Quality of Life and long-term side effects after anal cancer treatment

Department of Surgery

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2024

Cover illustration: Emelie Axelsson

anna.c.axelsson@gu.se

ISBN 978-91-8069-615-9 (PRINT)
ISBN 978-91-8069-616-6 (PDF)

Printed in Borås, Sweden 2024
Printed by Stema Specialtryck AB

Drawing on the cover made by Emelie Axelsson. It symbolizes the balance between cure and side effects. As caregivers we need to be light-handed in finding the right balance for each patient and strong-hearted in our mission to improve the outcome for all our patients.

Quality of Life and long-term side effects after anal cancer treatment

Anna Axelsson

Department of Surgery, Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Anal cancer is a rare type of cancer with approximately two hundred new cases in Sweden per year. Treatment usually consists of a combination of radiotherapy and chemotherapy. The overall prognosis is good but about 10% of patients require pelvic surgery to be cured. This is referred to as "salvage surgery". In this thesis we wanted to investigate patient reported quality of life (QoL) and long-term side effects after anal cancer treatment. Two hundred and five patients with anal cancer, diagnosed between 2011 and 2013 in Sweden, answered a comprehensive questionnaire at three and six years after diagnosis. One hundred and ninety-five patients returned the questionnaire at three years and one hundred and fifty-five patients at six years.

We found QoL to be good in 40% of the patients and low in 60% at both three and six years. Patients with bother from one or more functions had a higher risk of impaired QoL. Major bother was more prevalent in patients that reported low QoL. Impaired bowel function was common and remained stable between three and six years. The combination of chemotherapy and radiotherapy was associated with a higher risk of bowel side effects than radiotherapy alone. Both urinary and sexual function deteriorated between three and six years. Chemotherapy was not associated with a higher risk of urinary incontinence.

With a qualitative approach we explored patients' experiences of bodily functions and QoL after salvage surgery. Eighteen in-depth interviews were performed. Inductive content analysis resulted in 8 categories and 1 theme describing the acceptance and reorientation to a new life despite several long-term bodily changes and functional side-effects.

There are significant long-term side effects after treatment for anal cancer, and there is a clear relationship between symptom burden, bother and QoL. Although bodily functions deteriorate over time QoL does not, indicating an adaptation process between three and six years.

Keywords: Anal cancer, Long-term side effects, Quality of life

ISBN 978-91-8069-615-9 (PRINT)
ISBN 978-91-8069-616-6 (PDF)

SAMMANFATTNING PÅ SVENSKA

Analcancer är en relativt sällsynt cancersjukdom. Den har dock ökat i Sverige och övriga västvärlden de senaste decennierna. Idag drabbas cirka 200 personer av analcancer varje år i Sverige. Sjukdomen är vanligare hos kvinnor än män och genomsnittsåldern vid diagnos ligger mellan 65 och 70 år. De allra flesta fall uppstår på grund av infektion med Humant Papillom Virus (HPV). Behandling vid analcancer består av strålbehandling mot bäckenområdet i kombination med cellgifter, så kallad kemoradioterapi. Chansen till bot är god, men några patienter behöver i tillägg genomgå en större operation för att bli definitivt botade, så kallad ”salvage surgery”. Efter behandling finns en risk att det uppstår biverkningar på kort eller lång sikt som kvarstår och som påverkar kroppsliga funktioner.

Målet med den här avhandlingen var att skapa mer kunskap om hur patienterna som genomgått behandling för analcancer har det på lång sikt och hur detta påverkar deras livskvalitet.

Avhandlingens delarbeten baseras på ANCA-studien där samtliga patienter insjuknade i analcancer i Sverige mellan 2011 och 2013 erbjöds att delta. Av de 264 patienter som var i livet vid tidpunkten för studiens start tackade 195 ja till deltagande. Dessa fick svara på ett frågeformulär tre och sex år efter diagnos avseende livskvalitet samt tarm- urin- och sexuell funktion. Frågorna innefattade förekomst av symtom, frekvens och svårighetsgrad, samt hur mycket patienten besvärades av sina symtom. De patienter i ANCA-studien som hade genomgått salvage surgery bjöds in att delta i en djupintervju-studie. Av de 27 opererade patienterna som var i livet tackade 18 ja till att delta i intervju. Dessa intervjuer ägde rum cirka tio år efter operationen.

Avhandlingen visar att livskvaliteten efter analcancerbehandling är god hos 40% av patienterna och lägre hos 60% vid både tre och sex år efter diagnos. Långtidsbiverkningar är vanligt förekommande med stor påverkan på funktion avseende tarm, urin och sex och flera av dessa biverkningar har en tendens att förvärras mellan tre och sex år. Biverkningar från tarm och urin besvärar patienterna i högre grad än sexuella biverkningar. I djupintervjuerna framkom att trots många kroppsliga förändringar och funktionella symtom efter salvage surgery, så hade patienterna accepterat sin situation. Patienterna gav uttryck för en god livskvalitet och en tacksamhet över att vara i livet och att kunna leva så normalt som möjligt. De hade anpassat sig till ett nytt sätt att leva och fungera.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Axelsson A, Johansson M, Bock D, Haglind E, de la Croix H, Nilsson PJ, Angenete E.
Patient-reported QoL in anal cancer survivors 3 and 6 years after treatment-results from the Swedish national ANCA study.
Support Care Cancer 2022

II. Axelsson A, Johansson M, Haglind E, Li Y, Nilsson P J, Angenete E.
Patient reported long-term side effects on bowel function and anal pain in anal cancer survivors - 3 and 6-year results from the Swedish national ANCA study.
Colorectal Dis 2023

III. Axelsson A, Johansson M, Haglind E, Li Y, Nilsson P J, Angenete E.
Patient reported long-term side effects on urinary and sexual function in anal cancer survivors – 3 and 6-year results from the Swedish national ANCA study.
Submitted manuscript.

IV. Axelsson A, Liljedahl M, Johansson M, González E, Angenete E.
Experiences of long-term side effects and quality of life a decade after salvage surgery due to anal cancer.
Manuscript.

CONTENTS

Abbreviations 10
1 Introduction 12
1.1 Anal cancer 12
1.1.1 Epidemiology 12
1.1.2 Treatment 12
1.2 Radiotherapy 14
1.2.1 Long-term side effects of radiotherapy 14
1.3 Salvage surgery 16
1.3.1 Stomas in anal cancer 17
1.4 Cancer survivorship 17
1.5 Quality of Life 18
1.6 Patient reported outcome measures 18
1.7 Adaptation and Response shift 19
2 Aim 21
2.1 Specific aims 21
3 Patients and Methods 22
3.1 ANCA study 22
3.2 Study population 22
3.3 Patient reported outcomes 23
3.3.1 Paper I-III 23
3.3.2 Paper IV 26
3.4 Hypotheses 27
3.5 Statistics 28
3.5.1 Statistical considerations 29
3.6 Ethical considerations 32
4 Results 33
4.1 Quality of Life 33
4.2 Long-term side effects of bodily functions 34

4.2.1 Bowel function 34
4.2.2 Urinary function 34
4.2.3 Sexual function 35
4.2.4 Pain and sensory symptoms in the pelvic area 36
4.2.5 Acceptance and reorientation to a new life 36
5 Discussion 38
6 Conclusion 43
7 Future perspectives 44
Acknowledgements 45
References 47

ABBREVIATIONS

AIN	Anal Intraepithelial Neoplasia
AJCC7	American Joint Committee on Cancer
ANCA	ANal CAncer
APE	Abdominoperineal excision
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic Acid
EPM	Etikprövningsmyndigheten (the Swedish Ethical Review Authority)
ESMO	European Society of Medical Oncology
ESTRO	European Organisation for Research and Treatment of Cancer
FU	Follow-up
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesion
HRQoL	Health related Quality of Life
ICD	International Statistical Classification of Diseases and Related Health Problems
OR	Odds Ratio
PI	Principal Investigator
PROM	Patient Reported Outcome Measures

QLQ-ANL27	EORTC Quality of Life Questionnaire for Anal Cancer
QLQ-C30	EORTC Quality of Life Questionnaire Core 30
QLQ-CR29	EORTC Quality of Life Questionnaire for Colorectal cancer 29
QLQ-CR38	EORTC Quality of Life Questionnaire for Colorectal cancer 38
QoL	Quality of Life
RR	Risk Ratio
RT	Radiotherapy
SOC-29	Sense of Coherence 29-item scale
SSORG	Scandinavian Surgical Outcomes Research Group
TNM	Classification system for malignant tumors: T=primary Tumor, N=regional lymph Nodes, M=distant Metastasis
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
5-FU	5-fluorouracil

1 INTRODUCTION

1.1 ANAL CANCER

Anal cancer is a form of malignant tumor that arises in the anal canal or in the perianal skin. The most common type of anal cancer is squamous cell carcinoma.

1.1.1 EPIDEMIOLOGY

The incidence of anal cancer has increased in Sweden [1] over the last decades, a trend also seen in other countries in Western Europe and the USA [2]. Despite this, anal cancer is still a relatively rare disease with about 200 patients diagnosed per year in Sweden[1]. Median age at diagnosis is 65 years and the disease is more common in women than in men. Certain populations are at higher risk for anal cancer such as smokers, immunosuppressed individuals and men who have sex with men [1, 3, 4]. A majority only have human papillomavirus (HPV) infection as sole risk factor, with no other underlying risk factor. Between 80-90% of all cases of anal cancer are believed to be triggered by HPV infection. HPV is an endemic virus and the subtypes 16 and 18 are associated with a higher risk of cancer development, though only a small fraction of HPV-infected people develop cancer. It remains unclear who and why certain individuals infected with the virus develop cancer [5]. HPV 16 and 18 are associated with several other cancer forms such as cancer of the uterine cervix, vulva, penis, and oropharynx. The rise in incidence of anal cancer is seen mainly among postmenopausal women and may be attributed to changes in sexual behavior during the last century in industrialized countries [2, 6]. As of year 2010, all 12-year-old girls, and of year 2020, all 12-year-old boys in Sweden are offered a four-valent human papillomavirus vaccine. If adherence to the vaccination program remains high it is estimated that the HPV-associated cancer incidence will decrease significantly, but this will take another three or four decades [7].

1.1.2 TREATMENT

Recommended curative treatment for anal cancer is similar across contemporary guidelines globally, and consists primarily of chemoradiotherapy, i.e. external radiotherapy combined with chemotherapy for 4-6 weeks [8, 9]. The chemotherapy drugs that have been used historically are 5-Fu in combination with either mitomycin C or cisplatin. Two large

randomized clinical trials, one in the USA (Ajani 2008) and the UK (James 2013), both concluded that 5-Fu and mitomycin C is the preferred regimen in terms of efficacy, and that neoadjuvant (before chemoradiation) or adjuvant (after chemoradiation), chemotherapy do not lead to better results [10, 11]. Even after 2013, anal cancer treatment in Sweden was given with different treatment regimens according to geographic region. Some of these regimens included both neoadjuvant chemotherapy, as well as cisplatin instead of mitomycin C [12, 13]. In 2017 the first national clinical cancer care guidelines for anal cancer were implemented in Sweden and treatment became centralized to fewer treatment centers. The recommended chemotherapy regimen in these guidelines is 5-Fu and mitomycin C.

