, were considered
- All radiotherapy doses and regimens were admissible
- If the target population was a subgroup of a larger study, this data was admissible as long as the results were reported separately

Assessment of the methodological quality of included studies was conducted at the study and outcome levels. Applicable scoring systems for observational and retrospective studies were not established at the time the reviews were undertaken (72, 73). We therefore developed our own checklist (Table 3) based on the Cochrane scoring system (71) to structure our evaluation. Four reviewers worked independently on the evaluation of study quality. Where there was disagreement, decisions were made by consensus.

Criterion:	**Assessment:**	**Comments:**
1. Design		
2. Sample size /subgroup		
3. Representativeness of participants/subgroup	Yes / Unclear / No	
4. Homogeneity of participants/subgroup	Yes / Unclear / No	
5. Homogeneity of treatments	Yes / Unclear / No	
6. Confounders addressed appropriately	Yes / Unclear / No	
7. Appropriate control group	Yes / Unclear / No	
8. Appropriate outcomes	Yes / Unclear / No	
9. Validated instruments used to measure outcomes	Yes / Unclear / No	
10. Adequate follow-up	Yes / Unclear / No	
11. Appropriate statistics used	Yes / Unclear / No	
12. Adequate sequence generation	Yes / Unclear / No	
13. Allocation concealment	Yes / Unclear / No	
14. Blinding	Yes / Unclear / No	
15. Incomplete outcome data addressed	Yes / Unclear / No	
16. Free of selective reporting	Yes / Unclear / No	
17. Free of other bias	Yes / Unclear / No	
Preliminary decision:	Include Discuss Exclude	
Final decision - after discussion/consensus:	**Include / Exclude**	**Risk of bias:**

Table 3: Checklist for quality assessment of studies reviewed in full text

Two reviewers worked independently in the extraction of data (Table 4). Decisions were made by consensus.

	Description of variables:
Study characteristics	Publication type, study design
	Quality based on reviewers assessment
	Intervention: radiation method and fractionation
	Participant numbers and characteristics (age, sex, stage of disease, previous treatment, treatment setting, etc.)
	Control group, comparison
	Study duration and length of follow-up
Outcome 1: QOL	Outcome definition
	Measurement timing and method/tools
	Principle summary measures: Results and variance
	Patient number and missing data
Outcome 2: Symptom response	Outcome definition
	Target symptom (there are likely to be several: pain, bleeding, obstruction, etc)
	Measurement timing and method
	Principle summary measures: Results and variance, duration of response
	Patient number and missing data
Outcome 3: Toxicity	Outcome definition
	Target side effect (there are likely to be several)
	Measurement timing and method
	Principle summary measures: Results and variance, duration of toxicity
	Patient number and missing data
Comments	

Table 4: Data items extracted from included articles, for use in synthesis and analysis.

Data were presented in descriptive syntheses, mostly in table form, with supplemental narrative descriptions as needed.

4.2 Feasibility study *(SFK1)*

Participants

Patients were screened at a single center (Center for Cancer Treatment (SFK), Sørlandet Hospital, Kristiansand, Norway) over the course of one year (March, 2008 – April, 2009). All patients referred for fractionated palliative pelvic radiotherapy of soft-tissue prostate, colorectal and bladder tumors (i.e. not skeletal metastases), were eligible, regardless of stage of disease. All radiotherapy doses and fractionation schedules (other than single-fractions) were allowed. There were no restrictions placed on concomitant treatments given prior to, under, or after radiotherapy.

Radiotherapy

Radiotherapy dose and fractionation schedules were decided by the radiation oncologist prior to referral to the study. Treatment planning was performed by computerized tomography (CT) in which planning target volume (PTV) encompassed gross tumor volume (GTV) with a 1–2 cm margin. Field set-up was at the discretion of the treating physician.

Study design

At the outset of the study, three study visits were planned; at baseline prior to radiotherapy, six weeks after radiotherapy completion and 12 weeks after radiotherapy completion. An additional (not pre-planned) follow-up visit was set around the time of radiotherapy completion (+/- 3 days) once the first 12 participants had shown acceptable compliance and did not appear overburdened by the study procedures (Figure 8).

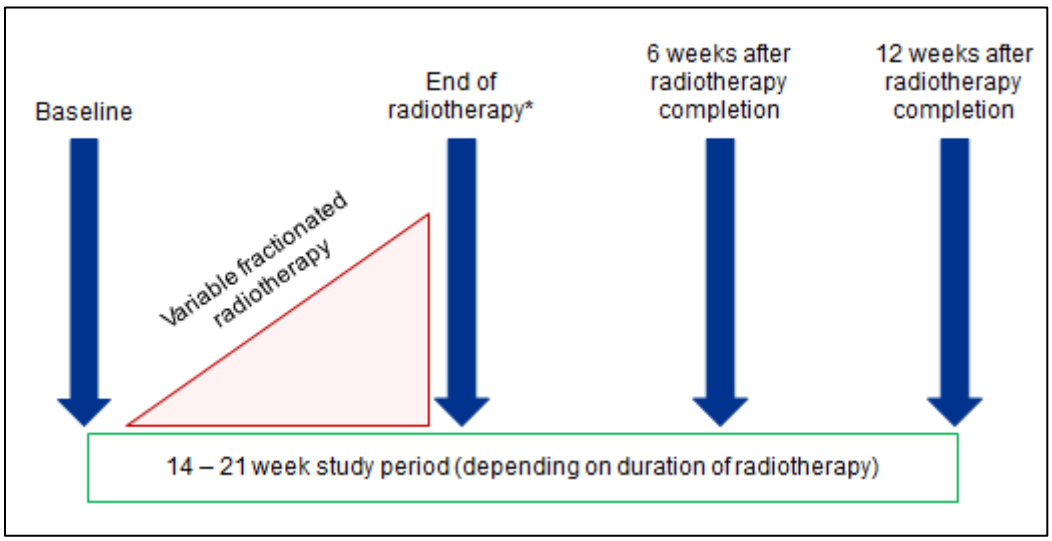

Figure 8: Schematic of the SFK1 feasibility study showing four study visits. A baseline study visit was followed by three follow-up visits starting at the end of the radiotherapy treatment (* the end of radiotherapy follow-up visit was added during the course of the study). Duration of radiotherapy courses varied and determined the total length of the study period for each participant (radiotherapy duration + 12 weeks of follow-up).

At each study visit, the physician evaluated symptoms and toxicities (using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0 score), ECOG-PS, medication use, and complications. Participants completed questionnaires while in the treatment center, assisted by a radiation therapist when necessary. The specific PRO tools used were the EORTC QLQ-C30 core questionnaire in combination with a site-specific module corresponding to the primary tumor type (PR25, CR38 or BL24).

Endpoint evaluation and analysis

Study enrollment and completion were assessed by numbers of patients screened, included and capable of producing evaluable PRO data, indicated by completion of over half of questionnaire items at the 12-week follow-up visit (74). The PRO, symptom, and toxicity data were not analyzed beyond whether or not the data were evaluable. Descriptive statistics were used to summarize

patient accrual, questionnaire completion, survival and withdrawals from the study, which were the outcomes of interest for the planning of follow-up studies.

4.3 Prospective multicenter study of palliative pelvic radiotherapy of symptomatic prostate and rectal cancers (PallRad1)

Participants

Screening and inclusion of patients began in November, 2009. Prostate cancer patients were included until June, 2014, and rectal cancer patients until July, 2015. Screening logs were not kept. Eight of the nine Norwegian radiotherapy centers chose to participate. This included four university hospitals and four regional hospitals, geographically spread throughout the country (Figure 9).

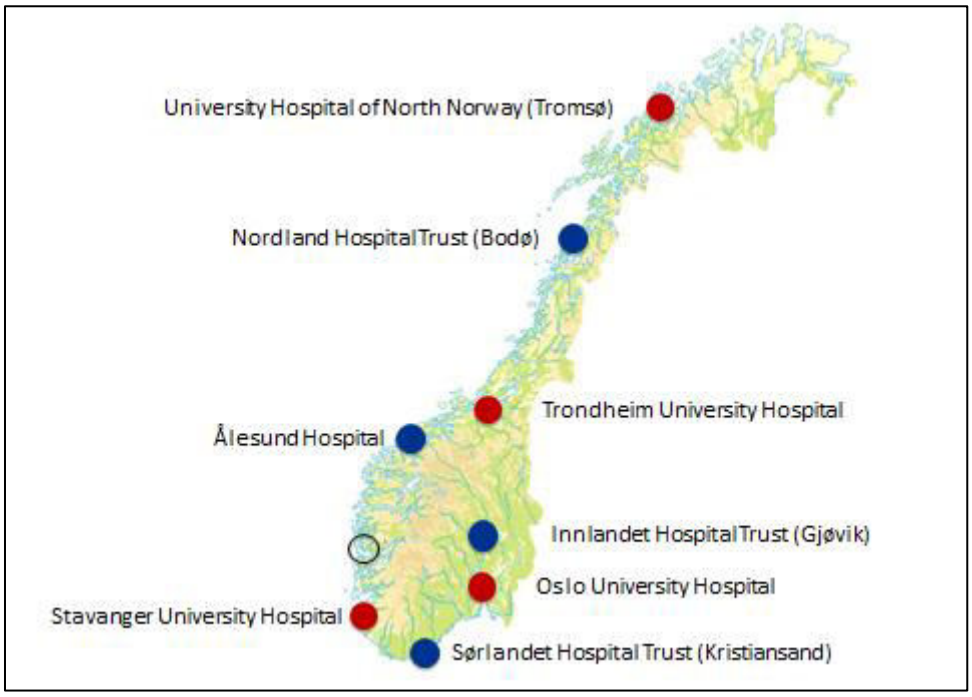

Figure 9: Eight radiotherapy centers participated in the PallRad1 study. Red indicates university hospitals and blue indicates community hospitals. The empty circle indicates the radiotherapy center that did not participate (Haukeland University Hospital, Bergen).

Patients that were prescribed palliative pelvic radiotherapy in the range of 30 to 39 Gy in 3Gy fractions for symptomatic prostate or rectal adenocarcinomas were eligible for inclusion. Radiotherapy targets were limited to primary or recurrent tumors, lymph node metastases, other soft-tissue tumor deposits, or a combination of these. Pelvic skeletal metastases did not qualify patients for inclusion. Patients in the prostate cancer study had to have CRPC to be included, but all stages of disease, including metastatic disease, were admissible in both diagnostic groups, provided treatment was regarded as palliative. Life expectancy had to be greater than three months (Figure 10). Patients could not have started a new systemic anticancer treatment (such as hormonal manipulation or chemotherapy) within the four weeks prior to study entry, and none could be planned within the first six weeks after radiotherapy completion. However, no restrictions were placed on concomitant treatments given during or after radiotherapy once patients were included.

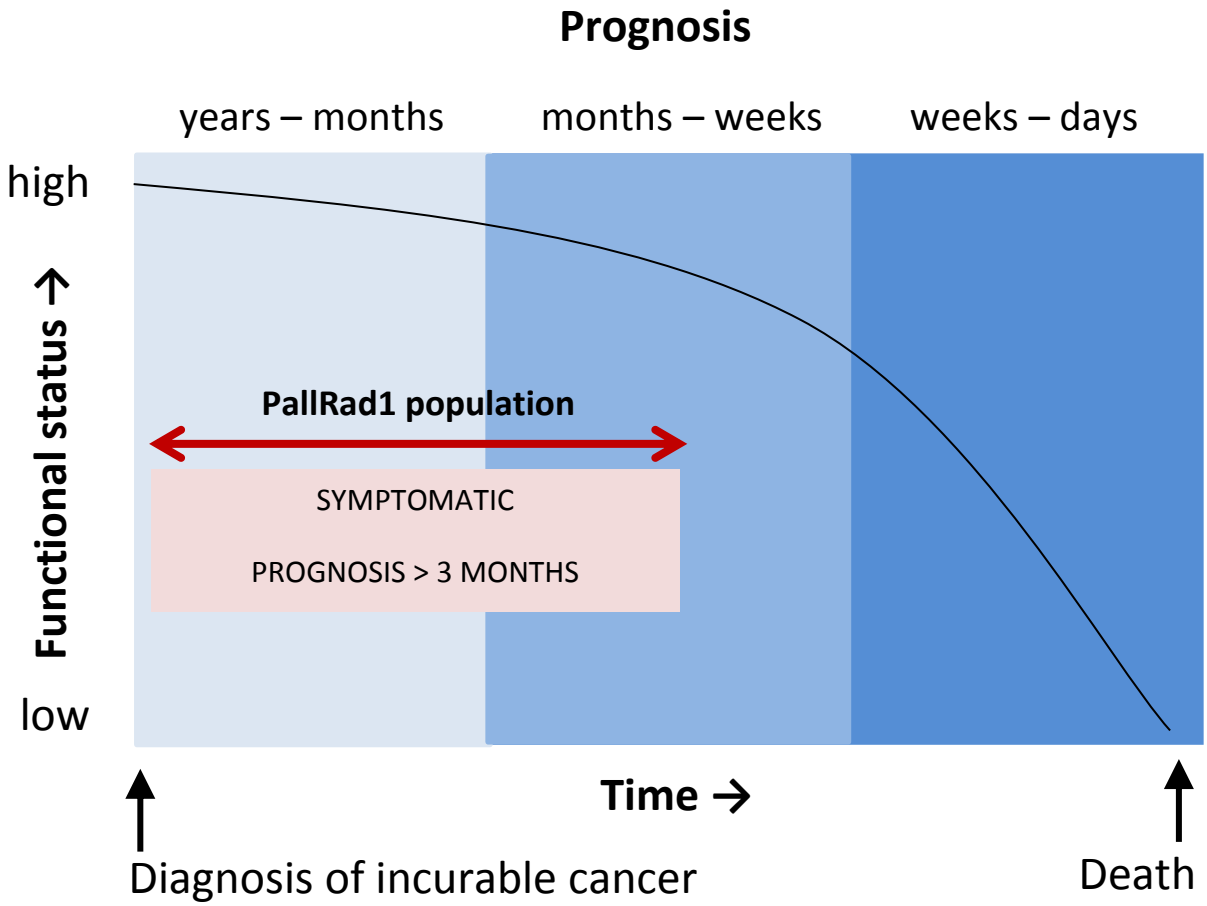

Figure 10: Illness trajectory for incurable cancer (10) divided into three hypothetical prognostic phases. The arrow indicates roughly where the target populations for the PallRad1 study fit based on their prognoses.

