Treatment and outcome of anal cancer in Norway

Anne Gry Bentzen

A dissertation for the degree of Philosophiae Doctor
June 2013
Treatment and outcome of anal cancer in Norway

Anne Gry Bentzen, MD

A dissertation for the degree of Philosophiae Doctor (PhD) at the University of Tromsø

June 13th 2013
CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................ 1

ABBREVIATIONS ............................................................................................................. 3

LIST OF PAPERS ................................................................................................................ 4

1 INTRODUCTION .............................................................................................................. 5

2 BACKGROUND ............................................................................................................... 7
  2.1 Epidemiology ............................................................................................................. 7
  2.2 Anatomy, lymphatic drainage and staging ................................................................. 8
  2.3 Treatment .................................................................................................................. 12
    2.3.1 Surgery .............................................................................................................. 12
    2.3.2 Radiotherapy ...................................................................................................... 12
    2.3.3 Chemoradiotherapy ............................................................................................ 13
    2.3.4 Inguinal lymph node irradiation ......................................................................... 16
    2.3.5 Treatment time .................................................................................................... 17
    2.3.6 Salvage surgery .................................................................................................... 17
  2.4 Prognosis .................................................................................................................... 17
  2.5 Late effects ................................................................................................................. 18
    2.5.1 Reporting of late effects ..................................................................................... 20
  2.6 Health-related quality of life ....................................................................................... 21
    2.6.1 Assessment of HRQOL ...................................................................................... 21
  2.7 Neurotoxicity .............................................................................................................. 23
  2.8 Faecal incontinence .................................................................................................... 23
    2.8.1 Assessment of faecal incontinence ..................................................................... 24

3 AIMS OF THE THESIS .................................................................................................... 25
4 METHODS AND MATERIALS .............................................................. 26

4.1 Patients ...................................................................................... 26

4.2 Treatment principles in Norway 2000-2007 .................................... 27

4.3 Evaluation of treatment and definitions of endpoints ...................... 31

4.4 Survivors .................................................................................. 32

4.5 Volunteers ................................................................................ 34

4.6 Assessment of long-term effects .................................................. 35

   4.6.1 HRQOL and neurotoxicity ....................................................... 35

   4.6.2 Faecal incontinence ................................................................. 36

4.7 Statistics .................................................................................... 37

5 SUMMARY OF THE RESULTS ....................................................... 39

5.1 Paper I ..................................................................................... 39

5.2 Paper II .................................................................................... 43

5.3 Paper III ................................................................................... 45

6 DISCUSSION ................................................................................. 47

6.1 Methodological considerations ................................................... 47

   6.1.1 Paper I ................................................................................ 47

   6.1.2 Papers II and III ................................................................. 48

6.2 Discussions of results ................................................................. 54

   6.2.1 Optimization of chemoradiotherapy regimen ............................ 54

   6.2.2 Targeted therapy ................................................................. 56

   6.2.3 Prognostic and predictive factors .......................................... 56

   6.2.4 Colostomy .......................................................................... 57

   6.2.5 Salvage surgery .................................................................... 58

   6.2.6 Identification, prevention and treatment of late effects ............. 59

   6.2.7 Increased focus on late effects and HRQOL ............................ 60
ACKNOWLEDGEMENTS

The work for this thesis was carried out at the Department of Oncology, University Hospital of North Norway and at the Institute of Clinical Medicine (IKM), University of Tromsø, from 2009-2013. The project was made possible by founding from the Northern Norway Regional Health Authority.

Many people have been important to me during my years as a PhD student. First of all I would like to thank my supervisors. I think you have represented a dream team:

I am greatly indebted to Lise Balteskard, my primary supervisor. You have been my mentor in oncology in the clinic and all the way through this project an excellent supervisor, full of enthusiasm and positive energy. Your constructive guidance, clear-thinking, resoluteness and encouragement have been invaluable, as well as your concern for my well-being. Thank you for always having time to discuss my work although I know you have a tight schedule.

I am also deeply grateful to my co-supervisor, Marianne Grønlie Guren. Your scientific knowledge, your unique ability to convert my vague ideas into more concrete sentences and your constant positive attitude has been crucial.

I would also like to express my gratefulness to my second co-supervisor, Barthold Vonen. Your scientific knowledge has been an important contribution, and your surgical approach has brought some counterweight into the female-oncologist-trio.

Special thanks to my other co-authors Eva Hoff Wanderås, Gunilla Frykholm, Kjell Magne Tveit and Olav Dahl, who have contributed both with data collection and with critically reading and valuable suggestions to improve the manuscripts, and to Tom Wilsgaard for valuable contribution to the statistics.
Special thanks to the participants of this project who generously shared their experience. This project could not be performed without your contribution.