The national clinical cancer care program includes three different treatment schedules with varying intensity of radiotherapy dose and numbers of chemotherapy cycles, depending on the tumor stage (TNM) [14].

Swedish national treatment guidelines				
	TNM‡	RT-dose to primary tumor	RT-dose to lymph nodes	Chemotherapy 5-FU +Mitomycin C
Schedule A	T1N0M0	44 Gray	40 Gray	1 cycle
Schedule B	T1-2(<4 cm) N0M0	54 Gray	40 Gray	1 cycle
Schedule C	T2(>4 cm) - T4 N+M0	58 Gray	58/50/40 Gray*	2 cycles

*Table 1. Adapted from the Swedish national treatment guidelines. (RT=radiotherapy). ‡Adapted from TNM 8th version[15] : T1 = tumor size 0-2 cm, T2 = 2-5 cm, T3 > 5 cm, T=4 any size involving adjacent organ, N =0 no involved lymph nodes N+= any lymph node involvement, M0=no distant metastases;*dose level of RT depending on lymph node involvement and size of the involved lymph nodes.*

Clinical trials, observational studies and national registries show an overall curation rate around 80% with chemoradiotherapy alone, with another 5-10% of the patients being permanently cured by the addition of surgery in cases of

local relapse or persistent tumor after primary treatment, so called salvage surgery [11, 12, 14, 16].

The prognosis varies among subgroups of patients. Among the elderly, comorbidity and age-related organ impairment require treatment modifications which can lead to an inferior outcome [12, 16]. In addition, patients diagnosed with a non-HPV-associated (HPV-negative) anal cancer have a worse prognosis independent of treatment. The reasons for this remain unclear and how to improve outcome among the patients with HPV-negative disease is still an unsolved problem in anal cancer research and treatment [17, 18].

1.2 RADIOTHERAPY

Radiotherapy is the therapeutic use of ionizing radiation, with the purpose of cure, or alleviation of disease, most commonly cancer. The effect of radiotherapy on a cellular level is believed to be exerted through damage to subcellular structures, most importantly DNA. These damages can lead to direct cell death (necrosis), or programmed cell death (apoptosis). Damages that do not lead to cell death can be repaired by repair enzymes before the next cell division takes place. Malignant cells display acquired deficiencies in cellular repair mechanisms and as a consequence tend to replicate with a higher risk of two non-viable cells being the result after DNA damage [19].

Normal tissue is inevitably affected by the radiation due to its proximity to the tumor tissue. Even though normal tissue has intact repair mechanisms, radiotherapy at therapeutic doses causes cell death and to some extent subsequent permanent changes in normal tissue as well.

1.2.1 LONG-TERM SIDE EFFECTS OF RADIOTHERAPY

Late or long-term side effects appear months or years after radiotherapy and depend on the dose and the exposed volume. These side effects are in general progressive over time and irreversible. Processes believed to be involved in the induced changes are endothelial damage in the microvasculature, fibroblast proliferation and collagen synthesis. These result in the exposed tissue becoming fibrotic and sometimes scar-like in its character, and the rate of the process is believed to be dependent on radiotherapy dose. The extent of organ-damage and deterioration of function is believed to be dependent on volume and the character of the organ involved [20]. Undesirable long-term effects in normal tissue are the dose-limiting factor in all radiotherapy prescription and

planning. So called tolerance doses are threshold doses believed to define the maximum tolerated normal tissue dose after which long-term side effect and function are kept at an acceptable level or frequency [21, 22].

Because of dose dependence on progression rate, late normal tissue effects after lower doses are observed at a later point in time than for higher doses. As a result, the tolerance dose for a defined late effect decreases with increasing follow-up time. Accordingly, the definition of tolerance doses or late effects always requires data about follow-up time on which the estimates are based.

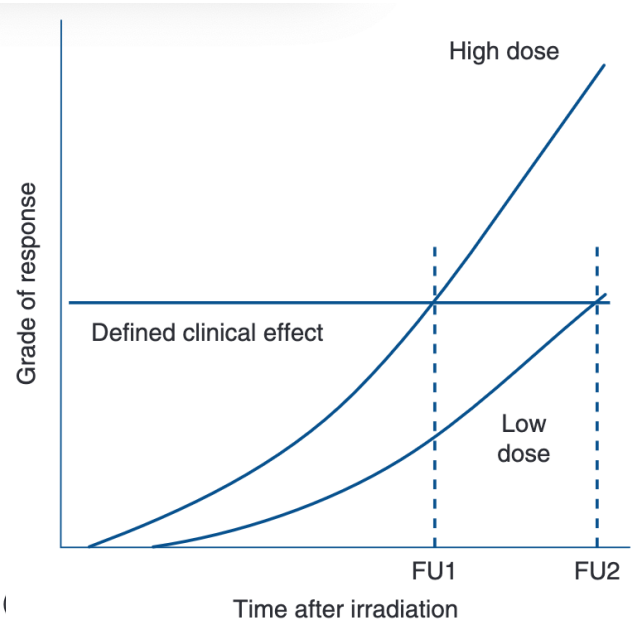

Figure 1. Illustration of the relation between absorbed dose and time after irradiation regarding response (change in normal tissue) and clinical effect (clinically detectable symptom or impaired function) (FU=follow-up). Adapted from Dörr W. (2018) Pathogenesis of normal tissue side effects. In: Basic Clinical Radiobiology (ed Joiner MC, & van der Kogel, A.J.), pp. 157-8. CRC Press, Boca Raton.

The effect of dose and volume on the risk of unwanted long-term effects is modulated by intrinsic patient factors, i.e. individual susceptibility to radiation [23, 24] as well as extrinsic factors such as smoking [25] and comorbidity [26].

The addition of chemotherapy to radiotherapy in chemoradiation is well known to increase the risk of acute toxicity during treatment [27, 28]. The role of chemotherapy in modulating the risk of long-term side effects of radiotherapy is less well known [29, 30].

1.2.1.1 LATE SIDE EFFECTS FROM PELVIC RADIOTHERAPY

Radiotherapy to the pelvic region causes unwanted long-term side effects that may impair function. This has repeatedly been shown across different cancer types [31-34]. Radiotherapy is a treatment option for rectal, prostate and gynecological cancer, but not necessarily for all patients with these forms of cancer. It is possible to estimate the side effects of radiotherapy in these diagnoses by using data from randomized trials where toxicity outcomes for patients exposed to radiotherapy can be compared to non-exposed patients.

In anal cancer, radiotherapy is the cornerstone of all curative treatment and comparison between exposed and non-exposed patients is therefore not possible. The two largest randomized controlled trials carried out (Ajani 2008, James 2013) comparing different chemoradiation schedules had identical radiotherapy protocols regarding dose and volume in the control and experimental arms. Late toxicity estimation was not an integral part of the study design in these two major trials [10, 11].

Observational studies on long-term side effects in anal cancer have been characterized by cross-sectional design, heterogeneous follow-up time with wide range, and small numbers of patients [35-37].

1.3 SALVAGE SURGERY

About 10-20% of patients treated for anal cancer either have persistent disease or relapse locally at the site of the primary tumor after chemoradiotherapy [10, 11]. Since full dose of radiotherapy has been applied primarily, surgery is the only alternative to achieve cure in this situation [38]. Salvage surgery includes resection of the anal canal and the rectum. This procedure is often referred to an abdominoperineal excision (APE) and results in a permanent stoma but may also include a posterior or total pelvic exenteration where more organs such as the uterus, vagina or urinary bladder are removed as well. This type of surgery is associated with substantial permanent anatomical changes for the patient. Almost all patients who undergo salvage surgery for anal cancer are previously irradiated. Conditions for healing after major surgery are therefore suboptimal. To improve healing, different surgical reconstruction techniques are used with

the use of musculocutaneous flaps. Despite this, healing complications are common [38-40].

1.3.1 STOMAS IN ANAL CANCER

A stoma, predominantly a colostomy, which consists of the exteriorization of the gross intestine through the abdominal wall, is sometimes performed as part of salvage surgery but also in other anal cancer situations.

Approximately 10% of patients need an upfront colostomy because of threatening intestinal obstruction before curative treatment, which provides symptom alleviation and enables full treatment. Another situation, when a permanent colostomy is performed, to improve overall function and quality of life, is when the patient suffers from severe long-term impairment on anorectal function due to radiotherapy induced late side effects [41].

1.4 CANCER SURVIVORSHIP

Early diagnosis due to screening programs, increasing incidence and improved treatment have led to a growing population of cancer survivors. Cancer survivorship as a term was introduced in the 1980´s and has since then been widely used without any consensus how to define it [42, 43]. The European Society of Medical Oncology (ESMO) has published a consensus statement for cancer survivorship with five domains that ought to be addressed to promote high-quality survivorship*: surveillance and management of physical effects of cancer and chronic medical conditions*; *management of psychological effects of cancer*; *social, work and financial effect of cancer*; *surveillance for recurrencies and new cancers*; *cancer prevention and promotion of health and well-being* [44]. For research purposes the following definition of cancer survivorship has been proposed: “a constantly evolving concept with the aim to organize a body of knowledge that will improve over time and ideally impact the health and well-being of those diagnosed with and treated for cancer” [45].

Despite anal cancer being a rare disease, the high curation rate yields a significant prevalence of anal cancer survivors. Assuming an incidence of 200 cases per year in Sweden, a probability of cure of 85% and a median survival of 15 years after cure, this would yield a prevalence of approximately 2500 anal cancer survivors in Sweden alone.

1.5 QUALITY OF LIFE

Quality of Life (QoL) refers to a person's well-being in general and is described as a multidimensional concept without consensus regarding definition [46]. The World Health Organization (WHO) have stated the definition "an individual´s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". The WHO also states that it is a complex concept influenced by a person's physical and psychological health as well as personal beliefs and perceptions [47]. The meaning of the concept QoL is probably unique for each person. Despite the different interpretations of the concept, QoL is a common outcome measure used in all areas of health-related research. All instruments with the purpose of estimating QoL have their own definition, which makes it challenging to compare QoL outcomes when different instruments are applied across different studies. The health-related quality of life (HRQoL) concept examines how patients' health affects their quality of life. In scientific research, disease-specific instruments are added to general QoL instruments to measure HRQoL.

1.6 PATIENT REPORTED OUTCOME MEASURES

Patient reported outcome measures (PROM) are patient-reported data on any experience defined as an outcome of interest [46]. PROM can collect patient experiences as self-reported data or by interview. The purpose of PROM is to collect patients' experiences and voices, as far as possible avoiding bias from caregivers' preconceptions and perceptions. One way to collect PROM data is by using instruments, usually combining a set of questions with different forms of scales. All instruments regardless of the method used for development require assessment regarding their clinical usefulness which is done by evaluating validity, reliability, sensitivity and responsiveness. Validity ensures the ability of the instrument to measure what it supposed to measure, reliability means stability and the ability to reproduce over time, sensitivity is an instrument´s ability to find true differences between two individuals or groups. Responsiveness is the ability of the used instrument to recognize changes over time [48].