Radiotherapy

As this was a study of a specific, predefined treatment, radiotherapy dose and fractionation was required to have been prescribed within the range described in the inclusion criteria (30–39 Gy) *prior* to study entry. Patients for whom the treating physician wished to use other doses or fraction sizes were ineligible.

As the radiotherapy was symptom-directed, only the symptom-causing pelvic tumor manifestations were defined as the GTV. Margin from the GTV to the PTV was limited to 1–2 cm, aiming for a degree of homogeneity in the field sizes. Field set-up was left to the discretion of the clinician in order to ensure optimal coverage and minimal toxicity. 3D CT planning was preferred, but not required (Figure 11).

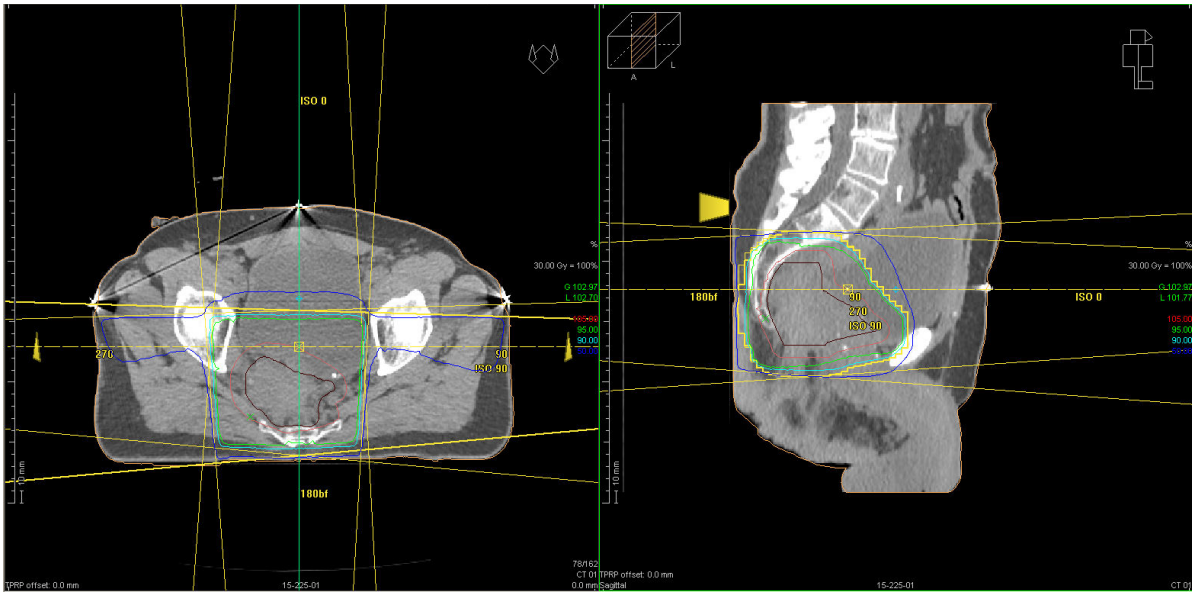

Figure 11: 3D treatment plan for palliative radiotherapy of rectal cancer in a PallRad1 study patient.

Study design

PallRad1 was a phase II study. The design was based on the experience from the SFK1 feasibility study, with some modifications (Figure 12). Study procedures for the two diagnostic groups were nearly identical except regarding matters specific to the underlying diagnoses (such as choice of diagnosis-specific EORTC questionnaire and tumor-marker measurement).

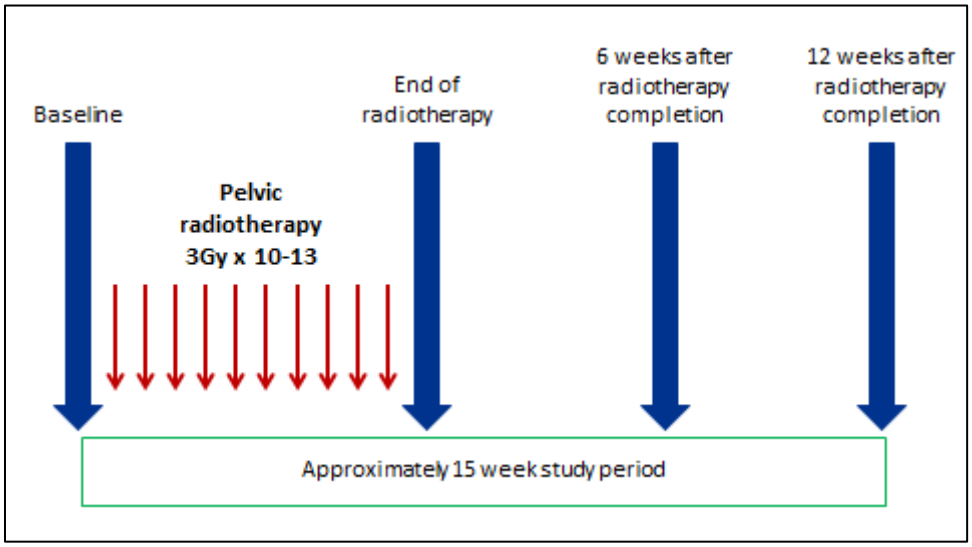

Figure 12: Schematic of the PallRad1 study showing four study visits. A baseline visit was followed by three follow-up visits starting at the end of the course of radiotherapy.

Evaluations

A combination of PROs and physician-reporting were used to evaluate study endpoints.

Pimary endpoint

The primary endpoint for the PallRad1 study was the proportion of patients in each diagnostic group reporting improvement or complete resolution of target symptom severity compared to baseline at the 12-week follow-up visit. Target symptom was defined as the symptom that the patient reported as being most troublesome and which they most hoped would be palliated by the radiotherapy. At baseline, patients were asked to identify one such target symptom. The severity of this patient-defined symptom was reassessed by the patient, anchor-based, at each of the three follow-up visits (end of radiotherapy and six and 12 weeks after its completion). Each time, patients were asked to describe the severity of the pre-defined target symptom as either "worse", "unchanged", "better" or "resolved" compared to baseline. "Target symptom response" was further defined as either "better" or "resolved", as reported by the patient.

Bleeding and pain were defined by the patients themselves. The entity "lower urinary tract symptoms" (LUTS) was defined as urinary storage symptoms (frequency, urgency, incontinence), voiding symptoms (abnormal stream, hesitancy, straining) and incomplete emptying, as defined by the International Continence Society (75). Rectal obstruction, incontinence, diarrhea, and mucous production were grouped as rectal dysfunction.

Secondary endpoints

- HRQOL, a secondary outcome, was assessed using the EORTC QLQ-C30 with accompanying diagnosis-specific modules (QLQ-PR25 for prostate cancer or QLQ-CR29 for rectal cancer). These were administered at each study visit.

- The BPI was administered at each study visit in anticipation that many patients would identify pain as either their target symptom or as a secondary symptom.

- The study physician graded pelvic symptoms and toxicities according to the National Cancer Institute CTCAE version 3.0 at each of the four study visits. In order to ensure that the recording of toxicities was as complete as possible, the study physician registratered *potential* toxicities, not only those spontaneously volunteered by the patient, by active capture of pre-defined items. To this end, a list of the most common toxicities encountered after palliative pelvic radiotherapy was developed. Each of the following symptoms/potential toxicities was graded by the study physician at each study visit:
    - Fatigue
    - Weight-loss
    - Anorexia
    - Hematuria
    - Cystitis
    - Dysuria
    - Urinary frequency / urgency
    - Urinary incontinence
    - Urinary retention
    - Nausea
    - Vomiting
    - Constipation
    - Diarrhea
    - Anal incontinence

- Proctitis
- Hematochezia
- Tenesmus
- Pelvic pain
- Lower limb / genital edema
- Vaginal bleeding

Study questionnaires were filled out by the study participants themselves, preferably while they were still at the treatment center. In cases where assistance was needed, a dedicated study nurse or study radiotherapist was available and they ensured that the forms were completed fully and correctly prior to submission. In cases where the patient was prevented from attending follow-up visits at the cancer center, consultation was done per telephone and questionnaires were administered by post if appropriate.

The following were also registered at each study visit:

- ECOG-PS
- Presence of urinary or gastrointestinal tract diversion or stent.
- Blood-tests (prostate-specific antigen or carcinoembryonic antigen, hemoglobin, albumin, creatinine)
- Medication use (specifically antiemetics, laxatives, urologic spasmolytics, anxiolytics, sleeping aids, analgesics). Dose of total analgesics used in the last 24 hours.
- Ancillary palliative interventions such as start of new systemic treatment or radiotherapy given to another region.

Background data, including participant demographics, cancer characteristics and past treatments, were gathered from patient records. Survival data was obtained from the Norwegian Cause of Death Registry.

Statistical considerations and data management

A target symptom response rate of at least 30–40% was deemed necessary in order to justify subjecting patients to 2–3 weeks of palliative radiotherapy. If the true response rate was 40%, a total of 47 patients would be needed to obtain 90% power to exclude a response rate of <20%, with significance level of 5%. Correspondingly, the power would be 80% with a total of 35 patients. With 40 evaluable patients, the maximum length of a 95% confidence interval for the proportion of responders is ±15%.

With regard to the secondary endpoint HRQOL, a change of ≥10 points in the EORTC QLQ-C30 global HRQOL score is considered clinically significant (76). Assuming a standard deviation in the range of 20–25 (77), 32–51 patients would yield a power of 80%. Thus, a total of 40 fully evaluable patients were deemed sufficient to detect relevant effects on both primary and secondary outcomes.

However, based on the 18% attrition rate in the feasibility study, inclusion of an excess of approximately 10 patients with each diagnosis was planned in order to ensure a sufficient evaluable patients. Since the study was non-randomized, complete case rather than intention to treat analyses were planned (78). However, all study participants were accounted for in the results and all were included in the outcome analysis, regardless of whether or not they completed the study (79).

Observational design without randomization or group comparison, and small study size limited the potential for statistical testing. Results for the two PallRad1 cohorts were analyzed separately. For each diagnostic cohort, overall target symptom results were examined for the whole sample, but also according to target symptom subgroups (pain, bleeding, etc), due to the clinical relevance of separating these subgroups. Descriptive statistics were generated to describe the sample of patients, treatment given, and the primary endpoint. 95% confidence intervals were estimated. This was supplemented by presentation of raw data indicating change in individual patient's symptom severity over time. Toxicity was presented as percent of patients with each grade of symptoms at the four study visits.

Longitudinal EORTC QLQ C30 scores were internally referenced. Changes in global HRQOL scores were reported using the threshold of clinical significance along with their p-values. Differences in median score from baseline to each follow- up visit were assessed by the two-tailed Wilcoxon-signed rank test (significance level of $p<0.05$) for paired data. Due to constraints on journal publication length, comprehensive HRQOL analysis, including results for symptom and functional scales and diagnosis-specific modules (QLQ-PR25 and QLQ-CR29) will be reported separately.

Kaplan-Meier survival analysis was performed with the observation time spanning from the start of radiotherapy to death or through 2013 for the prostate cancer study and through October 1st 2015 for the rectal cancer study.

In the rectal cancer cohort, where survival was limited, Fisher's exact test was used to assess the association between selected variables (age ≥ the median, ECOG-PS 0–1 versus 2–4, normal versus low albumin levels, presence or absence of metastases, and whether or not patients had been given prior anti-cancer treatment) and study attrition. Multivariable logistic regression was performed using study attrition as the dependent variable. Likelihood ratio tests were used to compare different models.