I wish to thank the project staff Ann Nyheim, Ingrid Sandstad, and Kristine Talseth for excellent support with data collection.

Warm thoughts go to all the nice colleagues at the department of oncology in Tromsø. I am grateful to Tone Nordøy, the head of the oncology department, for her support and willingness to facilitate of clinical work with this research project. I also want to thank Hege Sagstuen Haugnes for many constructive discussions and for friendship.

I wish to thank my very good and close friend throughout my life, Elin Foshaug. Your wisdom coupled with your professional acquired psychiatric insights has provided many valuable suggestions and discussions on this project and on life in general.

Warm thanks go to all my family, my parents, brother and sister for all support and care. My sister is deeply thanked for careful and patient proofreading of manuscripts, for fashion guidance and for helping her auntie-kids with homework.

Finally and most of all, I want to thank my husband, Børge, for continuous support, for your love and for always being there for me, and our three children Henning, Iver, and Eline for all happiness and joy.

Tromsø, March 2013

Anne Gry Bentzen
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>APR</td>
<td>Abdominoperineal resection</td>
</tr>
<tr>
<td>CDDP</td>
<td>Cis-diamine-dichloro-platinum - Cisplatin</td>
</tr>
<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>CSS</td>
<td>Cancer-specific survival</td>
</tr>
<tr>
<td>CT</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>EBRT</td>
<td>External beam radiotherapy</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation of Research and Treatment of Cancer</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>LRR</td>
<td>Locoregional recurrence</td>
</tr>
<tr>
<td>MMC</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NACT</td>
<td>Neoadjuvant chemotherapy</td>
</tr>
<tr>
<td>NGICG</td>
<td>Norwegian Gastrointestinal Cancer Group</td>
</tr>
<tr>
<td>NOAC</td>
<td>Nordic Anal Cancer Group</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient reported outcome</td>
</tr>
<tr>
<td>RFS</td>
<td>Recurrence-free survival</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SCIN</td>
<td>Scale of Chemotherapy-Induced long-term Neurotoxicity</td>
</tr>
<tr>
<td>QLQ</td>
<td>Quality of life questionnaires</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>QUANTEC</td>
<td>Quantitative Analysis of Normal Tissue Effects in the Clinic</td>
</tr>
</tbody>
</table>
LIST OF PAPERS

This thesis is based on the following papers:

**Paper I**


**Paper II**


**Paper III**

1 INTRODUCTION

Squamous cell carcinoma of the anal region is a rare malignancy. In Norway, 50-60 patients are diagnosed per year [1]. Diagnosis, treatment, and follow-up are based on multidisciplinary collaboration between the oncologist, the surgeon and the radiologist. The treatment is centralized to five university hospitals. Anal cancer is mainly a locoregional disease and distant metastasis generally occurs late. Locoregional failure is a feared condition which could be difficult to treat, and may lead to pain, odour, infection, and impaired function if not successfully treated.

The treatment is advised by national guidelines and consists mainly of radiotherapy (RT), combined with chemotherapy (CT), and occasionally surgery depending on tumour stage. In 2008, a large randomised study was published that supported the treatment given for localized anal cancer, but questioned the role of cisplatin that had been recommended in Norway since 2000 for more locoregional advanced cancer [2]. The results from this study initiated the need for analyzing the treatment results obtained with the national guidelines in Norway from 2000. In this rare malignancy, the ability to review complete national results over several years was crucial.

Chemoradiotherapy (CRT) is an effective treatment of anal cancer, leaving many long-term survivors. From clinical practice with this patient group, we had the impression that many survivors seem to suffer from long-term sequelae of the disease and treatment toxicity. Data on long-term health-related quality of life in anal cancer survivors are limited. A growing interest in cancer survivorship warranted a follow-up study of the current national cohort. Through patient reported outcomes (PROs), a quantitative measure could be obtained and provide a more detailed description of impairments of function and symptoms.
Faecal incontinence is a known late effect after pelvic radiotherapy. Knowledge of prevalence and severity of faecal incontinence after CRT for anal cancer is sparse. Assessing the extent of this problem could provide important supplementary information about anal cancer survivorship.

As pelvic dysfunction and pelvic symptoms can be present in the general population to some extent, a comparison with a reference group from the general population would enable a better interpretation of the survivors’ responses.