Different PROM instruments have been used for research on patients with anal cancer to measure long-term side effects, QoL and HQRoL [49]. In 2018

European Organisation for Research and Treatment of Cancer (EORTC) developed the anal-cancer specific QLQ-ANL27 instrument [50]. Before that, researchers in the anal cancer field had to rely on generic scales and instruments such as EORTC QLQ-C30 (generic for different cancers) [51] or instruments developed and validated for other cancer forms such as EORTC QLQ-CR29[52] and QLQ-CR38 [53] for colorectal cancer. The QLQ-ANL27 can be used both to measure acute side effects and long-terms side effects after treatment. It is a questionnaire with 27 items mainly focused on functions that may be affected in or from the pelvic area. The instrument is adjusted for patients with or without a stoma [50]. However, some domains are not covered in total by the QLQ-ANL27 items. For example, urinary incontinence is not included while the need to urinate frequently is, and questions on sex do not include the ability to feel pleasure or orgasm. There is an apparent risk that the QLQ-ANL27 does not have sufficient sensitivity to capture all the domains that affect anal cancer survivorship, as well as nuances within each domain.

In addition to questions on symptoms, PROM instruments in some cases include questions on how bothersome the patient finds these symptoms - that is the degree of discomfort, worry or disturbance the symptoms cause. The terms *bother,* or *distress* have sometimes been used for this dimension [54, 55]. There are some differences in the original meaning of the terms. However, publications on PROMs in cancer survivorship tend to apply one or the other for the same purpose, that is to estimate the impact of symptoms on the patients' emotions and activities [56-59].

1.7 ADAPTATION AND RESPONSE SHIFT

To be diagnosed with and go through the process of a cancer disease is to be faced with a potential threat to life. This situation requires of patients to accommodate and adapt to their new situation. Adaptation is a process that effects patients experienced QoL. In 1999 Spangers and Schwartz coined the concept *response-shift* referring to the phenomenon of changes over time in the meaning of a person´s self-evaluation. This phenomenon is considered an important part of the adaption process that involves change in the patients' internal standards (recalibration), values (reprioritization) and conceptualization (reconceptualization). Response-shift was defined as a model to understand the changes in patients' self-evaluation of QoL in the context of patient reported research and interpret perceptions of QoL [60].

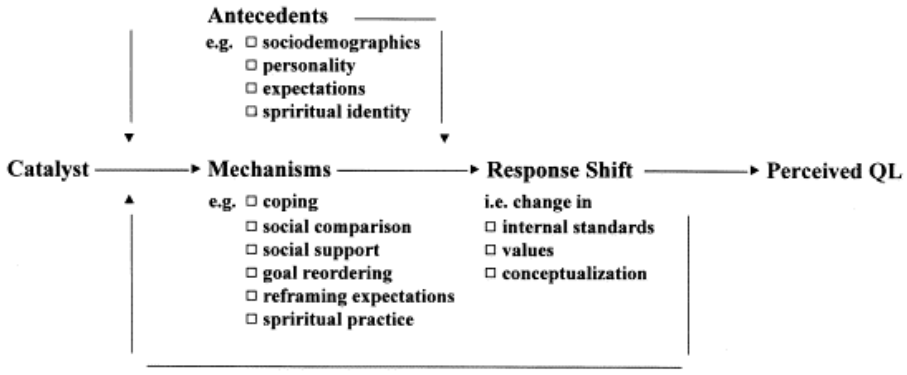

Figure 2. A theoretical model of response shift and Quality of Life. Adapted from Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999; 48: 1507-15.

Response-shift has been interpreted differently among different researchers. The concept has been regarded by some as an unwanted bias, which hinders correct conclusions on casuality between exposure and outcome. Others have seen it as a discrepancy between expected and measured outcomes, which can be quantified and adjusted for [61-63]. Another way of discerning response-shift is to consider it an integral part of all adaptation to changes in life, whether inflicted by disease, treatment for disease or other factors [64].

Patient adaptation and response-shift have to be considered and taken account when making assumptions on the effect of time on PROM and QoL outcomes.

2 AIM

The overall aim of this thesis was to investigate long-term side effects and QoL after anal cancer treatment.

2.1 SPECIFIC AIMS

PAPER I

To describe patient reported QoL and bother due to dysfunction in bodily functions in patient treated for anal cancer at three and six years after conclusion of treatment and to study the relationship between QoL and bother.

PAPER II

To assess the occurrence of long-term bowel function impairment and anal pain at three and six years after anal cancer diagnosis, and to investigate if chemoradiotherapy increased the risk for bowel impairment on bowel function, compared to radiotherapy alone.

PAPER III

To assess the occurrence of long-term urinary and sexual dysfunction at three and six years after diagnosis and to investigate the additive effect of chemotherapy in the combined chemoradiotherapy on urinary incontinence, compared to radiotherapy alone.

PAPER IV

To explore experiences of long-term side effects and QoL a decade after salvage surgery.

3 PATIENTS AND METHODS

3.1 ANCA STUDY

The ANCA study included a Swedish national cohort of patients diagnosed with anal cancer between 1 January 2011 and 31December 2013. The cohort was identified through the Swedish Cancer Register at National Board of Health and Welfare. The design of the study is longitudinal and explorative, investigating QoL and long-term side effects three and six years after diagnosis.

3.2 STUDY POPULATION

The flowchart illustrates inclusion in the ANCA study and the study population on which Papers I-III are based.

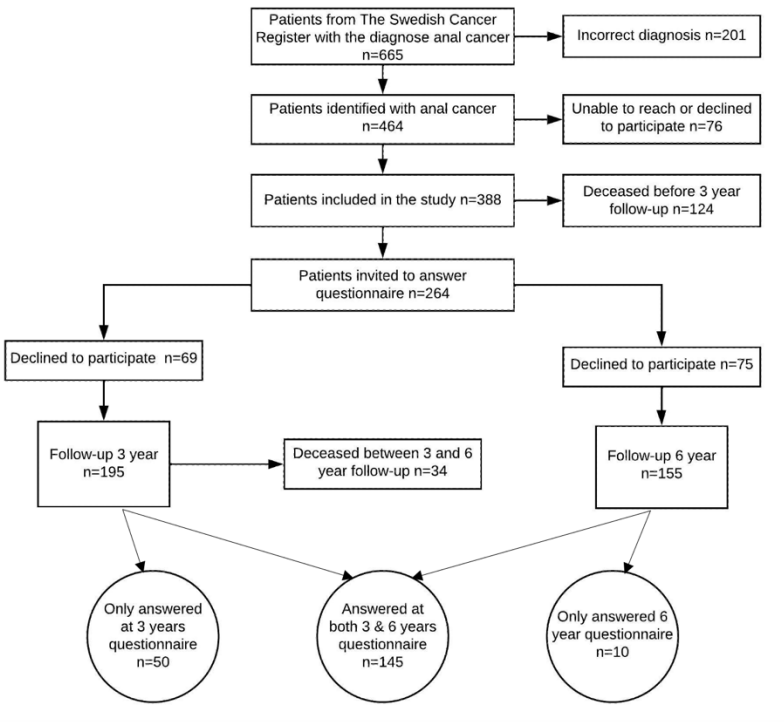

Figure 3. Flowchart for the ANCA cohort and study population for Paper I-III.

In Paper I we used a reference group of 1078 persons drawn from the Swedish population registry for comparison [65]. The reference group had answered a PROM questionnaire similar to the one used in the ANCA study. In Paper III the same reference group is referred to in the discussion section.

The study population for Paper IV was selected from the ANCA cohort. Out of 388 patients, 43 patients had undergone salvage surgery. When the study started 2023, 27 patients were still alive. Of those, 18 patients accepted to participate in the study and were interviewed.

3.3 PATIENT REPORTED OUTCOMES

3.3.1 PAPER I-III

At the time of the design of the ANCA study there was no pre-existing anal cancer specific questionnaire or scale to use, and the commonly used instruments like EORTC QLQ-C30 were considered too unspecific for the purpose of this study.

3.3.1.1 CONSTRUCTION OF QUESTIONNAIRE

A study-specific questionnaire was constructed with 260 questions relating to the effects of anal cancer treatment on patients' lives. To achieve this, a group of surgeons, oncologists, and research nurses with clinical experience of anal cancer care was gathered. Questions used in other questionnaires [66-68], developed by Scandinavian Surgical Outcomes Research Group for other pelvic malignancies were used if considered valid for anal cancer. In addition, new specific topics were defined. To make sure that all topics and questions were covered and relevant, four in-depth interviews were performed with patients treated for anal cancer. The interviews were conducted by two research nurses and recorded and transcribed verbatim. After that, content analysis was performed using codes and categories to see if new content areas were found or not covered. Then, a final version of the questionnaire was constructed with categorical questions about bowel, urinary and sexual function, perceived QoL, social and mental function, daily activities, personal characteristics, and comorbidity. All items about functions had questions on severity, occurrence, duration and bother [54]. Besides the study-specific instrument, the 29-item Sense of Coherence scale (SOC-29) [69] was included.

Finally, a face-to face validation technique was used with another three patients, who had been treated for anal cancer, to make sure that all questions were easily understood and formulated in a coherent way.

This multi-step procedure for questionnaire development, described by Steineck et al [54], has been used in several other cancer survivorship studies [57, 59, 70]. Having applied this method, we believe the questionnaire to have high content validity, that is, covering all relevant aspects of life after anal cancer treatment.

3.3.1.2 SELECTED OUTCOMES AND EXPLANATORY VARIABLES

Paper I: Patient reported QoL was evaluated by the question "How would you describe your quality of life in the past month?" (Figure 4). Patients responded on a Likert scale from 0 to 6 anchored between the reference points 0 = *"no QoL"* and 6 = *"best possible QoL"*. This question with a similarly anchored Likert scale has earlier been used by Steineck et al [59].

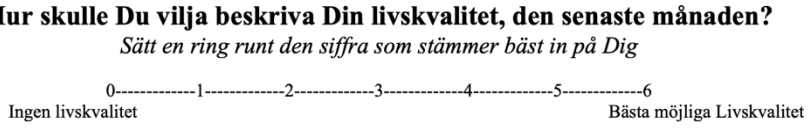

Figure 4. Question on Quality of Life.

Sense of coherence and depression were selected as possible explanatory variables for low QoL. Sense of coherence was measured by Sense of Coherence scale (SOC-29) developed by Antonovsky [69]. This instrument was validated to be reliable in the Swedish population [71]. Sense of coherence has previously been demonstrated to have an impact on QoL in patients with rectal cancer [66]. Antonovsky stated that a human could be of good health despite physical illness, if experiencing a sense of coherence. The scale measures comprehensibility (11 items), manageability (10 items) and meaningfulness (8 items). Each question is constructed with response categories on a Likert scale from 1-7 with two anchoring phrases. The item scores of the 29 question-scale are summed up in an overall score. Total possible overall scores range between 29-203. A high value is referred to as a high reported sense of coherence [69].

Depression was assessed by the question "are you depressed?" Response alternatives were *"no", "yes" and "don't know"*. This specific question has

been found to have a sensitivity of 81% when validated against the Hospital Anxiety Depression Scale [72].

Bother of bowel, urinary and sexual function and anal pain was assessed using the question "how would you feel if the last month's impairment was to remain the same for the rest of your life?" for each category. This question had five optional response categories, *"not relevant, I haven´t had any impairments the last month", "it wouldn´t bother me at all", "it would bother me slightly", "it would bother me moderately", "it would bother me a lot."*. (Figure 5).

Om Du resten av Ditt liv skulle leva med Dina sammantagna tarmbesvär, som det varit den senaste månaden, hur skulle Du uppleva det?