5. SUMMARY OF RESULTS

5.1 Paper 1: Palliative pelvic radiotherapy of symptomatic incurable prostate cancer – a systematic review

This systematic literature review screened 970 publications, yielding nine studies that described symptomatic results of palliative pelvic radiotherapy of prostate cancer. The nine included studies reported results of treatments given between 1961 and 2007. There were no prospective studies identified and no reports of PROs.

The total number of patients was 315, with a median of 26 patients per study. Patient characteristics were heterogeneous, both within and between studies, with regard to their CRPC status and whether or not there were documented metastases. The most commonly described symptoms were LUTS, hematuria and pelvic pain, although patients were often described as having several simultaneous symptoms.

Radiotherapy method, dose, fractionation, and target definitions were heterogeneous across the included studies and there were large variations also within studies. Fraction sizes varied from <2 to 8 Gy and total doses ranged from 8 to 76 Gy. Most radiotherapy was given with fractions of 2–3 Gy daily.

Responses were measured at variable time points after palliative pelvic radiotherapy and based on the authors' own definitions. None of the studies used standardized scales for symptom evaluation. The pooled overall response rate where no symptom was specified was 75% (78/104) with a range of 60–100% across studies. The corresponding response rates for the specific symptoms were: LUTS 63% (76/120), hematuria 73% (58/80), pain 80% (32/40), rectal symptoms 78% (29/37), and ureteric obstruction 62% (16/26).

Six studies mentioned toxicity, which was described as mostly mild to moderate. Reported toxicities included proctitis, diarrhea, tenesmus, pollakisuria, dysuria, hematuria, dermatitis, emesis, lethargy and worsening ureteral obstruction; all of which were physician-reported.

Generalizations regarding duration of symptomatic relief could not be made due to heterogeneous reporting of varied outcome variables and the retrospective nature of the studies. However, there was a tendency for hematuria to respond most rapidly. Comparisons of the effects and toxicities of different treatment schedules were not possible due to heterogeneity and the retrospective nature of the studies. Therefore, the presence of a dose-response relationship could not be evaluated.

Conclusion: Despite the shortcomings of identified studies, the systematic literature review gives an indication that palliative pelvic radiotherapy of prostate cancer is likely to be an effective palliative treatment across a spectrum of radiotherapy doses. However, there is no conclusive evidence that there is a dose-response or that one fractionation scheme is preferred over others. The review highlights the fact that there is an evidence gap, and that clinical practice in this area is subsequently not sufficiently evidence-based, which in turn obviates the need for further research.

5.2 Paper 2: Palliative pelvic radiotherapy of symptomatic incurable rectal cancer – a systematic review

This systematic review screened 484 publications resulting in 27 included studies that reported symptomatic response after palliative pelvic radiotherapy of rectal cancer. The studies described treatments given from the 1930s until 1991. Twenty-three of 27 included studies were retrospective chart reviews. Of the four prospective studies, two were randomized controlled trials, one was nonrandomized, and one was an observational study including patients assessed both prospectively and retrospectively. None of the studies reported PROs.

The total number of evaluable patients included in the synthesis was 1759, with an average of 65 patients in each study. Three studies included only patients with primary tumors, 14 included only patients with recurrent or residual pelvic disease, and the remaining 10 studies included a combination of these. The majority of studies included patients with distant metastases. The most common symptoms reported were pain, hematochezia, and mass-effect.

There was a great deal of variation in radiotherapy method, dose, and schedules across and even within studies. The most commonly used fraction size was 2 Gy and total doses ranged from 5 to 70 Gy, most often in the range of 30–60 Gy.

Response criteria were generally poorly defined and varied across studies, as did the time points for symptom evaluation. Overall response rates (without specifying the symptoms) varied from 56% to 100% in individual studies. When pooled, this yielded an overall response rate of 75% (818/1084). Corresponding pooled response rates for specific symptoms were: pain 78% (437/561), hematochezia and discharge 81% (251/308), and mass-effect and tenesmus 71% (65/91).

Symptomatic responses were reported after low total doses of radiotherapy (20 Gy), during fractionated treatment and after single fractions of 5–10 Gy. Several authors reported no difference in effectiveness across a range of doses and there were conflicting reports regarding whether duration of response depended on dose given. Retreatment after good initial response was reported to be effective. Symptomatic improvement lasting from 1–44 months was reported in three prospective studies delivering doses ranging from 30 to 50 Gy. Over half of the retrospective studies reported symptomatic responses lasting well over one year.

Twenty-one publications addressed the toxicity of radiotherapy, although it was evaluated prospectively in only two of these. Toxicity was largely characterized as mild to moderate.

Conclusion: The reviewed publications report effective palliation of symptomatic incurable rectal cancer across a range of radiotherapy schedules. However, due to shortcomings in many of the included studies it is impossible to draw conclusions regarding onset, duration or degree of palliation, or the toxicity of palliative pelvic radiotherapy. Treatment recommendations can therefore not be provided by existing evidence. Prospective studies are needed.

5.3 Paper 3: Patient reported outcomes of symptoms and quality of life among cancer patients treated with palliative pelvic radiation: A pilot study

Over the course of one year, the Center for Cancer Treatment (SFK) in Kristiansand, Norway, serving a population of 295,000, screened 26 patients with prostate, colorectal, or bladder cancers who were referred for fractionated palliative radiotherapy of symptomatic pelvic soft-tissue tumors (primary, recurrent or metastases). Twenty-two (85%) of these patients were enrolled in the study over the course of 13 months. Reasons for non-enrollment were patient choice (belief that the study procedures were too demanding) in three cases and cancellation of planned radiotherapy due to clinical deterioration in one case.

The median age of the cohort was 75 years (range 62–90) and comprised 17 males and five females. Fourteen patients had prostate cancer, five had colorectal cancer, and three had bladder cancer. Median radiotherapy dose was 50 Gy (range 20–60 Gy) with the prostate cancer patients prescribed the highest doses.

Six weeks after radiotherapy completion, 20/22 (91%) patients were still in the study. After 12 weeks, 18/22 (82%) patients remained in the study. 91% of patients survived for 3 months, and eight patients survived at least 24 months after the radiotherapy.

At baseline, 21/22 patients had valid responses on the EORTC QLQ C-30 questionnaire. At six and 12-week follow-up, this figure was 20/20 and 17/18, respectively.

Conclusion: Among patients with prostate, colorectal, and bladder cancer, compliance to questionnaires assessing symptoms and HRQOL six and 12 weeks after palliative pelvic radiotherapy is sufficient to justify evaluation in a larger patient group. Radiotherapist assistance in study procedures is likely to have contributed to compliance. Study withdrawal due to clinical deterioration is a challenge that must be taken into consideration in further study development.

5.4 Paper 4: Palliative pelvic radiotherapy for symptomatic incurable prostate cancer – A prospective multicenter study

Forty-seven patients were included in the study, all of whom completed radiotherapy as prescribed. Seven patients were not evaluable at the 12-week follow-up due to failing health (n=2) or death (n=5).

The median age was 79 years and 34 patients had documented metastases at baseline. The median time since diagnosis was 68.5 months. Twenty-one patients had urinary tract diversion, stent or catheter at baseline, and 10 used opiates. The most frequent patient-reported target symptoms were LUTS (n=21), macroscopic hematuria (n=12), and pain (n=9). Mean total radiotherapy dose delivered was 34.5 Gy (range 27–39 Gy). Median volume irradiated to 90% of the target dose was 737 cm^3.

Twelve weeks after palliative pelvic radiotherapy, 18/40 patients reported complete resolution of their target symptom, 10/40 reported improvement, 10/40 reported unchanged severity and 2/40 reported worsening of their target symptom. Response of the target symptom was achieved in 62% of evaluable patients at the end of radiotherapy, 80% after six weeks, and 70% after 12 weeks. Eighty-seven percent (41/47) of all included patients reported response of the target symptom at least at one of the three follow-up visits.

Response of macroscopic hematuria was reported in 92%, 100%, and 100% of patients at the end of treatment, 6-week and 12-week follow-ups, respectively. Pain was palliated in 9/9 patients after six weeks and in 7/9 at 12 weeks. The time-course of responses for patients with LUTS was slower, with only 6/21 patients reporting responses at the end of treatment. At the six and 12-week follow-ups these figures were 8 and 10 out of a possible 18 patients, respectively.

Median global QOL score for evaluable patients increased by 12.5 points from baseline to the six-week follow-up. Clinically meaningful improvement was reported by 16/41 patients at the six-week follow-up and 15/40 patients at the 12-week follow-up.

Transient mild to moderate (grade 1–2) diarrhea at the end of radiotherapy was the most frequent toxicity seen (50%). There were no grade 4 toxicities. Median overall survival among included patients was 20 months from the time of radiotherapy start.

Conclusion: Palliative pelvic radiotherapy of a symptomatic prostate tumor contributes to effective palliation without significant toxicity in patients with CRPC. Findings indicate that radiotherapy is effective across a range of pelvic symptoms, which respond differently. The study also demonstrates stable and improved HRQOL among selected patients.

5.5 Paper 5: Palliative pelvic radiotherapy for symptomatic rectal cancer – A prospective multicenter study

Fifty-one patients were included in the study. Five patients had their prescribed radiotherapy shortened for medical reasons. Sixteen patients were not evaluable at the 12-week follow-up due to failing health (n=6) or death (n=10). Two patients dropped out of the study for non-medical reasons, leaving 33 patients evaluable at the 12-week follow-up visit. The study was closed prior to reaching its goal of 40 evaluable patients.

The median age was 79 years. Twelve patients had pelvic recurrences and 41 had documented metastases at baseline. Thirty-two patients had not been given previous systemic oncologic treatment. Twenty-three patients had a stoma and 21 used opioids at baseline. The most frequent patient-reported target symptoms were pain (n=24), rectal dysfunction (n=16), and hematochezia (n=9). Median total radiotherapy dose delivered was 36 Gy (range 6–39 Gy). Median volume irradiated to 90% of the target dose was 1190 cm^3.

Twelve weeks after palliative pelvic radiotherapy, 17/33 (52%) patients reported complete resolution of their target symptom, 11/33 (33%) reported improvement, 4/33 (12%) had unchanged severity and 1/33 reported worsening target symptom. Overall, 28/33 (85%) evaluable patients reported response of the target symptom at the 12-week follow-up visit. Response of the target symptom was achieved in 28/47 (60%) evaluable patients at the end of the radiotherapy and 35/41 (85%) at the 6-week follow-up. 42/51 (82%) study participants reported response of the target symptom at least at one follow-up visit.

Hematochezia maintained a 100% response rate from the first evaluation through the 12-week follow-up. Nine of ten patients with rectal dysfunction reported response 12 weeks after treatment, but the effects were more delayed in this group, with only 4/15 (27%) reporting response at the end of radiotherapy. Pelvic pain response was intermediate, with 14/21 (67%) reporting response at the end of treatment and 10/13 (77%) at the 12-week follow-up.

According to statistical tests, HRQOL among the 33 patients capable of complying with study procedures remained stable throughout the study. However, 38-40% of patients reported clinically significant improvement in HRQOL at each of the three follow-up visits.

Pelvic toxicities, largely comprising grade 1–2 proctitis, diarrhea, nausea, dysuria and urinary frequency, peaked at the end of radiotherapy. With the exception of dysuria, all of these subsequently decreased to lower prevalence than baseline levels. There were no grade 4 toxicities. In general, pelvic symptoms improved during the study.

Median overall survival among the included patients was nine months. Low albumin and lower than the median age were identified as independent predictors of study attrition.

Conclusion: Palliative pelvic radiotherapy for symptomatic primary or recurrent rectal cancer contributes to effective palliation without significant toxicity. Treatment with 30–39 Gy is effective across a range of pelvic symptoms which often occur simultaneously and may respond differently. Although HRQOL remains stable or even improves in some patients after palliative pelvic radiotherapy, a large proportion have such limited survival that simpler fractionation schedules should be considered in selected patients.

6. DISCUSSION

This research project was designed to study symptomatic effects of palliative pelvic radiotherapy of prostate and rectal cancers using a step-wise methodological approach. Systematic reviews of the literature demonstrated clear gaps in the evidence for palliative pelvic radiotherapy in both prostate and rectal cancers. A pilot study explored prospective evaluation of PROs in these clinical scenarios and confirmed feasibility. Finally, a prospective multicenter study documented for the first time the magnitude and time course of symptomatic effects and toxicities of palliative pelvic radiotherapy of prostate and rectal cancers using PROs. This PallRad1 study demonstrated that palliative pelvic radiotherapy in the range of 30–39 Gy is effective across a range of symptoms and is well-tolerated.

6.1 Evaluation of the evidence: two systematic reviews

At the time the two literature reviews were conducted, there was an almost complete lack of prospective trials examining palliative radiotherapy of both prostate and rectal cancers (68, 80). Therefore, it was not feasible to restrict inclusion of evidence to prospective trials reporting PROs. Instead, the majority of the studies included were retrospective case-series and non-randomized trials (level III or IV in the hierarchy of EBM, Figure 6). The two literature reviews do not comply with all of the standards of EBM guidelines and instead follow some of the principles of the CER model of evidence synthesis. CER aims to answer a slightly different question than EBM, namely whether an intervention is *capable* of having the desired result, rather than asking if an isolated intervention is *adequate* to accomplish a purpose (57).

The two literature reviews included in this thesis are referred to as *systematic* reviews because they have followed a methodical, reproducible scientific process including a thorough literature search and rigorous evaluation of results. This transparent process aims to make research findings and limitations (including risks of random and systematic errors) clear to the reader, thereby reducing the risk of bias in drawing conclusions and making recommendations.

As part of the systematic evaluation of studies, a formal assessment of methodological quality of a short-list of the studies screened in full text was done (Table 4). At the time in which the literature reviews were conducted, scoring systems to evaluate observational studies had not been standardized. Although there is still no consensus, an item bank for assessing risk of bias in observational studies has since been published (81, 82). The checklist items used were largely in agreement with those currently recommended.

Synthesis of study results in meta-analyses was not feasible due to the heterogeneity of studies reviewed and the way in which data were presented in the primary studies. However there is value in a clearly synthesized presentation of data from observational studies (83). We therefore opted to present results descriptively, with arguments for and against the significance of the primary studies, rather than refraining from conducting the reviews. It is left up to the reader to determine how to apply the results of the literature reviews (84).

For physicians seeking guidance for clinical practice, neither of the reviews was able to provide clear practice recommendations. Above all, this is due to the methodological shortcomings of the included studies. The studies were largely outdated, small and retrospective, with a large degree of

heterogeneity. Patients, treatments, outcomes, and definitions of key concepts such as "palliative intent" were variable and confounders not accounted for in the reports. These factors limit the robustness of the summative review of evidence.

However, the take-home message for clinicians is that there is an appreciable degree of consistency in the studies indicating that palliative pelvic radiotherapy of both prostate and rectal cancers appears to be effective for a range of pelvic symptoms, across a range of total doses. In fact, symptomatic response rates and toxicity profiles were similar for the two diagnoses and consistent with findings in other pelvic cancers (85). Both of the reviews support the practice of palliative pelvic radiotherapy, but neither was able to conclude with a description of the expected onset, magnitude, or durability of symptom palliation. Nor could conclusions be reached regarding toxicity or with respect to recommendations for preferred fractionation schedules for different symptoms or clinical scenarios.

For researchers, however, the systematic literature reviews have more tangible and applicable recommendations. They demonstrate the fundamental value of the PallRad1 study. By elucidating the paucity of scientific evidence, they make a strong argument for the need to explore palliative pelvic radiotherapy of prostate and rectal cancers prospectively, in order to build a valid evidence base consistent with modern standards and practices (56).

6.2 Ethical considerations regarding the clinical studies

Ethical concerns regarding research among patients receiving palliative treatment are in principle no different than among other patient groups. However, as in nearly all fields of research, there are hallmarks of the population under study that make certain ethical questions particularly relevant.

One such issue is that patients with incurable cancer may be considered especially vulnerable. Many are frail, elderly, and may in addition be cognitively impaired due to disease-processes or side-effects of medications. This vulnerability is especially relevant because of patients' reliance on caregivers and their physicians. In the PallRad1 study, treating oncologists were often also the ones carrying out study procedures. This is not ideal, but was necessary in order for the study to be feasible.

Patient care takes precedence over research, and patients undergoing palliative treatment often have complex and unpredictable clinical courses, with changing needs from day to day. Therefore, symptom-targeted research requiring standardization of procedures is notably difficult in this group. Consequently, these patients are underrepresented in clinical research. In comparison to patients treated with curative intent, scientific documentation has not been as highly prioritized in palliative populations. This has led to a lower standard of research and a relatively weak evidence-base. Rather than "gate-keeping" by defining this patient group as one which should not be burdened with study procedures toward the end of life, the current project is built on the premise that it is unethical not to address the evidence gap in this patient group. Researchers must instead strive to maintain the same scientific standards for palliative treatments as are held for curative interventions.

Radiotherapy, even at low doses, carries some risk of side effects and complications. However, as the radiotherapy delivered in the context of the SFK1 and PallRad1 studies was prescribed prior to inclusion, toxicities cannot be attributed to the studies.

For participants in the PallRad1 study, the burden of participation lay in attending one or two additional follow-up visits and added time at each of these visits filling in study questionnaires. In many cases, patients would have been seen at the hospital on these occasions regardless of study participation, as they had advanced cancer and therefore required further care and close follow-up. Patients could, at any time, withdraw their consent to participate. In addition, they were given the option of follow-up by a combination of telephone interview and mailed questionnaires if the burden of the study visits became too great. However, the feasibility study had given an indication that patients generally appreciated the opportunity for more thorough follow-up with an oncologist after radiotherapy.

Patients who receive palliative care are given multidisciplinary treatment where not only their physical, but also their psychosocial and spiritual needs are addressed. The present study could not possibly account for the numerous confounders that affected treatment outcomes. However, to ensure the continued ethical treatment of patients, no restrictions were placed on other palliative measures during the study period once patients were included.

6.3 Methodological considerations: feasibility testing (SFK1 study)

The SFK1 feasibility study sought to find an appropriate, realistic balance in the tradeoff between optimal scientific method and acceptable burden of study procedures on participants. The central research questions were:

1. How many patients can be included and how many of these will complete the study?
2. Are PROs acceptable endpoint measurements and what assessment schedule is reasonable?
3. Is it feasible to develop this model into a larger, multicenter study?

Concept validity refers to the capability of study data to provide the answer to a given research question. In order to do so, study endpoints must be appropriate and the chosen measurements able to capture them. In the projected PallRad1 study PROs were the preferred endpoints to examine symptomatic effects of palliative radiotherapy. Tools for assessing PROs are often complicated, frequently involving multiple repeated questions. Their use requires time, concentration, insight, and cooperation on the part of study subjects. This approach may therefore be unfeasible given the potential burden it may place on the patient and on the health-care environment.

This dilemma, coupled with the general challenges of prospectively studying the target patient groups (Table 1), called for a dedicated feasibility study to guide planning of the projected larger PallRad1 study.

Due to the exploratory nature of SFK1, broad eligibility criteria were chosen. Inclusion of a heterogeneous sample with many potential confounders may be seen as a methodological shortcoming. However, it was important at the feasibility testing stage in order to ensure external

validity and to identify factors, such as which radiotherapy doses and diagnostic groups to pursue in PallRad1.

Inclusion of heterogeneous patients can also be a disadvantage in feasibility testing. One of the questions explored in SFK1 was whether patients were willing and able to complete the study and to comply with study procedures. These answers largely depended on the individual's health status, which in turn, was related to prognosis. Based on their good general health and expected survival time, several study patients with asymptomatic prostate cancer limited to the pelvis had been prescribed relatively high total radiotherapy doses (50–60 Gy). Inclusion of these patients made the SFK1 cohort as a whole relatively "healthy" and, therefore, potentially better able to fulfill study procedures than patients with symptomatic prostate and rectal cancers selected for 3Gy x 10–13, as intended in the PallRad1 study. This treatment selection bias was among the issues that had to be considered in the planning the PallRad1 study.

Care was taken to set realistic goals regarding what could be expected of the study participants, while bearing in mind that the follow-up study would benefit from robust outcomes. Evaluations were kept to a minimum in order to reduce the burden on participants and avoid missing data. Timing of outcome measurements was based on clinical judgment.

It was not the aim of the feasibility study to report the results of symptom responses, toxicity scores, or HRQOL. Serial measurements were nonetheless undertaken in order to test whether a follow-up study would be able to assess response over time. Serial measurements provide a clinically meaningful aspect of symptom outcomes. Although daily symptom registration would have been preferred to explore the time-course of symptoms and toxicities, compromises had to be made in order to reach a feasible balance.

Because the number of visits had to be limited, these were set at time points most likely to reflect changes in the outcomes of interest, and which were also practical for the patients. The follow-up visit set six weeks after radiotherapy completion was intended to represent a time point for which potential responses to radiotherapy would be apparent in the majority of responders. The subsequent visit, 12 weeks post-radiotherapy completion was intended to capture continued response, thereby giving an indication of durability of the effect. During the course of the study (once the first 12 patients had shown acceptable compliance and did not appear overburdened), an end-of radiotherapy visit was added. Patients were already receiving daily treatment and the additional study visit had the potential added value of providing information about the time course of the effects and side effects of treatment.

Patient questionnaires were completed while study participants were still at the treatment center. This procedure ensured that any questions or confusion regarding the forms could be clarified and the forms quality-assured (e.g. Are all items filled out? Is only one answer provided per question?), and collected immediately. The use of radiotherapists to this end, as part of a multidisciplinary research team, appeared to minimize missing data.

SFK1 was vital for the planning of the PallRad1 study. It demonstrated physicians' willingness to include patients in a study of palliative radiotherapy, patients' willingness to enter the study, and their ability to comply with procedures despite advanced stages of disease. Moreover, it gave an indication of the distribution of diagnoses, the number of patients available, and an indication of the doses and fractionations being used at that time. Finally, it demonstrated the feasibility of using PROs, including repeated use of somewhat complex questionnaires, and suitability of the number and timing of the study visits. All of these factors were considered in the planning of PallRad1.

6.4 Methodological considerations and appraisal of results: the PallRad1 study

6.4.1 Study design

As evidence describing the effects of the various radiotherapy doses was lacking when the PallRad1 study was being designed, a phase II approach was the natural next step in investigating symptomatic effects and toxicities of palliative pelvic radiotherapy in prostate and rectal cancers. Withholding treatment from control-groups was deemed unethical based on strong clinical traditions maintaining that the radiotherapy is beneficial and on the existence of some, albeit weak, evidence corroborating this tradition (68, 69). A comparative study, randomizing between different radiotherapy doses and fractionation schedules was not undertaken due to the potentially prohibitive number of patients necessary as well as a lack of robust effect data on which to base the determination of sample size.

The Pallrad1 study intended to explore the magnitude and timing of effects of pelvic radiotherapy in terms of symptom palliation, acute toxicity and changes in HRQOL. Duration of follow-up was limited to 12 weeks after radiotherapy completion and timing of each study visit was based on the expected clinical course and on experience from the SFK1 feasibility study. In order to avoid overburdening study participants, only three post-radiotherapy evaluations were conducted. The end of treatment follow-up was intended to capture acute side-effects and early responses, while the six and 12 week follow-ups were intended to provide information about the degree, timing and duration of symptom responses, side-effects, and HRQOL changes.

The PallRad1 study was designed according to principles of CER, which focuses on assessments made within real clinical practice. Rather than "artificially" controlling the clinical contexts in order to eliminate their influence on the outcome, these were largely maintained within the study (57). This is in line with the nature of much palliative care research (61).

By the same token, eligibility criteria for the PallRad1 study were kept relatively liberal. Factors favoring homogeneity and limiting confounding were balanced with measures facilitating enrollment and assuring representativeness of the study samples. The number of eligible patients was naturally limited by efforts to ensure that the samples were homogeneous. In order to compensate for this, a nationwide research network of radiotherapy centers was established in 2009. All but one of the nine treatment centers in Norway participated and all hospital types, including both community-based and large university hospitals participated. Despite a limited number of study participants, both PallRad1 study cohorts appear to be representative of real clinical practice.

6.4.2 Causality

Internal validity refers to the degree of confidence that a causal relationship exists between variables in a study. In the PallRad1 study, the critical question was whether the palliative pelvic radiotherapy was, in fact, responsible for the symptom, toxicity, and HRQOL changes reported. As these outcomes were studied without the use of a control group, the potential for confounding had to be given special attention.

Eligibility criteria excluded patients for whom concomitant treatments (e.g. chemotherapy) were likely to have affected the pelvic tumor. Such treatments could affect target symptom severity, making evaluation of the effect of palliative pelvic radiotherapy impossible. Particularly in non-randomized studies, both observed and unobserved confounders inevitably pose a risk of bias that cannot entirely be eliminated. Therefore, lesser concomitant interventions and treatments that did not prohibit study inclusion, but that potentially impacted upon patients' symptoms and HRQOL, were documented at each study visit. Particular attention was given to the dose of analgesics used. In a similar manner, separating toxicity of pelvic radiotherapy from potential toxicities caused by other interventions, or symptoms of progressive pelvic cancer, was not feasible. Consequently, treatment-related toxicity (although minimal) may have been overestimated.

Randomization of study participants to continued palliative care with or without palliative pelvic radiotherapy could in theory have reduced confounding. However, as mentioned previously, this approach was deemed unethical. According to the principles of CER, the presence of potential confounders is not a limitation, but strength of the PallRad1 study. The argument is that the complexity of multiple overlapping palliative interventions creates clinical scenarios that are more representative of real life. This contributes to the external validity of the study, that is, the degree to which results can be generalized.