1. ☐ ***Inte aktuellt***, jag har inte haft några tarmbesvär den senaste månaden
2. ☐ Det skulle inte beröra mig alls
3. ☐ Det skulle beröra mig lite
4. ☐ Det skulle beröra mig måttligt
5. ☐ Det skulle beröra mig mycket

Figure 5. Question of bother of bowel function.

Paper II: Outcomes selected to assess bowel function and anal pain are presented in the appendix of this dissertation (*supplement to Paper II)*.

Paper III: Outcomes selected to assess urinary and sexual function presented in the appendix of this dissertation (*supplement to Paper III)*.

3.3.1.3 DATA COLLECTION

All patients eligible for the study were invited to participate via a letter describing the purpose as well as practical details of the study. A research nurse contacted the patients by phone a few days after the letter was sent to obtain informed consent for participation and permission to send out the questionnaire. Two weeks after the patient had received the questionnaire a post card was mailed out with thanks for their participation and, if necessary, a reminder to return the questionnaire. If the patient did not return the questionnaire at this point, a research nurse made a final reminder by phone. This process has been successfully used to achieve high response rate (around 90%) in earlier studies performed by our research group and others [67, 68, 73-75].

Patient specific clinical data were obtained from the Patient Register at the Swedish National Board of Health and Welfare and patient medical records obtained from Swedish hospitals.

3.3.1.4 REFERENCE POPULATION

A reference group of 1078 persons of the Swedish population, randomly selected from the Swedish Tax Agency, was used for comparison in Paper I. This reference cohort has been described by Bock et al (2018) and answered the same questions as our study population in Paper I in a questionnaire between 2014 and 2015. Median age in this reference cohort was 63 years, and the male/female ratio 47% / 53%. [65].

3.3.2 PAPER IV

We used a qualitative approach and collected data through in-depth interviews. A semi-structured interview guide was developed based on clinical experience and results from papers I-III of identifying long-term side effects [76, 77]. We used the method content analysis [78] in an inductive way [79] to explore the field. This is in qualitative methodology considered to be suitable for unexplored fields like ours. With this method we attained a condensed description with categories that describes the phenomena experienced after salvage surgery.

3.3.2.1 STUDY POPULATION

In the original ANCA cohort of 388 patients, 43 patients that had undergone salvage surgery were identified. In February 2023 27 patients were alive and were invited to participate in the study among which 18 were included.

3.3.2.2 DATA COLLECTION

All patients who were eligible for the study were invited to participate by an informative letter. A phone call was made by a research nurse a few days after the letter was sent to follow up on interest in participation. Informed consent was collected from all patients who accepted participation in the study, and interviews were scheduled and took place in February and March 2023. Participants could choose a convenient location where they preferred to have the interviews. Interviews were held in patients' home, on digital meeting platform, or in a place near by their home. Authors AA and EG performed all interviews together alternating between interviewing or observing. The observer had the option to ask clarifying questions. The interviews were audio-recorded and lasted in median 41 minutes (range 19-63 minutes). All interviews were transcribed verbatim by a professional transcriber or by AA.

3.3.2.3 ANALYSIS METHOD

We performed an inductive content analysis in accordance with Elo & Kyngäs (2008) [78]. We explored the transcribed interviews for mainly manifest

content, but also latent content that appeared from the data. This is a stepwise interactive process as described in Figure 6. We used Microsoft Excel as a tool for the analysis process.

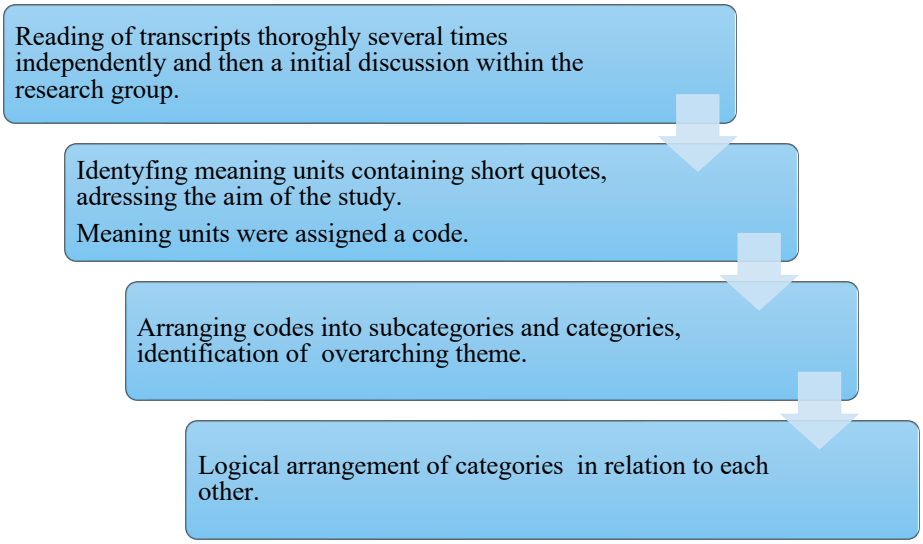

Figure 6. Process of content analysis.

3.4 HYPOTHESES

We hypothesized that patient reported QoL would deteriorate between follow-up at three and six years, and that low QoL would correlate with patients feeling bothered by one or more impaired bodily functions (Paper I), such as long-term side effects concerning bowel function and anal pain (Paper II), and urinary and sexual function (Paper III). We also hypothesized that the addition of chemotherapy to radiotherapy, compared to radiotherapy alone, would increase impairment of bowel function and urinary incontinence.

The research question for the qualitative study in Paper IV emerged during the interpretation of the results in Papers I-III. There was an apparent paradox in that worsening symptoms over time did not translate into deterioration of QoL. This motivated a need for a deeper understanding of the data collected in Papers I-III.

3.5 STATISTICS

To describe demographic and clinical characteristics of the ANCA cohort we used descriptive statistics that was numerically summarized. Categorical variables were presented by frequency and percentage and continuous variables were presented as mean and standard deviation.

The aim of the primary endpoints was to identify the QoL and bother from impaired bodily functions (Paper I), bowel function and anal pain (Paper II), and urinary and sexual function (Paper III), at three and six years after diagnosis. Descriptive statistics were used and presented with frequency and percentage.

The aim of the secondary endpoint in Paper I was to investigate the relationship between bother and QoL, which was assessed by modified Poisson regression analysis [80].

Responses to the QoL-question on the Likert scale ranging from 0 to 6 were dichotomized into two categories "**low QoL**" including the range 0-4 and "**good QoL**" including the range 5-6. The same dichotomization of answers to this question has been used by Steineck et al in prostate cancer survivorship [59], as well as in our reference cohort from the normal population [65].

The five response categories in the bother question were grouped into three new categories: "**no bother**" included "*not relevant, I haven´t had any impairments the last month*"; "**minor bother**" included "*it wouldn´t bother me at all*" and "*it would bother me slightly*"; "**major bother**" included "*it would bother me moderately"* and "*it would bother me a lot*".

For the secondary endpoint in Paper II and III, we used logistic regression to evaluate the additional effect of chemotherapy in chemoradiotherapy compared to radiotherapy alone on bowel function (Paper I) and urinary incontinence (Paper II).

Results from regression models are presented in odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CI) and p-values.

3.5.1 STATISTICAL CONSIDERATIONS

Papers I-III report on our findings when following survivors after anal cancer treatment longitudinally including measure points on group level. We have chosen to include all observations at both three- and six-years follow-up from a total of 205 patients. There was a dropout of 50 patients between the two measurements and there were another 10 patients that did not answer the three years questionnaire but chose to answer at six years. This resulted in two non-identical but largely overlapping groups, please see the Venn diagram below.

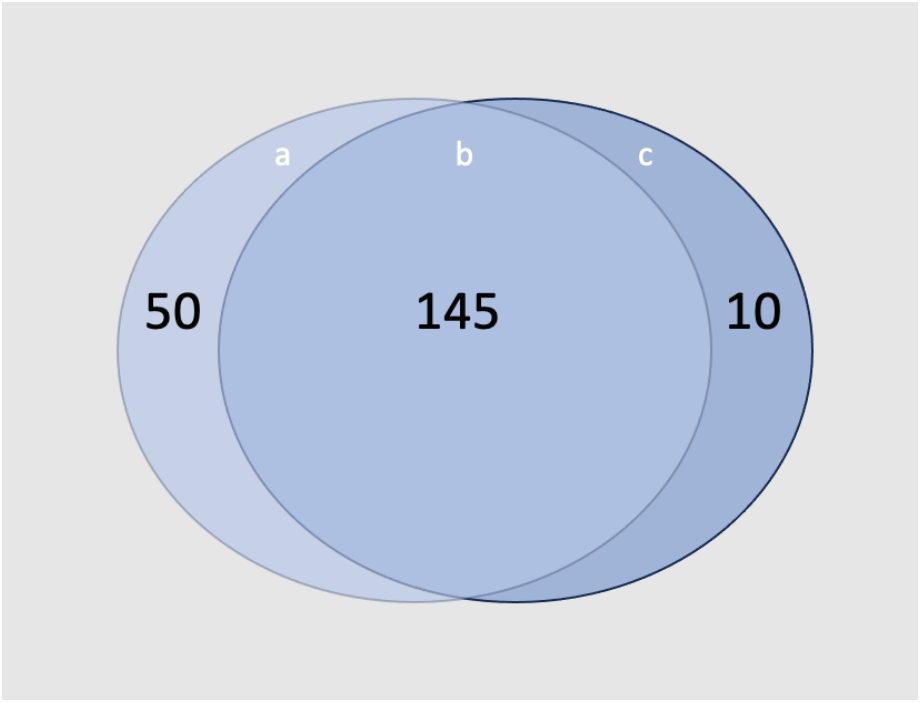

Figure 7. Venn diagram of study population in Paper I-III, a=participants at only three years; b=participants at both three and six years; c=participants at only six years.

Due to three late received questionnaires, Paper I consists of 152 observations at six years and paper II-III 155 at six years.

3.5.1.1 ATTRITION

The attrition from the whole cohort of 464 patients diagnosed with anal cancer 2011-2013 to the population of 205 that answered at least one questionnaire is a potential problem regarding the external validity of our results in Papers I-

III. External validity is the degree of transferability of estimations and conclusions to other populations than the one observed. In this case "other populations" could be another cohort similar to ours or could be referring to the concept "all patients in the whole world living after anal cancer diagnosis". The attrition from the 464 originally identified to the 388 included in the ANCA study is of unknown characteristics. The attrition from the 388 included in ANCA and the 205 answering at least one questionnaire is characterized by higher age, more advanced tumor stage, more often palliative treatment intention and less intensive treatment (Paper II). Comorbidity and age influences choice of treatment and choice of treatment influences prognosis including overall survival [12].

It is reasonable to assume that the 124 deceased patients between inclusion in the ANCA study and three years of follow-up is a reflection of real-world survival outcomes in anal cancer at the time, and therefore does not affect external validity when the aim is to study long-term survivors.

The dropout between three and six years is not random, but represents respondents with higher rates of cardiovascular comorbidity, smoking, and death of any cause (Table 2). The same problem has been reported in other studies that were designed with longitudinal intention but with attrition over time after cancer treatment [81, 82]. The non-random dropout between three and six years and the fact that the groups at three and six years are not identical has to be considered when assessing the internal validity of our assumptions on outcomes over time. Internal validity means the ability of the performed study to be able to answer the research question without bias. In this case there is a risk of underestimating the true degree of deterioration of symptoms over time.