6.4.3 Radiotherapy

The systematic literature reviews included in this thesis demonstrate that there is considerable variation in the radiotherapy approaches used to palliate pelvic symptoms of both prostate and rectal cancer (68, 80). Observational studies may justify leaving the spectrum of admissible radiotherapy doses and fractionation schedules open, as was done in the SFK1 feasibility study. However, standardization of a studied intervention is advantageous when aiming to understand its effects. It facilitates interpretation of results and application of findings in clinical practice. Some demarcation of the radiotherapy used in PallRad1 was therefore desired.

Standardization of radiotherapy for the PallRad1 study was based on informal feedback from Norwegian radiation oncologists after the project plan had been presented at a national radiotherapy conference on the subject of palliative radiotherapy (Norsk Stråleterapimøte, 2009). The practice most commonly used on a national level at that time was sought in order to facilitate inclusion of a sufficient number of patients within a reasonable timeframe and to ensure that the results would reflect current practice. Thirty to 39 Gy, delivered in 3 Gy fractions, was deemed a reasonable range, which also permitted grouping of the study participants in the analysis. Although there is a biological difference between the doses at either end of this spectrum in terms of both anti-tumor effect and

damage to healthy tissues, this was deemed to be a reasonable compromise so that sufficient patients would be available.

Short-course pelvic radiotherapy (25 Gy in 5 consecutive daily fractions) for palliation symptoms of rectal cancer gained popularity during the time that PallRad1 was recruiting patients. This was unforeseen, and limited the number of patients with rectal cancer eligible for inclusion.

When the PallRad1 study was being designed, CT planning was standard practice for palliative radiotherapy. It was therefore defined as the preferred radiotherapy planning procedure in the study. IMRT has subsequently become standard practice in some radiotherapy centers. As a consequence, the radiotherapy used in PallRad1 could by some standards now be considered outdated or imprecise. However, CT planning for palliative radiotherapy is still widespread and will likely continue to be used in the future. The fact that the level of radiotherapy precision used in PallRad1 was sufficient to achieve good results without significant toxicity is also important. It indicates that more technologically advanced procedures may not be necessary.

6.4.4 Outcomes

The PallRad1 study evaluated palliative pelvic radiotherapy in the setting of progressive, incurable malignancy where multiple simultaneous and varied treatments were given. Although palliative pelvic radiotherapy was the major and unifying intervention in the study, and the only one that was standardized, study outcomes must be interpreted as the effect of *palliative pelvic radiotherapy delivered within the greater context of palliative oncologic treatment*, rather than solely attributed to the isolated effect of radiotherapy.

6.4.4.1 *Target symptoms*

Participants in the PallRad1 study defined for themselves the target symptom of the radiotherapy they were given. They then made serial anchor-based assessments of how the severity of this target symptom changed over time. As such, patients were responsible for evaluating whether or not the target symptom had changed in a clinically meaningful way. This approach was chosen to examine the primary endpoint because of its clinical relevance and simplicity, which was also anticipated to increase the likelihood of compliance compared to more complex tools of patient-reported symptom assessment.

Target symptoms identified by the patients were similar in the two diagnostic groups. Rectal dysfunction in patients with rectal cancer and LUTS in patients with prostate cancer both indicate a degree of obstruction. Target symptom severity over time for both diagnostic groups is presented schematically in Figure 13.

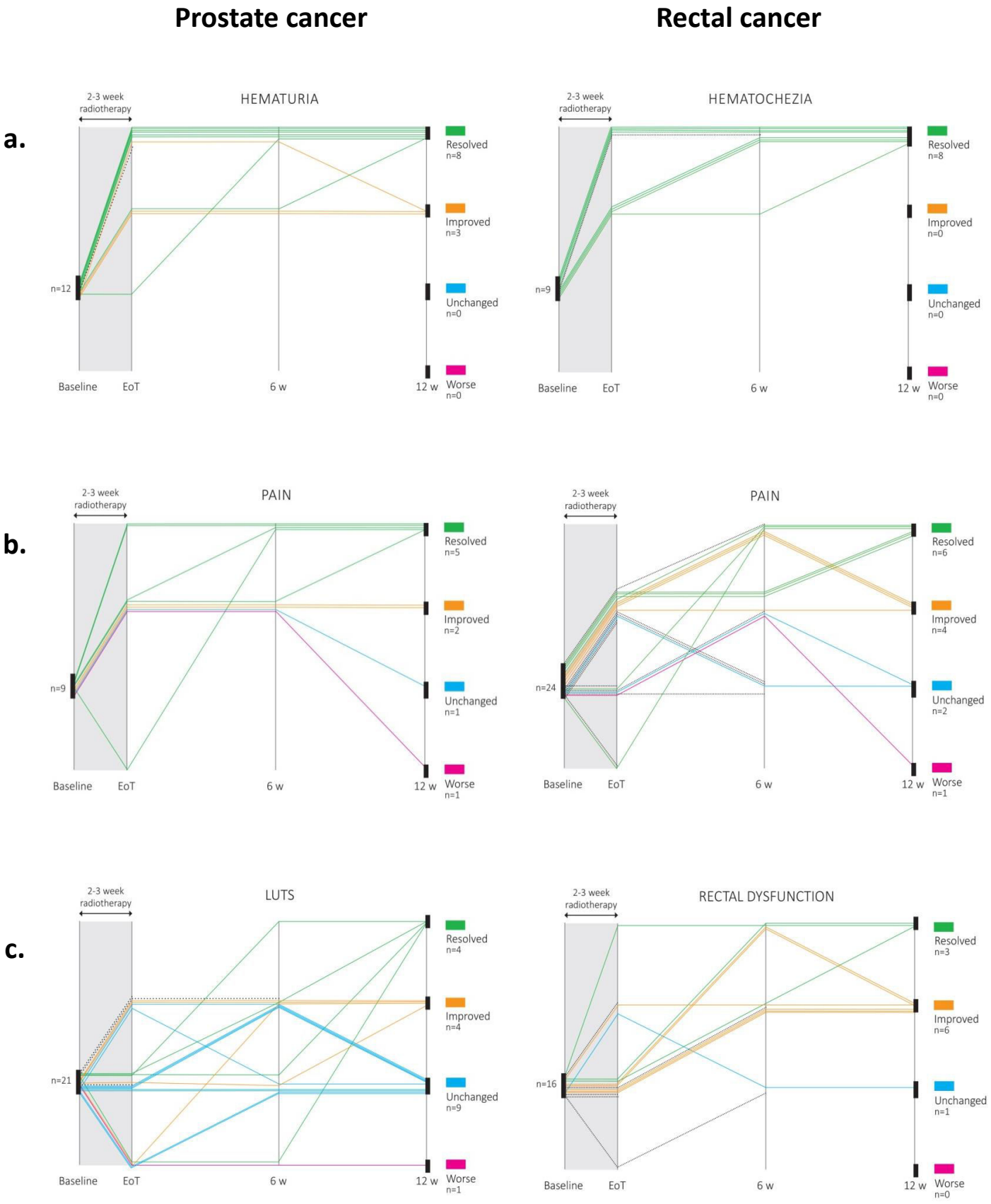

Figure 13: Target symptom severity in patients with prostate and rectal cancer treated with palliative pelvic radiotherapy. EoT = End of treatment; 6w = 6-week follow-up; 12w = 12-week follow-up; ⋮ = patient that did not complete the study; LUTS = lower urinary tract symptoms.

6.4.4.1.1 *Bleeding*

In both diagnostic groups of the PallRad1 study, bleeding was the most consistently well-palliated target symptom. Both hematuria and hematochezia responded quickly, often within days, and effects were sustained until at least 12 weeks after radiotherapy completion (Figure 13 a). This is in line with findings in other pelvic cancers where hypofractionation and delivery of large single doses (6–10 Gy) have gained popularity (85, 86).

The majority of studies of palliative pelvic radiotherapy of bladder cancer demonstrate positive effects on hematuria (87-89). The largest prospective trial of palliative pelvic radiotherapy of bladder cancer (N=272 evaluable patients) was a randomized study comparing 35 Gy in 10 fractions to 21 Gy in 3 fractions. There was no difference in physician-assessed symptom palliation or toxicity, with 68% of patients overall achieving symptomatic improvement three months after treatment (90). Several other studies examining symptoms of bladder cancer, including hematuria, have shown symptomatic response, acceptable tolerance and added convenience of hypofractionated radiotherapy (87-89, 91).

In palliative pelvic radiotherapy of cervical cancer, there is some evidence and a relatively well-established clinical tradition for hypofractionation (86, 92) and the use of single large fractions of 10 Gy, often repeated at 3-4 week intervals or as needed (85). A 2010 systematic review of the literature, including largely observational, retrospective studies, indicates that such repeated large fractions are effective and well-tolerated for control of bleeding (45–100% response rates), and may also have a positive effect on pelvic pain and vaginal discharge (85).

6.4.4.1.2 *Pain*

Pelvic pain was effectively palliated in both PallRad1 cohorts and the positive effects were seen early, often within the 2–3 week treatment period (Figure 13 b). Just as it has with bleeding, palliative pelvic radiotherapy has been shown to relieve pain caused by pelvic bladder and gynecological tumors with acceptable toxicity profiles (85, 86, 88-90, 92).

The BPI was used in an effort to improve documentation of pain in the PallRad1 study. However, in addition to advanced pelvic malignancy, the majority of study participants had distant metastases at the time of study entry. Only the pelvic tumor burden was targeted specifically by the studied radiotherapy. Distant metastases were therefore likely to progress, leading to more symptoms during the approximately four month study duration. Although attempts were made to limit confounding by non-pelvic symptoms and treatments thereof, the study was not designed to specify the location of pain that caused patients to alter their analgesic use. Pain scores and the amount of analgesic used to treat pelvic pain caused by cancerous growth may therefore be overrepresented by the BPI pain scores and amount of analgesic used. BPI responses were inconsistent, not always reflecting circumstances in the pelvis. Interpreting BPI results for the specific pain under study was therefore nearly impossible. As a consequence, BPI results were not reported in the publications. The same was true for pain scores from the EORTC questionnaires. Patients' anchor-based ratings of "target symptom" severity are more accurate indicators of the target pain severity than questionnaire scores or changes in analgesic dose.

The spectrum of pelvic pain targeted in PallRad1 represents combinations of visceral, musculoskeletal, and neuropathic pain entities. Pain due to malignant invasion is generally considered moderate to severe; therefore, opiates are often indicated. Systemic opioids have the advantages of efficacy, the potential to target pain in several areas simultaneously, and ease of administration and titration. However, there are draw-backs to the use of opioids, particularly in an elderly population. Specifically, constipation, urinary retention, sedation, risk of delirium, and drug-interactions pose threats to safety and patient acceptance of opioids. These factors are generally dose-dependent and may limit appropriate titration, leaving patients with insufficient doses for adequate pain control. Adjuvant analgesics such as NSAIDS, paracetamol, steroids and anticonvulsants may also play a role, but these also have side-effects and add to the risk of polypharmacy. Palliative radiotherapy may therefore be indicated not only to relieve pain, but also to spare patients from the untoward effects of analgesics.

6.4.4.1.3 *Obstructive symptoms*

Of the three main target symptom categories, obstructive symptoms were least well-palliated in both prostate and rectal cancer cohorts and more often required several weeks to respond (Figure 13 c).

The PallRad1 protocol did not call for radiological evaluation of the pelvic tumor after the studied radiotherapy. CT scan or MRI could potentially have documented tumor shrinkage or lack thereof, but this information would not necessarily have had clinical implications in patients' further management. Evaluation of the palliative pelvic radiotherapy was based purely on symptom response, as it is in routine clinical practice. As such, subjecting study participants to standardized radiological investigation, purely for academic interest, was not justified within the context of the Pallrad1 study.

Endoscopic resection, stent placement, catheterization and surgical diversion may palliate symptoms of rectal or bladder obstruction due to pelvic cancer. However, patients may be troubled by the inconvenience and discomfort of these invasive procedures, which also carry risks. Brachytherapy and local ablative techniques (93) have been investigated, yet evidence is not sufficient to recommend these techniques above radiotherapy (94). More aggressive surgical options such as palliative primary tumor resection would appear unjustified in most of the studied patients given their considerable extrapelvic tumor burden and limited life-expectancies.

6.4.4.1.3.1 *Obstructive symptoms in prostate cancer*

Although palliative pelvic radiotherapy in the PallRad1 study was shown to be a good treatment across a range of target symptoms in prostate cancer, LUTS stood out as not responding to the same degree as did the other major target symptoms - bleeding and pain (Figure 13).