In Papers II-III we analyzed the association between chemotherapy and long-term side effects. The sub-set of long-term survivors that initially were treated with radiotherapy represent a smaller portion of this category than long-term survivors after chemoradiotherapy. This is due to the fact that radiotherapy only as treatment category is associated with worse survival [12]. This does not necessarily introduce any bias in the analysis. However, "radiotherapy only" patients constitute an older and more comorbid category than patients treated with chemoradiotherapy. This carries a risk of introducing bias and of compromising the internal validity of the results on late-side effects among the two groups. In this case there is a risk of underestimating the additive effect of chemotherapy on long-term side effects.

Table 2. Demography of respondents to three-years questionnaire only (n=50), both three- and six-years questionnaires (n=145) and six-years questionnaire only(n=10).

	n=50 (%)	n=145 (%)	n=10 (%)
Age, median (range)	68 (35–86)	63 (36-83)	61 (50-74)
Female	36 (72%)	114 (79%)	9 (90%)
Male	14 (28%)	31 (21%)	1 (10%)
No smoker	15 (30%)	55 (38%)	4 (40%)
Ever smoker	17 (34%)	74 (51%)	5 (50%)
Current smoker	15 (30%)	15 (10%)	1 (10%)
Missing	3 (6%)	1 (1%)	0
Comorbidity			
Diabetes	3 (6%)	10 (7%)	1 (10%)
Cardiovascular diseases	9 (18%)	16 (11%)	1 (10%)
Cerebrovascular diseases	3 (6%)	1 (1%)	0
Renal dysfunction	1 (2%)	1(1%)	0
COPD/Asthma	2 (4%)	8 (6%)	1 (10%)
HIV-positive	1 (2%)	1(1%)	0
Immunosuppression	1 (2%)	8 (6%)	0
Stage of disease (AJCC7)			
0	1 (2%)	4 (3%)	1 (10%)
I	7 (14%)	20 (14%)	4 (40%)
II	18 (36%)	54 (38%)	4 (40%)
IIIA	3 (6%)	28 (20%)	1 (40%)
IIIB	16 (32%)	36 (25%)	0
IV	2 (4%)	1 (1%)	0
Missing	0	2 (1%)	0
Primary treatment at diagnosis			
Chemoradiotherapy	24 (48%)	78 (54%)	3 (30%)
Radiotherapy	12 (24%)	32 (22%)	2 (20%)
Chemotherapy followed by radiotherapy	10 (20%)	29 (20%)	1 (10%)
Chemotherapy followed by surgery	1 (2%)	0	0
Surgery	3 (6%)	4 (3%)	2 (20%)
Surgery followed by chemoradiotherapy	0	1 (1%)	
Surgery followed by radiotherapy	0	1 (1%)	1 (10%)
Reason for dropouts between 3- and 6-years follow-up			
Deceased between 3- and 6-years follow-up	17 (34%)		
Declined participation without reason	6 (12%)		
Declined due to physical disease or psychological reasons	3 (3%)		
Unable to be reached	11 (22%)		
Questionnaire is not returned	12 (24%)		
Emigrated	1 (2%)		

3.6 ETHICAL CONSIDERATIONS

All patients included in the ANCA study have voluntarily agreed to participate, in accordance with the Helsinki declaration, and have signed an informed consent [83]. For the qualitative study, which took place several years after the original ANCA study, we sought a supplementary ethical approval.

The ANCA study was approved by the Regional Ethical Committe (EPM) in Gothenburg. (Dnr. 495-15). The study was registered at Clinical Trials NCT02546973.

For Paper IV a supplementary approval was received by the national Ethical Review Board. (Dnr. 2022-03944-02).

When applying for ethical approval we asked for permission to collect data from patients charts before approaching the patients. This request was approved by the research ethics committee, but the National Board of Health and Welfare which administers the cancer registry required that we contacted patients registered with the ICD-code C21 in the cancer registry to obtain consent for study participation prior to retrieving patient charts. Subsequently we sent all patients with C21 diagnosis between 2011-2013 a letter asking for consent to take part in the ANCA study based on their anal cancer diagnosis. This resulted in a few patients, who were distressed by the invitation, to contact the research center, as they had never been aware of having a cancer diagnosis. These patients had been treated for premalignant anal lesions (i.e. dysplasia; carcinoma in situ; HSIL/AIN3). The affected patients received an apology from the PI of the study with an explanation of why they had been approached and offered an opportunity to be put in immediate contact with doctors in the research group.

The incident led to discussions in the research group about what we could have done differently. We concluded that the only way to avoid this kind of distress inflicted on patients was by first having had access to patients' medical records, which on the other hand would be contrary to the patients right to voluntarily choose whether to participate in a study. In our opinion this incident highlights the right of the patient to receive full information when clinical data are registered in registries, and which might be used for research purposes in the future. The ethical consequences of including premalignant conditions in a cancer registry must be reflected on when such decisions are made.

4 RESULTS

4.1 QUALITY OF LIFE

Patients treated for anal cancer reported of a good QoL in 40% of cases at three years follow-up but 60% reported a low QoL. This ratio remains stable at six-year follow-up. In the Swedish normal population QoL was measured to be 50% / 50% of low versus good QoL. Sense of coherence and depression are known to have effect on QoL in earlier studies. Our result shows a stability in sense of coherence (155) between three and six years of follow-up and reports at the same median level (154) as in the normal population. Depression was reported in 14% of the normal population, and slightly higher in patients treated for anal cancer with 19% at three years. The rate of depression was slightly improved to 17% at six years.

Major bother from long-term side-effects of bowel and urinary function were more prevalent for those reporting low QoL (at three years; bother from bowel function RR 1.42, ((95% CI 1.06-1.90) p-value 0.02) (at six years; bother from bowel function RR 1.52, ((95% CI 1.03-2.24) p-value 0.03) and bother from urinary function RR 1.44, ((95% CI 1.08-1.91) p-value 0.01). We also found a tendency of a risk of low QoL for those reporting more than one bothers of bodily functions after anal cancer treatment at both three and six years.

The reports of bother seemed to differ between bodily functions. Bowel and urinary long-term side-effects caused more bother than long-term side effects of sexual function after three and six years. This finding was confirmed in interviews by patients in study IV after salvage surgery. The interviews took place in median 10 years after salvage surgery (range 7-12) and diagnosis (range 10-12).

In Paper IV patients described that they experienced a very high QoL in median 10 years after salvage surgery. When asking for specific HRQoL the majority stated that it was slightly lower than total QoL, but they were all united by the fact that they had survived and were able to live. To survive cancer overshadowed all bodily long-term side effects and was identified as important for high QoL, and they were grateful that they had survived.

4.2 LONG-TERM SIDE EFFECTS OF BODILY FUNCTIONS

4.2.1 BOWEL FUNCTION

At both three and six years, side effects from bowel function were commonly reported. Patients with stoma was excluded from bowel function analysis, 49 (25%) at three years and 40 (26%) at six years. The most common side-effect was bowel urgency, i.e. the urge to defecate. Fifty-seven percent described bowel urgency once a week or more at three years and 59% at six years. Patient reported on their ability to stay continent while experiencing urgency. At three years 39% had 1-5 min before they had to defecate and at six years 46%. Twenty percent reported less than one minute at both three and six years. Bowel incontinences once a week were more common in case of liquid stool (three years 28%, six years 21%) than solid stool (three years 9%, six years 11%). The majority of patients at both three (94%) and six years (93%) suffered from leakage of gas. Only 6% of the patients believed that a stoma could facilitate their life. Long-term side effects due to bowel function was reported in similar frequencies at three and six years. Our result indicates that the addition of chemotherapy (in chemotherapy compared to radiotherapy alone) results in a higher risk for impaired bowel function. Patients (included patients with a stoma) reported major bother from bowel function in 51% at three years and 44% at six years.

The experience that was told from patients a decade after salvage surgery of functional bowel side effects was that a stoma was of no concern. They had all adapted to their stoma and to what they had to change to make it function, for example what to wear and what to eat. Several patients experienced episodes of bowel obstruction after surgery which affected them a lot.

4.2.2 URINARY FUNCTION

Long-term side effects from urinary function on the other hand seem to increase from three to six years of follow up. Urinary urgency was reported by 63% at three years and 73% at six years. Urinary incontinence during the day was reported by 46% at three years and 51% at six years. At three years 47% of patients reported that they had sensations of incomplete bladder emptying, at six years the same was reported by 58%. Chemotherapy in chemoradiotherapy versus radiotherapy alone did not have an additive effect worsening urinary incontinence. Although the proportion of long-term side

effects was higher at six years compared to three years patients reported the same level of major bother from urinary function at both three (33%) and six (32%) years. Minor bother was reported in three (24%) and six (35%) years.

A decade after salvage surgery the majority of patients in this group expressed urinary incontinence as common.

4.2.3 SEXUAL FUNCTION

Ninety-two percent of patients did not recall having had problems of sexual functions before treatment for anal cancer. Our result reports of long-term side effects in sexual function for both women and men. Preserved elasticity of the vagina was reported at three years in only 4% of cases and 2% at six years. One quarter of women used a vaginal dilator more than once a month, trying to improve elasticity while a fifth of women used the vaginal dilator on single occasions. At three years (62%) and six years (70%) women reported that they did not know what their elasticity of the vagina was. Erectile dysfunction was reported by 54% of men at three years and by 67% at six years. Erectile dysfunction aids were used by 18% at three years and 16% at 6 years. Men's self-esteem was affected due to the deterioration of erectile function in 42% at three years and 48% at six years. We report a significant proportion of patients with long-term side effects on sexual function. This is also shown by the percentage of those reporting that intercourse was not part of their sex-life after treatment for anal cancer (at three years 77%, at six years 83%) and that sex was not an important part of their life (60% at three years, and 64% at six years).

In the group that underwent salvage surgery, none of the male patients had any erectile function at all. This dysfunction reportedly started immediately after the surgery in all cases. The men reported that they missed not having preserved erectile function, but they expressed acceptance and compared themselves to others of the same age who due to aging or disease were suffering the same problems. For women that underwent salvage surgery with a reconstruction of the posterior vaginal wall with a flap expressed a sensation of a short or a non-existing vagina. They found that their genitalia had changed their appearance. Their labia majora had been removed giving a sensation of an unprotected vagina. When trying to have intercourse they experienced a sensation of burning and pain.

4.2.4 PAIN AND SENSORY SYMPTOMS IN THE PELVIC AREA

In paper I-III anal pain was reported once a week or more in 18% at three years and 10% at six years. Anal pain on single occasions was more commonly reported by 17% at three years and 23% at six years. Of those that reported anal pain, 19% experienced major bother at three years and 13% at six years.

For those patients in study IV buttock pain and altered sensations was commonly expressed. Those that underwent a reconstruction with a myocutaneous flap experienced a feeling of being skewed or sitting on a ball. Mobility and physical strength were affected in legs and hips. Almost all experienced a limitation of the ability to sit on hard surface. A sensation of not being completely healed in the pelvic area a decade after the surgery was expressed by several patients. This sensation was reported to get worse from various triggers, for example a common cold and was described in inflammation-like terms.

4.2.5 ACCEPTANCE AND REORIENTATION TO A NEW LIFE

In Paper IV patients´ lived experience a decade after salvage surgery was described with a main theme - *Acceptance and reorientation to a new life*, - from latent content. Eight categories with manifest content were identified. Bodily changes and functions; impaired psychological well-being; knowledge and information; impact of other circumstances in life; adjustment of daily living; adaptation of bodily perception with perceived self-image; gratitude for being alive; QoL and HRQoL.

The patients expressed gratitude for being alive despite several bodily and functional changes. Patients expressed trust in the information and care they had received from the healthcare system. They were not sure how they had changed anatomically after surgery and how their pelvis looked like. There was a fear of recurrence and a lack of knowledge about which side-effects and symptoms were related to treatment. There was an unfulfilled need of access to rehabilitation resources.

QoL were described as high with references to the fact that they had survived their cancer and that they were able to work or to be with their close ones. HRQoL was described as a bit lower than total QoL and were related to experienced long-term side effects form treatment and, in addition, to other

comorbidities that comes with age. Patients had accepted and adapted to their situation. Patients voiced strategies to cope with loss of sex life and sexual abilities such as comparing themselves with others in the same age who they assumed also probably suffered from impairment of sexual functions. They considered losing sexual abilities as a normal development when getting older.

A decade after salvage surgery, patients described a process of reorientation and a sense of having entered a new way of living a normal life.

5 DISCUSSION

My intention from the outset of this research project has been to add new knowledge in the field of anal cancer survivorship. The scope of this thesis involves the interface between various domains in this field, domains which I have summarized in the introduction.

The most common factor for most of the patients treated for anal cancer is exposure to radiotherapy. The character and frequency of reported symptoms overall, as well as the emerging time patterns between our two measurements, can be explained by the effect of radiotherapy on normal tissue. The fact that impairment of bowel function was stable, but a deterioration of urinary and sexual function could be detected between the two measurements, is well in accordance with radiobiologic explanation models (Figure 1).

Based on this model, the fact that the sphincter complex is always included in the high-dose volume of radiotherapy in anal cancer explains why functional impairment appears early after treatment and becomes clinically detectable well before three years. In addition to the radiobiological explanation, the location of the primary tumor itself and its remission after therapy can cause irreversible anatomical changes in the anal region which appears before or directly after treatment.

Urinary function involves volumes exposed to lower doses and accordingly impairment becomes clinically evident at later time points after radiotherapy. In addition to this lag time between exposure and worsening of symptoms, urinary function domains are probably subjected to other causes of deterioration such as normal ageing. Sexual function involves volumes exposed to both higher and lower doses and is probably a result of both early and later changes, and other causes of deterioration between three and six years.

Symptoms and functional outcomes showed stability or deterioration between our two measurements while QoL and bother showed stability or improvement over time. We believe this contrast can in part be explained by response shift. Indication of this effect in our study population could be detected in the interviews of Paper IV.

Our cohort for the outcome analysis consisted of 205 unique individuals, who lived at least three years after anal cancer diagnosis. Even though not an impressive figure in absolute numbers, this is one of the largest cohorts described in cancer survivorship research for this diagnosis including PROMs.

Bentzen et al (2013) reported in a cross-sectional study on 128 patients treated between 2000-2007, and with a median follow-up of 66 months. The authors used EORTC QLQ-C30 and EORTC QLQ-CR29. They found significant impairment in general QoL domains compared to healthy controls. Functional impairment in bowel and sexual function was common [35]. In another cross-sectional study Sunesen et al (2015), 84 patients diagnosed between 1996-2003 answered a study-specific questionnaire at a median time of 33 months after diagnosis. Faecal incontinence and urgency were common as well as urinary urgency and incontinence. Fifty-eight percent of patients reported no sexual desire at all and only 24% reported satisfying sexual function. Bowel impairment had the greatest influence on degree of distress [36]. Knowles et al (2015) conducted a cross-sectional study including 42 patients treated between 1990-2007 at a median time of 63,8 months after diagnosis. The authors used EORTC QLQ-C30 and EORTC QLQ-C38 and a generic PROM instrument for bowel function. Leakage of stools and gas was frequent with 39% of patients reporting constant need of a protective pad and 29% had to make daily adjustments in their social life because of low bowel function [37].

In a cohort study by Koerber et al (2018) including 47 female patients treated for anal cancer, a study-specific questionnaire was used cross-sectionally at a median time of three years (range 1-16). The authors refer to patient-reported data at baseline, i.e. at treatment, used as comparator, without specifying how baseline data was retrieved [84].

In a retrospective study Taylor et al (2022) looked at prospectively collected PROMs before and after chemoradiation for anal cancer at a single institution. The authors analysed data from 178 patients who in all completed 316 PROM surveys. At no specific time-point were there more than 42 patients contributing. The total number completed PROM surveys after 2 years of follow-up was 29 at 3 years, 18 at 4 years and 4 at 5 years [85]. The authors discuss their results without having stated any pre-specified hypotheses. Their main conclusion highlights the finding that worse bowel function at baseline was associated with worse bowel function at follow-up.

These studies included either no repetitive measurements at all [35-37], or repetitive measurements but not as part of a prospective study design [84, 85]. As a consequence, they were unable to adequately address evolvement over time of QoL and functional symptoms.

To be able to put our results in a larger context, it is wise not to focus on studies on anal cancer solely due to the rarity of the disease and the lack of prospective design in the studies mentioned above. Prospective studies including data on late side effects and QoL in other squamous cell carcinoma diagnoses, or other pelvic malignancies can be used for comparison. Patients in these studies have been exposed to similar treatment as the patients in the ANCA study, that is predominantly radiotherapy, often combined with chemotherapy and less frequently surgery. Several of these studies include PROMs on functional outcomes and QoL at two or more time-points, with the longest follow-up ranging from three to 12 years. Oskam 2013, Townes 2020, Van den Bosch 2021 and Aghajanzadeh 2023 in head and neck cancer as well as Barker 2009, Post 2021 and Vittrup, 2023 in cancer of the uterine cervix and endometrium are all longitudinal in design with the intention of analyzing time as a factor on side-effects collected via PROMs [81, 82, 86-90].

Common patterns emerge when comparing results between these studies as well as comparing the results in these studies with our findings in Paper I-III.

First, long-term side effects of radiotherapy show no tendency of meliorating after two years. When multiple assessments are made, symptoms appear stable between two-three years and five years. However, when attrition is taken into account, the interpretation is that this apparent stability may be a result of bias where the healthier patients are overrepresented at later follow-up assessments [81, 82, 87-90].

Second, function related to normal tissue exposed to lower radiotherapy doses tend to deteriorate later than impaired functions related to organs and tissues exposed to higher doses [87, 89, 90].

Third, general QoL domains remain relatively stable over time and show low correlation to deterioration of function. This is in several studies attributed to the phenomenon of response shift [81, 82, 86, 89, 90]. Severity, persistence,

and quantity of side effects do however correlate to QoL on an individual level [81, 82, 86-90], as we found in Paper I.

Precise predictive models for long-term toxicity after radiotherapy are lacking. One of the challenges remaining is to estimate the additive or synergistic effect when radiotherapy is combined with drugs, most often chemotherapy. Our secondary hypothesis in Paper II and III was that chemotherapy added to the symptom burden compared to radiotherapy alone.

Some of the longitudinal studies above have also tried to estimate the effect of the addition of chemotherapy on late side effects, compared to radiotherapy alone. These estimations in population-based cohorts as ours, are hampered by treatment selection. Chemotherapy is added more frequently in more advanced disease and the subgroups are therefore not comparable because of treatment bias. Even if the design of the study is a randomized controlled trial, with planned long-term follow-up on side effects and quality of life, there are difficulties of measuring the effect of chemoradiotherapy alone since chemotherapy is added before (neoadjuvant) or after radiotherapy (adjuvant) depending on the study and diagnosis. Our results on the effect of chemotherapy were conflicting. We have no biological rationale to believe that chemotherapy added to radiotherapy does not have an effect on long-term function compared to radiotherapy alone. We attribute the absence of a clear effect in Papers II-III to the methodological issues raised above.

Our qualitative study including in-depth interviews after salvage surgery for anal cancer including 18 patients in Paper IV is, to our knowledge, the first of its kind. A similar study design was used by Saunders et al (2021) after rectal cancer surgery including 15 patients. The authors did not report median time of follow-up since surgery. Only seven of the patients had gone through surgery requiring reconstructive measures. Themes reported by Saunders included impact of daily life; information needs; relation between attitude and lifestyle and perceived QoL [77].

Our overarching theme in Paper IV – “acceptance and reorientation to a new life” provide a deeper explanation of the results in Paper I - III. It also connects the challenges of anal cancer survivorship with other conditions of survivorship in a general way. There are similarities of studies across different settings where patients describe their adaptation strategies in depth after having to face life-changing disease and treatment [91-93]. It is plausible to assume that the coping strategies patients use for reorientation when confronted by

disease are basic human abilities to adapt to major changes in life, including normal aging [94].

6 CONCLUSION

We found that patients living after anal cancer were affected in various domains in aspects related to the physical effects of their treatment. There was a clear relationship between symptom burden, bother and quality of life. There was also a relationship between time after treatment and deterioration of function. There was however no clear relationship between time after treatment and quality of life, indicating an adaptation process between three and six years.

Performing in-depth interviews with patients that had undergone extensive surgery as a part of their treatment revealed valuable clues that we believe strengthen the assumption of response shift in the cohort as a whole.

7 FUTURE PERSPECTIVES

The high curation rate in anal cancer and the burden of physical changes inflicted by treatment indicates a need for better precision and differentiation in anal cancer treatment, both regarding oncological outcome as well as long-term side effects. The best balance can only be achieved if both outcomes and side effects are measured in studies with high methodological standards.

This thesis shows that it is feasible to follow anal cancer survivors over time with longitudinal intention and to use PROMs. The discrepancy between symptom burden and reported QoL indicates a clear effect of adaptation and response-shift. Future studies should aim to describe and quantify the process of adaptation, possibly by adding repetitive in-depth interviews in longitudinal designs.

The apparent risk of patients' adaptation concealing true tissue changes and symptom burden could be addressed by combining repetitive PROMs with objective measurements like tissue biopsies or other less invasive methods.

Objective measurements should be taken into consideration together with PROM-data to quantify side effects correctly for development of predictive modelling of radiotherapy and choosing the best balance between treatment and side effects.

Development of PROM instruments must continue to take adaptation and response-shift into account and adjust for these phenomena when PROMs are used in efforts to estimate toxicity of cancer treatments.

ACKNOWLEDGEMENTS

Eva Angenete, my main supervisor. Thank you for being such an inspiration, full of energy and enthusiasm. Thank you for believing in me and for your expertise. Without your guidance, this would not have been possible. You have become a dear friend!

Mia Johansson, co-supervisor, colleague, and friend! Thank you for your knowledge in the field of anal cancer and PROM, and for being thorough and supportive in ups and downs.

Eva Haglind, senior researcher at SSORG. I am immensely grateful for all your advice and for all our discussions about science and life. You have made me grow in my role as a PhD student. Your door has always been open for me.

David Bock, for your limitless patience when teaching me R and with all my questions on statistics.

Ying Li, for making me understand those things I find most difficult.

Matilda Liljedahl for your enthusiasm and collaboration on Paper IV.