Palliative transurethral resection of the prostate (TURP) is commonly used to treat LUTS caused by prostate cancer. Although it is considered a safe procedure, it carries greater risk of complications in prostate cancer than in benign prostatic hypertrophy (95-98). Furthermore, it is estimated that 40% of patients with CRPC and LUTS do not benefit from TURP (97). This may be explained, in part, by the fact that a proportion of patients with LUTS and CRPC do not have urodynamic bladder outlet

obstruction, but rather a significant component of reduced bladder capacity and detrusor overactivity, or a combination of these conditions (95). It is hypothesized that as prostate cancer progressively invades the bladder or obstruction becomes chronic, the relative contribution of true bladder outlet obstruction decreases and other mechanisms such as detrusor overactivity dominate (95, 97).

In a retrospective study of patients with locally advanced PC undergoing palliative TURP for symptoms of bladder outlet obstruction, only a 48% decrease in the average International Prostate Symptom Score after TURP was found (99). This is not dissimilar to the 44% response rate found in the irradiated PallRad1 patients with target symptom LUTS 12 weeks after treatment. Furthermore, a similar study demonstrated that when pre-operative urodynamic testing was used to select only patients with manifest bladder outlet obstruction prior to surgery, response rates were much higher; with 84% of patients catheter and intervention-free and 95% voiding spontaneously, at one year follow-up. In the same study, over 50% of the men who underwent urodynamic testing did not proceed to TURP because of failure to identify bladder outlet obstruction (97).

In the PallRad1 prostate cancer cohort, the effect of palliative radiotherapy on LUTS was poorer, slower, and less durable than on hematuria and pain. Based on these findings and what is known about TURP in prostate cancer, it is reasonable to hypothesize that symptomatic response for the group of prostate cancer patients complaining primarily of LUTS may improve if only those patients with manifest bladder outlet obstruction were included, and in addition, those with secondary bladder dysfunction were treated with alpha-blockers and antimuscarinics prior to radiotherapy.

6.4.4.1.3.2 *Obstructive symptoms in rectal cancer*

All evaluable patients with rectal cancer who defined obstruction as their chief complaint reported benefit from the radiotherapy. The proportion of responders increased over time, indicating a slower onset of palliative effect compared with other target symptoms.

In the period of time since the literature searches for the systematic review of rectal cancer included in this thesis were performed, two prospective studies of patients with symptomatic obstructive rectal cancer treated with short-course palliative pelvic radiotherapy (25 Gy in 5 consecutive daily fractions) have been published. Both studies report improved obstructive rectal symptoms and reduced need for diverting stoma, with acceptable acute toxicity (100, 101).

Short-course radiotherapy is gaining acceptance in curative multidisciplinary treatment of rectal cancer. In this context, effects and tolerance have been shown to be positive, and significant down-staging several weeks after radiotherapy has been documented (102).

In an attempt to palliate symptoms and avoid surgery, Tyc-Szczepaniak and colleagues treated 40 patients with primary rectal cancer and synchronous distant metastases with short-course radiotherapy followed by systemic chemotherapy. 67% of patients reported a sustained positive palliative effect (non-validated patient self-report) after the combination of radiotherapy and

chemotherapy and only eight of 40 patients required surgery during the further course of their disease (101).

Picardi et al. conducted a small phase 2 study of 18 patients given short-course palliative pelvic radiotherapy alone for symptoms from an obstructive rectal tumor. Physician-assessed improvement or resolution of obstruction, pain, or bleeding was reported in 16 of 18 participants (89%). In addition, the study demonstrated radiological down-staging in 12 of 18 patients and meaningful results with regard to the avoidance of diverting stoma (100% 1-year colostomy-free survival) (100).

These studies have major weaknesses, including a lack of PROs and validated tools for symptom assessment, large gaps in symptom and toxicity assessments and significant potential treatment confounders. However, they indicate that in addition to palliation of obstructive symptoms in the short-term, short-course radiotherapy may be used to delay and even avoid the need for surgical intervention of obstruction, despite impending luminal occlusion.

6.4.4.1.4 *Other target symptoms*

Although it was rarely identified as the target symptom, edema also improved after radiotherapy in the PallRad1 study. When caused by malignant invasion of pelvic lymph nodes, lymphedema cannot be satisfactorily reversed without targeting the cancer that is obstructing lymphatics upstream. Other symptomatic management options include manual lymphatic drainage and compression, exercise, and elevation of the extremity. However, these have limited efficacy and are often impractical toward the end of life.

6.4.4.2 Toxicity

In order to limit the burden of serial PRO questionnaires, physician rather than patient reporting was chosen to document toxicity in the PallRad1 study. Because it is inappropriate to infer that a symptom does not exist simply because it is not spontaneously reported by a patient, active capture of toxicity was used. CTCAE grading was chosen in order to standardize reporting using a scale familiar to readers of medical research. This scale evaluates symptoms without specifying their cause.

Acute toxicity was not a clinically significant problem in the PallRad1 study, as indicated by CTCAE v 3.0 scores which in fact decreased over time (Figure 14).

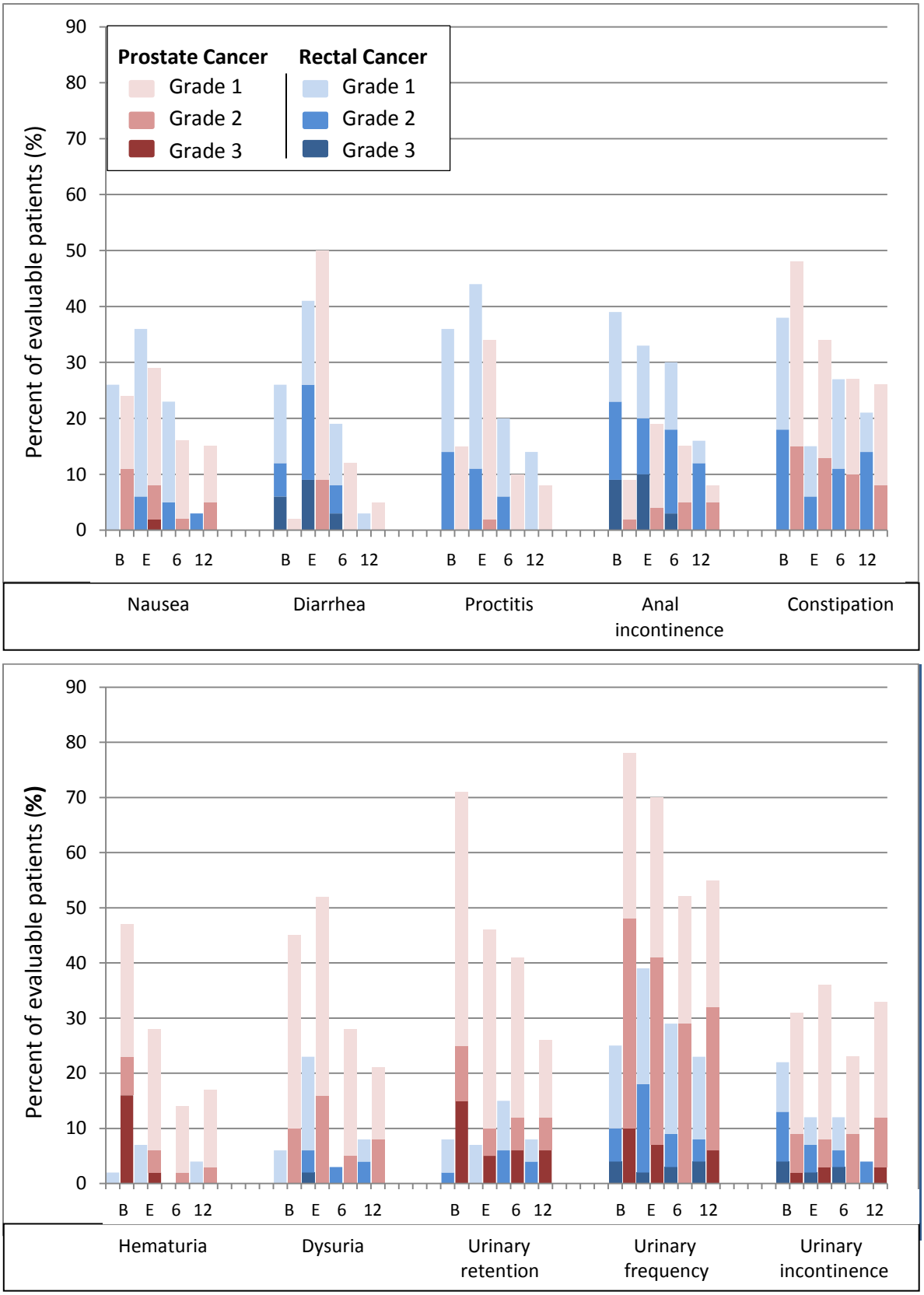

Figure 14: Toxicity. Percent of evaluable patients reporting various symptoms at each of the four study visits (B = baseline; E = end of treatment; 6 = 6-week follow-up; 12 = 12-week follow-up). Symptoms are graded according to NCI-CTCAE 3.0. There were no grade 4 symptoms reported.

Not surprisingly, urinary symptoms were more pronounced than rectal symptoms among patients with prostate cancer. The opposite was found for the patients with rectal cancer, among whom there was a predominance of gastrointestinal symptoms (Figure 14). Urinary tract symptoms that appeared in the rectal cancer cohort after radiotherapy, and gastrointestinal symptoms that appeared in the prostate cancer cohort after radiotherapy, may therefore more accurately reflect the true contribution of side-effects of radiotherapy on the total pelvic symptom burden.

Because symptoms of advanced pelvic prostate and rectal cancers are much the same as expected toxicities after pelvic radiotherapy, active capture of pelvic toxicity was able to demonstrate that the multitude of pelvic symptoms present at baseline improved over the course of the study. This leads to the conclusion that radiotherapy contributes to palliation of several cancer-symptoms simultaneously. Methodologically, this finding reflects "oversimplification" of tracking a single target symptom when the situation in the pelvis is decidedly more complicated than that which the course of a single pelvic symptom can convey.

Simultaneous improvement of multiple pelvic symptoms in the PallRad1 study is a clinically significant finding. It gives added value to palliative radiotherapy compared to other interventions such as stent placement or analgesics, which can target only one or a few isolated symptoms.

Lack of study follow up beyond 12 weeks precluded evaluation of late radiotherapy toxicity in the PallRad1 study. It has been shown that mild late toxicities manifest approximately a year after palliative pelvic radiotherapy of bladder cancer with doses in the range of 30–39 Gy (90). Although patients with metastatic CRPC generally have longer life-expectancies than patients with metastatic bladder cancer, results of PallRad1 indicate that few patients live for over a year after the radiotherapy. Thus, there is little risk of developing late complications, which in other cancers and in the reviewed literature have been described as acceptable (68, 80). Among the PallRad1 study patients with rectal cancer, where survival was considerably shorter, this is even less of a concern.

6.4.4.3 *Health-related quality of life*

Based on the outcome of the SFK1 feasibility study, the EORTC QLQ questionnaires were chosen to evaluate HRQOL in PallRad1. These are well-established instruments that have demonstrated validity and reliability across a range of conditions, including among patients with prostate and rectal cancers and in the setting of both palliative treatment and radiotherapy (47, 49, 50). Further validation of the instruments in the specific PallRad1 setting was therefore determined to be unnecessary and beyond the scope of this project.

Clinical significance in PRO research establishes a threshold that the patient defines as important. The notion of clinical significance is central in small studies, such as PallRad1, where statistically non-significant findings may otherwise be ignored (type II error). It has been suggested that the common statistical standards defining significance in biomedical science (p-value ≤ 0.05) may be too stringent in research of palliative treatment (61).

In both PallRad1 diagnostic cohorts *clinically* significant improvement was reported among patients evaluable for HRQOL scores six and 12 weeks after palliative pelvic radiotherapy (38–39% for prostate cancer and 40% for rectal cancer). When weighing the significance of these findings, consideration must be given to the illness trajectories of the PallRad1 cohort (Figure 10). Progressive

malignancy generally corresponds to increasing symptom burden and a downward trajectory of functional status and HRQOL. Treatment that does not slow cancer progression cannot be expected to result in durable improvement in HRQOL. Thus, despite the lack of statistical significance, it is clinically relevant that HRQOL in both PallRad1 cohorts remained stable or improved in many patients during the 12 weeks of follow-up.

6.4.4.4 *Timing of radiotherapy effects and side-effects*

It was not possible to determine precisely when patients experienced improvement or worsening of symptoms, toxicities, or changes in HRQOL in the PallRad1 study because assessments were conducted at fixed time points and limited in number. Evaluation at only 3 time points, rather than continuously, may have led to missing transient changes (including peaks and troughs) in symptom and toxicity severity, thereby, misrepresenting the true symptom and side-effect burden.

For the same reasons, duration of symptom, toxicity and HRQOL changes could not be accurately assessed. Twelve weeks of follow-up is insufficient to determine the duration of effect, the need for repeated intervention or to evaluate long-term side-effects of palliative pelvic radiotherapy. Additional evaluations beyond the 12-week follow-up would have been beneficial, particularly in the prostate cancer study, where survival was longer.