Elisabeth González, for your outstanding contribution and effort in carrying out the study for Paper IV. For all your knowledge and consideration. Your company made our travels around the country an unforgettable experience.

Carolina Ehrencrona, for everything I have learnt from you during my years at SSORG, and for your great support. You are brilliant!

Lars Ny, Head of Department of Oncology, for encouraging me and inspiring me during my first steps of my academic journey.

Annika Baan, Susanne Jörnvik Carlsson, Lisa Eek Branzell, Andreas Hellqvist, for your support.

To **Claes Hallenskiöld**, for always supporting me and for your friendship. Looking forward to your return, I miss my colleague and friend!

Andreas, Maria, Sofia, Sophia, Daniel, Eric, my PhD-colleagues at SSORG for great companionship and support.

Anette, Carina, Rebecca and all other past and present SSORG members. It has been a privilege to work with all of you.

To **all my colleagues** at Jubileumsklinikens out-patient clinic. Thanks for your cheerful support during all these years.

To my dear friend **Sanna Ewards** for our endless talks about all things in life and for always being there for me.

Hanna Larsson for taking me out on walks when I needed it the most, and for being a great friend.

To my bonus family **Sam** and **Sven, Rigmor** and **Kjell, Malin** with family - for welcoming me in your life.

To my loving family – my parents **Rolf** and **Eva**, for your endless love and support - and to my brother **Martin** and sister-in-law **Maria with family William, Oliver** and **Kajsa**, I am so grateful to have you all in my life.

To my beloved children **Emelie** and **Elias**, being your mum is the greatest thing of all. I love you with all my heart.

To **Mats**, my darling, for always believing in me. You are the one that challenge me the most, who makes me grow in all aspects of life. I love you forever and always.

Last but not least, my deepest gratitude to all patients whose participation in the ANCA study made this thesis possible.

REFERENCES

1. Regionalt cancercentrum i samverkan (2020) Nationellt vårdprogram Analcancer.
2. Mignozzi S, Santucci C, Malvezzi M, Levi F, La Vecchia C, Negri E. Global trends in anal cancer incidence and mortality. *Eur J Cancer Prev* 2023
3. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol* 2012; **13:** 487-500.
4. Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, et al. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. *Int J Cancer* 2021; **148:** 38-47.
5. Szymonowicz KA, Chen J. Biological and clinical aspects of HPV-related cancers. *Cancer Biol Med* 2020; **17:** 864-78.
6. Wellings K, Collumbien M, Slaymaker E, Singh S, Hodges Z, Patel D, et al. Sexual behaviour in context: a global perspective. *Lancet* 2006; **368:** 1706-28.
7. Ferris DG, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Mehlsen J, et al. 4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years. *Pediatrics* 2017; **140**
8. National Comprehensive Cancer Network (2024) NCCN Clinical Practice Guidlines in Oncology (NCCN Guidlines®) Anal Carcinoma.
9. Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen SE, et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol* 2021; **32:** 1087-100.
10. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas CR, et al. Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal: A Randomized Controlled Trial. *JAMA* 2008; **299:** 1914-21.
11. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013; **14:** 516-24.
12. Johansson M, Axelsson A, Haglind E, Bock D, Angenete E. Long-term survival after treatment for primary anal cancer- results from the Swedish national ANCA cohort study. *Acta Oncol* 2022; **61:** 478-83.
13. Leon O, Guren M, Hagberg O, Glimelius B, Dahl O, Havsteen H, et al. Anal carcinoma - Survival and recurrence in a large cohort of

patients treated according to Nordic guidelines. *Radiother Oncol* 2014; **113:** 352-8.
14. Johnsson A, Norman D, Angenete E, Cavalli-Björkman N, Lagerbäck C, Leon O, et al. Anal cancer in Sweden 2015-2019. Implementation of guidelines, structural changes, national registry and early results. *Acta Oncol* 2022; **61:** 575-82.
15. Brierley JD GM, Wittekind C. (2016) *TNM classification og malignant tumours.* Wiley-Blackwell, Hoboken (NJ).
16. Glynne-Jones R, Meadows HM, Lopes A, Muirhead R, Sebag-Montefiore D, Adams R. Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus: results of a post hoc analysis from the randomised phase III ACT II trial. *Ann Oncol* 2020; **31:** 1376-85.
17. Mai S, Welzel G, Ottstadt M, Lohr F, Severa S, Prigge ES, et al. Prognostic Relevance of HPV Infection and p16 Overexpression in Squamous Cell Anal Cancer. *Int J Radiat Oncol Biol Phys* 2015; **93:** 819-27.
18. Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, Hogdall E, Geertsen PF, Havsteen H. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. *J Clin Oncol* 2014; **32:** 1812-7.
19. Frey B, Derer A, Scheithauer H, Wunderlich R, Fietkau R, Gaipl US (2016) Cancer Cell Death-Inducing Radiotherapy: Impact on Local Tumour Control, Tumour Cell Proliferation and Induction of Systemic Anti-tumour Immunity. In: *Apoptosis in Cancer Pathogenesis and Anti-cancer Therapy: New Perspectives and Opportunities*. (ed Gregory CD), pp. 151-3. Springer International Publishing, Cham.
20. Dörr W (2018) Pathogenesis of normal tissue side effects. In: *Basic Clinical Radiobiology* (ed Joiner MC, & van der Kogel, A.J.), pp. 152, 5-8. CRC Press, Boca Raton.
21. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76:** S10-9.
22. Stewart FA, Akleyev AV, Hauer-Jensen M, Hendry JH, Kleiman NJ, Macvittie TJ, et al. ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs--threshold doses for tissue reactions in a radiation protection context. *Ann ICRP* 2012; **41:** 1-322.
23. Safwat A, Bentzen SM, Turesson I, Hendry JH. Deterministic rather than stochastic factors explain most of the variation in the expression of skin telangiectasia after radiotherapy. *Int J Radiat Oncol Biol Phys* 2002; **52:** 198-204.

24. Kerns SL, Hall WA, Marples B, West CML. Normal Tissue Toxicity Prediction: Clinical Translation on the Horizon. *Semin Radiat Oncol* 2023; **33:** 307-16.
25. Alsadius D, Hedelin M, Johansson KA, Pettersson N, Wilderäng U, Lundstedt D, et al. Tobacco smoking and long-lasting symptoms from the bowel and the anal-sphincter region after radiotherapy for prostate cancer. *Radiother Oncol* 2011; **101:** 495-501.
26. Marshall DC, Kerns SL, West CML, Rosenstein BS. A Comparison of Radiation Toxicity Outcomes in Patients With and Without Autoimmune Diagnoses on the REQUITE Study. *International Journal of Radiation Oncology Biology Physics* 2021; **111:** E238-E.
27. Hey J, Setz J, Gerlach R, Vordermark D, Gernhardt CR, Kuhnt T. Effect of Cisplatin on parotid gland function in concomitant radiochemotherapy. *Int J Radiat Oncol Biol Phys* 2009; **75:** 1475-80.
28. Parashar B, Edwards A, Mehta R, Pasmantier M, Wernicke AG, Sabbas A, et al. Chemotherapy significantly increases the risk of radiation pneumonitis in radiation therapy of advanced lung cancer. *Am J Clin Oncol* 2011; **34:** 160-4.
29. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76:** S3-9.
30. Wopken K, Bijl HP, Langendijk JA. Prognostic factors for tube feeding dependence after curative (chemo-) radiation in head and neck cancer: A systematic review of literature. *Radiother Oncol* 2018; **126:** 56-67.
31. de Boer SM, Nout RA, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, et al. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. *Int J Radiat Oncol Biol Phys* 2015; **93:** 797-809.
32. Chen TY, Wiltink LM, Nout RA, Meershoek-Klein Kranenbarg E, Laurberg S, Marijnen CA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clin Colorectal Cancer* 2015; **14:** 106-14.
33. Yeung AR, Deshmukh S, Klopp AH, Gil KM, Wenzel L, Westin SN, et al. Intensity-Modulated Radiation Therapy Reduces Patient-Reported Chronic Toxicity Compared With Conventional Pelvic Radiation Therapy: Updated Results of a Phase III Trial. *J Clin Oncol* 2022; **40:** 3115-9.

34. Groen VH, Zuithoff NPA, van Schie M, Monninkhof EM, Kunze-Busch M, de Boer HCJ, et al. Anorectal dose-effect relations for late gastrointestinal toxicity following external beam radiotherapy for prostate cancer in the FLAME trial. *Radiother Oncol* 2021; **162:** 98-104.
35. Bentzen AG, Balteskard L, Wanderas EH, Frykholm G, Wilsgaard T, Dahl O, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. *Acta Oncol* 2013; **52:** 736-44.
36. Sunesen KG, Norgaard M, Lundby L, Havsteen H, Buntzen S, Thorlacius-Ussing O, et al. Long-term anorectal, urinary and sexual dysfunction causing distress after radiotherapy for anal cancer: a Danish multicentre cross-sectional questionnaire study. *Colorectal Dis* 2015; **17:** O230-9.
37. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. *Eur J Oncol Nurs* 2015; **19:** 479-85.
38. Cyr DP, Savage P, Theodosopoulos E, Chesney TR, Swallow CJ. Outcomes of salvage surgery for anal squamous cell carcinoma: A systematic review and meta-analysis. *J Clin Oncol* 2019; **37:** 3571-.
39. Baloch N, Nordenvall C, Johansson H, Nygren J, Nilsson PJ. Perineal healing following salvage surgery for anal cancer. *Colorectal Dis* 2021; **23:** 1102-8.
40. Borg J, Garm Spindler KL, Havelund BM, Sørensen MM, Funder JA. Risk factors and outcome following salvage surgery for squamous cell carcinoma of the anus. *Eur J Surg Oncol* 2023; **49:** 107050.
41. Glynne-Jones R, Kadalayil L, Meadows HM, Cunningham D, Samuel L, Geh JI, et al. Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trial. *Ann Oncol* 2014; **25:** 1616-22.
42. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med* 1985; **313:** 270-3.
43. Marzorati C, Riva S, Pravettoni G. Who Is a Cancer Survivor? A Systematic Review of Published Definitions. *J Cancer Educ* 2017; **32:** 228-37.
44. Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G, et al. ESMO Expert Consensus Statements on Cancer Survivorship: promoting high-quality survivorship care and research in Europe. *Ann Oncol* 2022; **33:** 1119-33.
45. Feuerstein M. Defining cancer survivorship. *J Cancer Surviv* 2007; **1:** 5-7.