6.4.4.5 *Summary of palliative pelvic radiotherapy outcomes*

The findings of the PallRad1 study indicate that there is a potential for improved overall well-being after palliative pelvic radiotherapy in both prostate and rectal cancers, despite potential progression of metastatic disease. This is logical when one considers (a) effective palliation of the target symptom, which was defined by patients as their most troublesome symptom, (b) toxicity data indicating palliation of a spectrum of less troublesome pelvic symptoms, and (c) little to no imposed toxicity. The radiotherapy contributes to palliation of pelvic symptoms to a similar degree and in a similar manner, regardless of whether the underlying cause is prostate or rectal cancer. These findings are consistent with the conclusions of the systematic reviews included in this thesis and with results reported for palliative radiotherapy of other pelvic malignancies (85, 90).

6.4.5 Prognostication

In addition to understanding the likelihood and expected degree of symptomatic improvement and toxicity after a palliative intervention, it is important that physicians consider the predicted time course of these effects. The serial symptomatic assessments made in the PallRad1 study, although limited, were intended to explore the onset and duration of symptomatic improvement and toxicity after radiotherapy. These temporal aspects are valuable when prioritizing different treatment options and deciding on their timing.

A striking finding of the PallRad1 study was the rapid decline of many patients with rectal cancer despite the treating physician's prediction that they would live long enough to benefit from a 2–3 week course of radiotherapy. Although predicted survival of at least three months was an inclusion criterion, the PallRad1 study was closed for inclusion of patients with rectal cancer before reaching

the target of 40 fully evaluable patients, largely due to participants' failing health prior to 12 weeks of study follow-up.

Notwithstanding the positive symptomatic results of the PallRad1 study, subjecting patients to 2–3 weeks of radiotherapy towards the end of life must be carefully weighed given that toxicities may appear quickly and symptomatic improvement may be delayed for up to several weeks (103, 104). Due to progressive distant metastases, several PallRad1 participants did not live long enough to experience the potential benefits of the pelvic radiotherapy they had been given. In retrospect, it is clear that these patients should not have been treated with 2–3 weeks of palliative radiotherapy in the first place. Further hypofractionation, such as 5 Gy x 5 may have been appropriate for some patients whereas others should not have been given radiotherapy at all. Unfortunately, however, prognostication is challenging. The curve of a patient's downward trajectory (Figure 1) is often difficult to predict, even at the end of life (105, 106).

Radiation oncologists tend to overestimate survival among patients undergoing palliative treatment (105, 107). Specific efforts have been made to improve prognostication in this group, but this has proven difficult. Among other efforts, scoring systems have been developed (108) but these have not made their way into routine clinical practice. While not a study endpoint, limited survival among the PallRad1 rectal cancer patients is a very important study finding. It emphasizes the value of sound prognostication and patient selection, as well as the importance of not delaying effective treatments until it is too late.

6.5 FUTURE DIRECTIONS

Findings from this thesis highlight several issues surrounding palliative pelvic radiotherapy of prostate and rectal cancers that deserve further study and should be considered in clinical practice.

6.5.1 Research questions

6.5.1.1 *Symptomatic effects and toxicities*

The likelihood and magnitude of symptomatic effects and side-effects, the time it takes for these to become apparent, and the anticipated duration of these effects should be investigated for the different radiotherapy fractionation schemes commonly in use. This includes further characterization of the range of treatments used in the PallRad1 study. Studies may be conducted using a similar design to PallRad1 or may be randomized with a control-group, where a dose within the range already investigated in the PallRad1 study could serve as the control arm treatment.

6.5.1.2 *Radiotherapy dose and fractionation*

All patients in the PallRad1 study were given daily fractions of 3 Gy. Several of these patients reported relief of bleeding (both hematuria and hematochezia) after a single or a few fractions, while those with obstructive symptoms generally responded late (Figure 13). This finding raises the question of the appropriateness of using different radiotherapeutic approaches for the different target symptoms.

Higher up-front total doses (requiring fractionation) such as those given in the PallRad1 study may be necessary to palliate obstructive symptoms where tumor-shrinkage is necessary. However, pain relief and bleeding, which appears to have an early response pattern, may lend themselves to shorter treatments. The reviewed literature (68, 80) and studies in other diagnoses suggest that lower total radiotherapy doses, given as single fractions and repeated as needed, may be appropriate for palliation of pain and bleeding (86, 90). Response-patterns for the different symptoms and radiotherapy regimens should be specifically investigated.

The target symptoms presented in this study are distressing regardless of where they appear along the patients' illness trajectories. If the effects of lower doses or more hypofractionated courses can be shown to be equivalent to those achieved with more protracted regimens, with acceptable acute and late toxicity, then this would have benefits in terms of convenience and lower treatment costs for all patients, not just the elderly or those with limited life expectancies (Figure 1).

6.5.1.3 Timing of radiotherapy

As palliative treatment options for prostate and rectal cancers increase in number and therapeutic potential, understanding the effects of pelvic radiotherapy becomes increasingly important for clinicians to be able to sensibly prioritize and time the various treatments.

Although unlikely to significantly affect the life expectancy of a patient with metastatic disease, palliative pelvic radiotherapy delivered early in a patient's illness trajectory (Figure 1) increases the likelihood that the patient will survive long enough to glean its full effects. Early radiotherapy may, in addition to palliating existing symptoms, delay the onset of new symptoms and need for further interventions (19, 100, 101). Investigating this aspect requires a study with significant follow-up duration.

Studies such as PallRad1 in which other tumor-targeted therapy is restricted in order to limit confounding are likely to become increasingly difficult to conduct. This challenge may be particularly relevant when investigating radiotherapy given early in the course of metastatic cancers (101), when systemic treatments play a significant role and survival is relatively long, leaving room for many confounding treatments.

6.5.1.4 LUTS

As discussed in section 6.4.4.1.3.1 (obstructive symptoms in prostate cancer), it appears worthwhile to study the use of urodynamic testing prior to palliative pelvic radiotherapy targeting LUTS in prostate cancer. Such an augmented diagnostic approach could help to select only those patients with objective findings of bladder outlet obstruction for radiotherapy. This may lead to improved identification and, consequently, more appropriate management of patients with secondary bladder dysfunction.

6.5.2 Clinical implications

Palliative pelvic radiotherapy of prostate and rectal cancers should be considered along most of the disease trajectories (Figure 1). Although duration of radiotherapy effects and need for retreatment could not be determined in the PallRad1 study, several participants, particularly those with rectal cancer, may have benefitted from earlier treatment.

Radiotherapy courses should generally be kept short, provided that this is feasible without significantly compromising efficacy and safety. In addition to conserving resources, this reduces the time cancer patients spend in treatment, which is particularly meaningful toward the end of life. Short treatment series also lend themselves well to being incorporated into the increasingly complicated treatment landscapes of prostate and rectal cancers.

Re-irradiation with higher, curative doses of pelvic radiotherapy has been shown to be effective and tolerable in pelvic rectal cancer recurrences (109), indicating that retreatment is a viable option in a palliative approach as well.

One barrier to palliative radiotherapy is the increasing complexity and cost of high-technology treatment. By keeping treatment simple, as it was in the PallRad1 study, radiotherapy remains available to more patients. Rather than spending resources to make the radiotherapy technically more complicated, efforts to improve palliative radiotherapy should focus on continuity and fluid transitions of care, broad availability of treatment (110), and dedicated research.

7. CONCLUSIONS

Symptom-targeted pelvic radiotherapy of CRPC and rectal cancer (with a dose of 30 to 39 Gy) contributes to clinically relevant palliation and is well-tolerated in the majority of patients. Bleeding, pain, and obstruction are the most common symptoms reported and they are all well-palliated, although with different response rates and time-courses. Patients often present with a constellation of these and other pelvic symptoms and radiotherapy has the unique advantage of targeting several symptoms simultaneously.

Questions of optimal radiotherapy dose and fractionation schemes in these contexts remain unanswered but findings from the present study provide a more solid foundation of evidence upon which to build. Better patient selection is needed and simplified, shorter courses of radiotherapy, delivered earlier in the course of the disease, may have the potential to improve results further while making the treatment more readily available to the patients that are most likely to benefit.

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PROJECT NOTE Open Access

Patient reported outcomes of symptoms and quality of life among cancer patients treated with palliative pelvic radiation: a pilot study

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Abstract

Background: There is limited high-quality research investigating the efficacy of palliative radiation (PPR) with regard to symptoms and quality of life (QOL) among cancer patients with pelvic soft tissue tumors. As a result, clinicians are left with mainly retrospective studies, without reliable data on which to base treatment decisions. As a first step of a subsequent analysis of PPR's efficacy, we aimed to determine whether it is feasible to prospectively measure symptoms and QOL among patients treated with PPR. A secondary aim was to explore patients' willingness to answer existential questions in the setting of palliative pelvic radiation.

Methods: Patients referred for palliative radiation of soft-tissue pelvic tumors were invited to enter the study. Symptoms were scored by study physicians and QOL was assessed by the EORTC QLQ C-30 questionnaire and site specific modules (PR25, CR38 or BL24) prior to start of radiation and 6 and 12 weeks after its completion. In addition, patients answered existential questions at each of the study visits. A radiation therapist was available to participants in order to answer their questions and ensure that questionnaires were completed.

Findings: Five female and 17 male patients with prostate cancer (14), colorectal cancer (5) and bladder cancer (3) were included in the study. The median age of the participants was 75 years (range 62-90). Twenty patients were still in the study at the 6-week follow-up and 18 patients at the 12-week follow-up. Twenty-one patients had valid responses within all the EORTC QLQ C-30 scales at baseline, 20/20 at the 6-week follow-up and at the 12-week follow-up 17/18 patients still in the study had valid responses within all scales. This level of response was similar in the site-specific modules and among the existential questions.

Discussion: Among patients with prostate, colorectal and bladder cancer, compliance to questionnaires assessing symptoms, QOL and existential questions 6 and 12 weeks after PPR is sufficient to enable evaluation in a larger and more homogeneous patient group in order to reach clinically valid conclusions as to the efficacy of PPR.

Background

The incidences of prostate, colorectal and bladder cancers continue to rise in many western societies [1] as well as in many developing countries as they adopt a more "western" lifestyle [2]. Steadily increasing life-expectancy contributes to increased incidence [3] and with advancements in systemic treatments such as hormonal manipulation, biological agents and chemotherapy, patients can potentially live for many months and even years with advanced stages of malignancy. Palliative pelvic radiation (PPR) is a treatment option with a long clinical tradition in cases of symptomatic pelvic tumors [4-6].

In PPR, there exists a fine balance between ameliorating cancer symptoms versus the potential drawbacks of treatment toxicity and complications, as well as valuable time spent ("lost") in treatment. Radiation oncologists use PPR to treat pain, bleeding, and obstruction, in an effort to indirectly enhance patients' quality of life (QOL) [7]. Physician assessment of symptoms and patient well-being often falls short [8] and ultimately, it is the patients' subjective experience of symptom burden, treatment-related side effects and quality of life that are the important and clinically valid endpoints in palliation. There is, however, limited evidence-based information to support

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the efficacy of PPR with regard to symptoms and QOL of patients with bladder cancer [9,10] and even less so in cases of prostate [11], and colorectal [12] cancers.

Potential areas of practical and ethical conflict in the investigation of palliative treatments include: (a) defining the patient group, (b) inclusion and follow-up of terminally ill patients in a research protocol, and (c) addressing the effects of confounding treatments [13]. Consequently, palliative treatment regimens are often based on local tradition and clinical anecdotes, without hard scientific evidence.

To the best of our knowledge, there exist no published prospective evaluations of PPR among patients with prostate, and colorectal cancer, and only one randomized trial among patients with bladder cancer, that adequately describe its effects on symptoms and QOL. In order to clarify the indication for and dosage of this common procedure, reliable documentation of its effects is necessary. Due to the challenges inherent to this type of research, a pilot study was regarded as a natural first step in this process. The purpose of this study was to determine whether it is feasible to prospectively measure symptoms and QOL among patients treated with PPR. A secondary aim was to explore patients' willingness to answer existential questions in the setting of palliative pelvic radiation.

Methods

Patients

All patients referred to the Center for Cancer Treatment, Sørlandet Hospital Trust, Kristiansand for fractionated palliative radiation of soft-tissue pelvic tumors were screened for eligibility. Eligibility criteria were as follows: age ≥ 18 years, histologically or cytologically proven colorectal (CRC), bladder (BC), or prostate cancer (PC), planned palliative fractionated radiotherapy of soft tissues (not skeletal metastases), life expectancy > 3 months, ability to understand spoken and written Norwegian, no significant cognitive impairment, no treatment with investigational therapy and signed informed consent.

In our institution, fractionated pelvic radiotherapy is given to patients with Eastern Cooperative Oncology Group (ECOG) functional status [14] two or better. ECOG functional status three or worse was therefore an indirect exclusion criterion. Due to the exploratory nature of the feasibility study, concomitant treatment with other anti-tumor therapies (chemotherapy, hormonal manipulation, etc.) was not an exclusion criterion.

Radiation treatment

Fractionation schemes were determined by the treating radiation oncologist prior to referral to the study. Two to four radiation fields with six or 15 megavoltage photon beam radiation were used. Treatment fields were planned based on computed tomography of the pelvis and the target volumes consisted of gross tumor with 1-2 cm margins.

Measurements/evaluation

There were three study visits. The baseline evaluation took place just prior to radiation, and follow-ups were done six and twelve-weeks after completion of radiotherapy. At each visit, the study physician completed a prospective evaluation of symptoms, functional status, medications and complications. Participants completed questionnaires while in the treatment center, assisted by a radiation therapist when necessary. Blood tests, consisting of hematology, liver and renal function, electrolytes, and tumor markers were taken as pre-radiation routine.

QOL was assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30, v.3.0) core questionnaire, developed and validated for use among cancer patients world-wide [15]. It covers aspects of QOL considered to be relevant to most cancer patients, and includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea and vomiting), a global QOL scale as well as five symptoms common among cancer patients (dyspnoea, anorexia, insomnia, constipation and diarrhea) and perceived financial impact of the disease and treatment. This questionnaire has been validated for use among Norwegian patients with heterogeneous cancer diagnoses [16] and among those receiving palliative radiation [17]. In addition, patients filled out site specific modules, depending on their diagnosis (PR25 = Prostate cancer module [18], CR38 = Colorectal cancer module [19] or BL24 = Bladder cancer module), in order to cover additional aspects of QOL considered relevant to these specific cancer types.

At each of the three study visits, patients also answered a seven-item module of questions regarding existential issues and life outlook, extracted from the 81-item Impact of Cancer (IOC) Instrument [20]. These questions can be found in Table five.

Analysis

Descriptive statistics were used to summarize patient accrual, survey completion, survival and withdrawals from the study.

Ethics

Participants were given written and oral information about their planned palliative radiation treatment and about the pilot study by an oncologist. All participants signed an informed consent form. Approval for the study was granted by the Regional Ethics Committee, the Norwegian Social Science Data Services and the Hospital Research Board.

Findings

The study screened 26 and enrolled 22 patients between March 2008 and April 2009 (table 1). Reasons for non-enrollment were patient choice (belief that the study procedure and questionnaires were too demanding) in three cases and cancellation of planned radiotherapy due to clinical deterioration and progressive disease in one case.

Eight patients were still alive 18 months after the pilot study was closed. All but one patient survived for the duration of the study (duration of radiation treatment plus 12 weeks follow-up). Three patients did not complete the study due to clinical deterioration and one patient moved away from the region prior to the 6 week follow-up.

Radiotherapists assisted patients as-needed and encouraged them to complete the questionnaires independently. The amount of time used per patient ranged from zero to 30 minutes. The primary reasons for radiotherapist assistance were difficulty reading questions and difficulty with written responses. In addition, there were occasional issues of question clarification and reminders to fill out the forms in their entirety (table 2).

Questions regarding sexuality were answered by 20 patients (91%) at baseline, 18 (82%) at the 6-week follow-up and 13 (59%) at the 12-week follow-up. These were the most frequent single-item omissions.

Pre-treatment responses to EORTC QLQ-C30 (table 3) and existential questions (table 4) are reported in order to give an indication of the baseline symptom burden and general health of our cohort.

21/22 patients answered the IOC questions about existential matters at baseline. At the six week follow-up 19 patients answered the existential questions fully and at the 12-week follow-up 16 patients answered the existential questions fully.

Table 1 Characteristics of included patients (N = 22)

Age, years	
Median	75
Range	62-90
Sex	
Male	17
Female	5
Diagnosis	
Prostate cancer	14
Colorectal cancer	5
Bladder cancer	3
Baseline ECOG performance status	
0	3
1	14
2	5
Radiation schedules	
2 Gy × 25 = 50 Gy	7(6 PC, 1 CRC, 1 BC*)
3 Gy × 10 = 30 Gy	6(3 PC, 2 CRC, 1 BC)
2 Gy × 30 = 60 Gy	4(4 PC)
3 Gy × 13 = 39 Gy	2(1 CRC, 1 BC)
2 Gy × 20 = 40 Gy	1(1 PC)
4 Gy × 5 = 20 Gy	1(1 CRC)
Survival (in months) from last radiation treatment	
3 month survival	91%
6 month survival	73%
1 year survival	68%
2 year survival	36%

*One patient with bladder cancer did not complete the planned radiotherapy regimen (completed 13 fractions of the planned 2Gy × 25) due to general fatigue and a wish to be discharged from the hospital. The remaining 21 patients completed their prescribed treatments.

Discussion

The findings of the present pilot study show that it is feasible, within a research project, to prospectively evaluate symptoms, QOL and existential issues among patients undergoing PPR for locally advanced prostate, colorectal and bladder cancers.

Patient accrual in this pilot study was good, with 85% of potential candidates included, despite a rather demanding protocol, with over two hundred questionnaire items per participant.

Study withdrawal was the largest contributor to the decline in response rates between baseline and the six and 12-week follow-ups. Reasons for study withdrawal depended on patients' declining general health. This is to be expected in a population with such advanced malignancy and relatively limited life-expectancy [22].

For the patients that remained in the study for its duration, however, completion of questionnaires did not appear to be too rigorous and as seen in previous reports, it was the questions related to sexuality that were most commonly omitted by patients filling out the EORTC questionnaires [23]. In our small cohort, patients who were physically able to come to the follow-up appointments all filled out the required questionnaires sufficiently and reported that they enjoyed participating, despite the fact that the questionnaire procedure required roughly thirty minutes of additional time spent at each of the three study visits. The fact that the radiation therapist ensured that the forms were complete prior to patients leaving the treatment center is likely to have improved questionnaire response rates [24].

This feasibility study used clinically acceptable methods, while exploring the question of QOL using validated research tools (BL24 was the only module not finally validated). An overly ambitious protocol can hamper accrual, questionnaire response rates, and study completion, particularly in a palliative population. The EORTC QLQ

Table 2 EORTC QLQ completion rates

Study contact	Number of completed C30 and site-specific questionnaires/eligible patients	Diagnoses of patients who filled out the questionnaires/eligible patients	Overall response rates
Baseline	21/22	14/14 PC 4/5 CRC 3/3 BC	95%
6 week follow-up	20/22	13/14 PC 5/5 CRC 2/3 BC	91%
12 week follow-up	17/22	11/14 PC 4/5 CRC 2/3 BC	77%

Table 3 Baseline responses to EORTC QLQ-C30

	Not at all (n)	A little (n)	Quite a bit (n)	Very much (n)
1. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase?	6	8	5	2
2. Do you have any trouble taking a long walk?	7	4	5	5
3. Do you have any trouble taking a short walk?	14	3	2	2
4. Do you need to stay in bed or a chair during the day?	5	6	7	3
5. Do you need help with eating, dressing, washing yourself or using the toilet?	21	0	0	0
During the past week:				
6. Were you limited in doing either your work or other daily activities?	4	9	4	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	5	6	4	5
8. Were you short of breath?	14	1	6	0
9. Have you had pain?	6	5	8	2
10. Did you need to rest?	1	9	8	3
11. Have you had trouble sleeping?	11	5	3	2
12. Have you felt weak?	5	8	5	3
13. Have you lacked appetite?	10	6	3	2
14. Have you felt nauseated?	15	4	2	0
15. Have you vomited?	17	3	0	0
16. Have you been constipated?	8	8	2	3
17. Have you had diarrhea?	14	4	2	1
18. Were you tired?	3	9	6	3
19. Did pain interfere with your daily activities?	7	5	5	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	18	2	1	0
21. Did you feel tense?	14	5	1	1
22. Did you worry?	11	8	1	1
23. Did you feel irritable?	13	5	3	0
24. Did you feel depressed?	11	7	2	0
25. Have you had difficulty remembering things?	13	5	3	0
26. Has your physical condition or medical treatment interfered with your family life?	10	4	6	1
27. Has your physical condition or medical treatment interfered with your social activities?	6	7	6	2
28. Has your physical condition or medical treatment caused you financial difficulties?	20	1	0	0

	Very poor						Excellent
	1	**2**	**3**	**4**	**5**	**6**	**7**
29. How would you rate your overall health during the past week? (n)	0	1	7	5	2	4	2
30. How would you rate your overall quality of life during the past week? (n)	0	1	4	5	4	5	2

As answered at baseline by 21 of the 22 included patients. There were three single-item omissions (questions 7, 15 and 24) among these 21 responders.

Table 4 Seven Existential questions taken from the IOC Instrument

	Completely agree (n)	Agree (n)	Neutral (n)	Disagree (n)	Completely disagree (n)
Positive Outlook					
Having had cancer has made me realize that time is precious.	8	7	4	0	2
Having had cancer has strengthened my religious faith or my sense of spirituality.	9	0	8	2	2
I learned something about life because of having had cancer.	3	10	6	0	2
Negative Outlook					
Having had cancer makes me feel unsure about my future.	6	5	6	1	3
I worry about my future.	3	5	4	3	6
I am afraid to die.	1	3	4	6	7
I feel like time in my life is running out.	3	5	2	9	2

As answered at baseline by 21 of the 22 included patients. There were no single item omissions.

questionnaires were chosen because of their comprehensiveness, ease of use, and the high levels of reliability and validity they have demonstrated in two decades of international research [25]. We chose the EORTC QLQ-C30 and its corresponding diagnosis-specific modules rather than the EORTC palliative module (QLQ-C15-PAL) because of the more comprehensive symptom data that could be gathered using the diagnosis-specific modules.

The use of selected existential questions taken from the IOC instrument is a limitation of this pilot study. Psychometric tests of these items were not carried out on our small cohort and as far as we know, these questions have not been tested for validity or reliability among patients with advanced cancer. The complete IOC questionnaire, which is a larger and more complex instrument, has been psychometrically tested among long-term cancer survivors [27]. Fundamental differences between the context of palliative treatment and the context of long-term cancer survivorship are likely to impact on the responses to existential questions, thereby limiting our ability to interpret these findings.

This pilot study did not seek to evaluate the effects of the PPR but to test the feasibility of such an evaluation. With a hypothetical primary endpoint of QOL at 12 weeks post-radiation, 17 patients (77%) would have been evaluable in this study (table 2). At 6 weeks, this number was 90%. Considering the obstacles inherent to research among palliative patients, these are encouraging results. This study also demonstrates that patients receiving palliative radiation are willing and able to answer selected existential questions regarding their illness and outlook on life.

The survival statistics in table 2 as well as the baseline questionnaire responses with regard to symptom burden and QOL (table 3) demonstrate that many of the patients in this small cohort were in relatively good health, considering their diagnoses of incurable cancer. Although this was not an inclusion criterion, it does potentially limit the generalizability of this pilot study.

Our study included all-comers scheduled to receive fractionated PPR. Treatments were prescribed based on patients' general health and estimated life-expectancies. The group of ten prostate cancer patients who received 50-60 Gy (five or six weeks of treatment) was a subgroup of patients with relatively long life-expectancies (often over a year). In contrast, some of our patients had life expectancies of little more than 12 weeks and were chosen for shorter treatment courses (20-30 Gy), for precisely that reason. Such inhomogeneity of the patient cohort, with respect to life expectancies, may represent a problem in a scientific study, but is a common experience in the palliative cancer care practice.

There is no clear consensus for the optimal dose or schedule of PPR in prostate, rectal and bladder cancers. Preferred radiation dose and method of delivery often depend not only on target symptom and tumor type, but also on a range of non-clinical factors such as distance to treatment center. Just among the 22 patients studied here, six different fractionation schedules were used, varying in faction sizes from two to four Gy and total doses of 20-60 Gy. These treatment approaches entail significantly different burdens on the patients. A more homogeneous population and fractionation schedule would therefore be needed in order to reach conclusions about the effects and side-effects of the studied treatment.

Conclusions

This evaluation of symptoms, QOL and existential questions among PPR patients at 6 and 12 weeks after treatment yields encouraging response rates. The greatest challenge is patient withdrawal because of clinical

deterioration. While it is inherent in the population we are studying, this problem is beyond the scope of the protocol and must therefore be taken into consideration in further protocol development. The availability of a radiation therapist to assist patients during data collection appears to have contributed to response rates. The procedure used among these 21 heterogeneous study patients has shown feasibility and is therefore being implemented in a larger Norwegian multicenter study with a more uniform treatment regimen and sample of prostate and rectal cancer patients, in order to reach clinically significant conclusions about the effects of PPR [28].

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Authors' contributions
MC, IV, CK, RvH, GR and SDF contributed to the development of the idea for this pilot study. MC, RvH and CK administered the study and collected data. MC and GR entered the data and together with IV, analyzed the data. MC wrote the first draft. IV, CK, RvH, GR and SDF provided feedback on the manuscript and all six authors approved the final version.

Competing interests
The authors declare that they have no competing interests.

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