46. Fayers PM (2016) Introduction. In: *Quality of Life: The assesment, analysis and reporting of patient-reported outcomes*. pp. 3-33. John Wiley & Sons. Ltd.
47. Organization. WH WHOQOL:Measuring Quality of Life.
48. Fayers PM (2016) Scores and measurements: validity, reliability, sensitivity. In: *Quality of Life: The assessment, analysis and reporting of patient-reported outcomes*. pp. 89-90. John Wiley & Sons. Ltd.
49. Sterner A, Derwinger K, Staff C, Nilsson H, Angenete E. Quality of life in patients treated for anal carcinoma-a systematic literature review. *Int J Colorectal Dis* 2019; **34:** 1517-28.
50. Sodergren SC, Johnson CD, Gilbert A, Tomaszewski KA, Chu W, Chung HT, et al. Phase I-III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer. *Radiother Oncol* 2018; **126:** 222-8.
51. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365-76.
52. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer* 2009; **45:** 3017-26.
53. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *Eur J Cancer* 1999; **35:** 238-47.
54. Steineck G, Bergmark K, Henningsohn L, Al-Abany M, Dickman PW, Helgason A. Symptom Documentation in Cancer Survivors as a Basis for Therapy Modifications. *Acta Oncol* 2002; **41:** 244-52.
55. Hong F, Blonquist TM, Halpenny B, Berry DL. Patient-reported symptom distress, and most bothersome issues, before and during cancer treatment. *Patient Relat Outcome Meas* 2016; **7:** 127-35.
56. Stensvold A, Dahl AA, Brennhovd B, Småstuen MC, Fosså SD, Lilleby W, et al. Bother problems in prostate cancer patients after curative treatment. *Urol Oncol* 2013; **31:** 1067-78.
57. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med* 1999; **340:** 1383-9.
58. Jeong CW, Herlemann A, Cowan JE, Broering JM, Ten Ham RMT, Wilson LS, et al. The Relative Impact of Urinary and Sexual Function vs Bother on Health Utility for Men With Prostate Cancer. *JNCI Cancer Spectr* 2020; **4:** pkaa044.

59. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; **347:** 790-6.
60. Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* 1999; **48:** 1507-15.
61. Hammas K, Sébille V, Brisson P, Hardouin JB, Blanchin M. How to Investigate the Effects of Groups on Changes in Longitudinal Patient-Reported Outcomes and Response Shift Using Rasch Models. *Front Psychol* 2020; **11:** 613482.
62. Preiß M, Friedrich M, Stolzenburg JU, Zenger M, Hinz A. Response shift effects in the assessment of urologic cancer patients' quality of life. *Eur J Cancer Care (Engl)* 2019; **28:** e13027.
63. Brill IT, Stark T, Wigers L, Brill SM. Response shift in hearing related quality of life after cochlear implantation - effect size and clinical significance: a then-test study. *Health Qual Life Outcomes* 2023; **21:** 37.
64. Schwartz CE, Rohde G, Biletch E, Stuart RBB, Huang IC, Lipscomb J, et al. If it's information, it's not "bias": a scoping review and proposed nomenclature for future response-shift research. *Qual Life Res* 2022; **31:** 2247-57.
65. Bock D, Angenete E, Gonzales E, Heath J, Haglind E. Assessing health, quality of life and urogenital function in a sample of the Swedish general population: a cross-sectional study. *BMJ Open* 2018; **8:** e021974.
66. Asplund D, Bisgaard T, Bock D, Burcharth J, Gonzalez E, Haglind E, et al. Pretreatment quality of life in patients with rectal cancer is associated with intrusive thoughts and sense of coherence. *Int J Colorectal Dis* 2017; **32:** 1639-47.
67. Asplund D, Prytz M, Bock D, Haglind E, Angenete E. Persistent perineal morbidity is common following abdominoperineal excision for rectal cancer. *Int J Colorectal Dis* 2015; **30:** 1563-70.
68. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderang U, Thorsteinsdottir T, et al. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. *Eur Urol* 2015; **68:** 216-25.
69. Antonovsky A. The structure and properties of the sense of coherence scale. *Soc Sci Med* 1993; **36:** 725-33.
70. Helgason AR, Adolfsson J, Dickman P, Fredrikson M, Arver S, Steineck G. Waning sexual function--the most important disease-specific distress for patients with prostate cancer. *Br J Cancer* 1996; **73:** 1417-21.

71. Söderhamn O, Holmgren L. Testing Antonovsky's sense of coherence (SOC) scale among Swedish physically active older people. *Scand J Psychol* 2004; **45:** 215-21.
72. Skoogh J, Ylitalo N, Larsson Omerov P, Hauksdottir A, Nyberg U, Wilderang U, et al. 'A no means no'--measuring depression using a single-item question versus Hospital Anxiety and Depression Scale (HADS-D). *Ann Oncol* 2010; **21:** 1905-9.
73. Angenete E, Correa-Marinez A, Heath J, Gonzalez E, Wedin A, Prytz M, et al. Ostomy function after abdominoperineal resection--a clinical and patient evaluation. *Int J Colorectal Dis* 2012; **27:** 1267-74.
74. Alsadius D, Olsson C, Pettersson N, Tucker SL, Wilderäng U, Steineck G. Patient-reported gastrointestinal symptoms among long-term survivors after radiation therapy for prostate cancer. *Radiother Oncol* 2014; **112:** 237-43.
75. Lundstedt D, Gustafsson M, Steineck G, Alsadius D, Sundberg A, Wilderäng U, et al. Long-term symptoms after radiotherapy of supraclavicular lymph nodes in breast cancer patients. *Radiother Oncol* 2012; **103:** 155-60.
76. Pedersen TB, Juvik AF, Koren SF, Gocht-Jensen P, Klein MF. Quality of life following salvage surgery for squamous cell carcinoma of the anus. *Eur J Surg Oncol* 2019; **45:** 995-8.
77. Saunders CH, Goldwag JL, Read JT, Durand MA, Elwyn G, Ivatury SJ. 'Because Everybody is so Different': a qualitative analysis of the lived experiences and information needs of rectal cancer survivors. *BMJ Open* 2021; **11:** e043245.
78. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008; **62:** 107-15.
79. Lauri S, Kyngas H. Developing nursing theories. *Vantaa, Finland: Werner Söderström, Dark Oy* 2005
80. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159:** 702-6.
81. Post CCB, de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, et al. Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial. *Int J Radiat Oncol Biol Phys* 2021; **109:** 975-86.
82. Van den Bosch L, van der Laan HP, van der Schaaf A, Oosting SF, Halmos GB, Witjes MJH, et al. Patient-Reported Toxicity and Quality-of-Life Profiles in Patients With Head and Neck Cancer Treated With Definitive Radiation Therapy or Chemoradiation. *Int J Radiat Oncol Biol Phys* 2021; **111:** 456-67.
83. Association. WM (2024) WMA Declaration of Helsinki - Ethical Principles.

84. Koerber SA, Seither B, Slynko A, Haefner MF, Krug D, Liermann J, et al. Chemoradiation in female patients with anal cancer: Patient-reported outcome of acute and chronic side effects. *Tumori* 2018**:** 300891618811273.
85. Taylor JP, Wei IH, Smith JJ, Tin AL, Aiken N, Vickers AJ, et al. Assessment of Patient-Reported Outcomes in Patients with Anal Squamous Cell Cancer Undergoing Combined Modality Therapy. *Dis Colon Rectum* 2022
86. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, Witte BI, de Bree R, Doornaert P, et al. Prospective evaluation of health-related quality of life in long-term oral and oropharyngeal cancer survivors and the perceived need for supportive care. *Oral Oncol* 2013; **49:** 443-8.
87. Townes TG, Navuluri S, Pytynia KB, Gunn GB, Kamal MJ, Gilmore KR, et al. Assessing patient-reported symptom burden of long-term head and neck cancer survivors at annual surveillance in survivorship clinic. *Head Neck* 2020; **42:** 1919-27.
88. Vittrup AS, Kirchheiner K, Pötter R, Fokdal LU, Jensen NBK, Spampinato S, et al. Overall Severe Morbidity After Chemo-Radiation Therapy and Magnetic Resonance Imaging-Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancer: Results From the EMBRACE-I Study. *Int J Radiat Oncol Biol Phys* 2023; **116:** 807-24.
89. Aghajanzadeh S, Tuomi L, Karlsson T. A 5-year prospective study of health-related quality of life in irradiated head and neck cancer patients: three trends of HRQL over time. *Eur Arch Otorhinolaryngol* 2023; **280:** 2617-22.
90. Barker CL, Routledge JA, Farnell DJ, Swindell R, Davidson SE. The impact of radiotherapy late effects on quality of life in gynaecological cancer patients. *Br J Cancer* 2009; **100:** 1558-65.
91. Corrigan KL, Rooney MK, De B, Ludmir ED, Das P, Smith GL, et al. Patient-Reported Sexual Function in Long-Term Survivors of Anal Cancer Treated With Definitive Intensity Modulated Radiation Therapy and Concurrent Chemotherapy. *Pract Radiat Oncol* 2022; **12:** e397-e405.
92. Nilsson MI, Fugl-Meyer K, von Koch L, Ytterberg C. Experiences of Sexuality Six Years After Stroke: A Qualitative Study. *J Sex Med* 2017; **14:** 797-803.
93. Saghafi E, Andås CA, Bernson J, Kjeller G. Patients' experiences of adverse symptoms, emotions, and coping strategies in connection to treatment of head and neck cancer - an interview study. *BMC Oral Health* 2023; **23:** 641.

94. Barclay R, Tate RB. Response shift recalibration and reprioritization in health-related quality of life was identified prospectively in older men with and without stroke. *J Clin Epidemiol* 2014; **67:** 500-7.

APPENDIX

Paper II: Supplement 1. Questions and response categories for bowel function and anal pain (first endpoint)

Paper II: Supplement 2. Questions and response categories for secondary endpoint

Supplement 1. Questions and response categories for bowel function and anal pain (first endpoint)

Question	Response category
Did you have bowel problems before you got symptoms from the anal cancer?	No, i had no bowel problems before
	Yes, same problems as now
	Yes, but the problems have deteriorated
Did you and your physician talk about bowel side effects before treatment?	No
	Yes
	Do not know/ do not remember
Do you have a stoma today?	No
	Yes
How often have you had to open your bowels, the last month?	0-3/week
	4-6/week
	1-3 times/day
	4-7 times/day
Has it happened that you had to open your bowel again within one hour of last bowel opening, the last month?	No
	Yes, at least 1/week
	Yes, on a single occasion
	Yes, at least 1/month
	Yes, 1-3 times/day
Has it happened that you have had leakage of liquid stool, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
Has it happened that you have had leakage of solid stool, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
Has it happened that you have had leakage of gas, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week

Has it happened that you have had such a strong urge to open your bowels that you have to rush to the toilet, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
For how long have you been abel to stay continent in case of bowel urgency, the last month?	Not applicable, no urgency
	< 1 minute
	1-5 minutes
	5-10 minutes
	10-30 minutes
	> 30 minutes
Have you had anal pain the last month?	No
	Yes, at least 1/week
	Yes, on a single occasion
	Yes, at least 1/month
	Yes, at least 3 times/week
	Yes, at least 1/day
Has it happened that you had a bleeding from your rectum the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
If you had to live with your current bowel problems the rest of your life, do you think a stoma would facilitate your daily life?	No
	Yes
	Do not know

Supplement 2. Questions and response categories for secondary endpoint

Question	Response category
How often have you had to open your bowels, the last month?	0-3/week
	4-6/week
	1-3 times/day
	4-7 times/day
Has it happened that you had to open your bowel again within one hour of last bowel opening, the last month?	No
	Yes, at least 1/week
	Yes, on a single occasion
	Yes, at least 1/month
	Yes, 1-3 times/day
Has it happened that you have had leakage of liquid stool, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
Has it happened that you have had leakage of gas, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week
Has it happened that you have had such strong urge to open your bowels that you had to rush to the toilet, the last month?	No, never
	Yes, but not every week
	Yes, at least 1/week
	Yes, 1-3/week
	Yes, > 3/week