Our main purpose was to evaluate the treatment results from patients with anal cancer treated according to the national guidelines from 2000 to 2007 and to survey their self-reported late effects of the given treatment.
2 BACKGROUND

2.1 Epidemiology

Squamous cell carcinoma of the anal region is a rare malignancy with an incidence of approximately 1-1.5 in 100,000 persons per year [1, 3].

![Graph showing incidence of anal cancer in residential areas, RHA regional health areas, in Norway 1991-2010. Data from the Cancer Registry of Norway.](image)

**Figure 1:** Incidence of anal cancer in residential areas, RHA regional health areas, in Norway 1991-2010. Data from the Cancer Registry of Norway.

The median age at diagnosis is between 60-70 years and a higher incidence has been associated with female gender [4-10].
Infection with human papilloma virus (HPV) [11, 12], human immunodeficiency virus (HIV) [13, 14] and other chronic disorders associated with immunosuppression [15], and cigarette smoking [11, 16] are important risk factors. Sexual practice with high lifetime number of sexual partners and receptive anal intercourse seems to increase the risk [11, 12].

2.2 Anatomy, lymphatic drainage and staging

The anal canal is the terminal part of the gastrointestinal tract. The length of the anal canal is 3-4 cm. The cranial border is anatomically at the palpable junction of the puborectalis muscle and the external sphincter. This is approximately 1 to 2 cm above the dentate line, which is a transformation zone where squamous epithelium is replaced by transitional epithelium before entering the rectal mucosa. The caudal border is at the anal verge where the squamous cells histologically blend with the hair-bearing perianal skin. The anal margin is usually defined as a 5-cm radius perianal from the anal verge [17].
Figure 3: The normal anal canal (above) and the anal canal with a tumour (below).
Lymphatic drainage depends on the anatomic site of the primary tumour [18]. Tumours originating above the dentate line drain primarily to perirectal and paravertebral lymph nodes. More caudal tumours originating in the level of the dentate line drain to nodes in adherence to the internal pudendal artery, the internal iliac artery and the obturator artery. The most caudal tumours originating below the dentate line drain primarily through a subcutaneous pathway to the superficial inguinal nodes in the groins.

Squamous cell carcinoma of the anal region is mainly a locoregional disease. Early onset of lymphatic spread may occur, but distant metastases most often occur late in the course. About one quarter to one third has regional lymph node metastasis at the initial diagnosis. Distant metastases are infrequent and are found in less than 10% at the time of diagnosis [5, 7, 10, 19].

Clinical staging utilizes information from physical examination and imaging (magnetic resonance imaging (MRI), anorectal ultrasound and computed tomography). The Tumour Node Metastasis (TNM) [20] classification of malignant tumours is commonly used. It is based on tumour size, invasion of adjacent structures, status of regional lymph nodes, and status of distant metastases.
**TNM clinical classification**

**T - Primary tumour**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>The primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but not more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour of any size invades adjacent organ(s), e.g. vagina, urethra, bladder¹</td>
</tr>
</tbody>
</table>

¹ Direct invasion of the rectal wall, perianal skin, subcutaneous tissue, or the sphincter muscle(s) *alone* is not classified as T4.

**N - Regional lymph nodes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in perirectal lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in unilateral internal iliac and/or unilateral inguinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or bilateral inguinal lymph nodes</td>
</tr>
</tbody>
</table>

**M - Distant metastasis**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**Stage grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N2, N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
2.3 Treatment

2.3.1 Surgery

Historically, anal carcinoma was treated with surgery, which implied abdominoperineal resection (APR) with a permanent stoma. However, as lymphatic spread occurs early to areas difficult to excise surgically, resection was considered an inadequate treatment for many patients. A further approach with curative RT or multimodal therapy including CRT and surgery emerged as a possible way of improving outcome. Even though there are no randomised studies comparing surgery and (chemo-) radiotherapy in anal cancer, several retrospective studies have reported improved survival after (chemo-) radiotherapy [9, 21].

2.3.2 Radiotherapy

In the past, RT was used infrequently due to fear of toxicity and because of concern that the radiation beams could not cure deeply penetrating tumours. However, along with modernised radiation techniques and equipment, promising data of curative sphincter-conserving RT were published [22, 23]. RT gradually replaced surgery during the eighties as the primary treatment of anal cancer, based on a growing recognition of the radiosensitivity of squamous cell carcinoma and the limitations of surgery in this area. Previously, the field borders were defined by skeletal structures to include the primary anal tumour and pathological regional lymph nodes as well as prophylactic irradiation to regional lymph nodes in the pelvis. The superior border was usually at the promontorium, the caudal border at the perineum, and the lateral border 1-1.5 cm outside of the pelvic brim. Anterior/posterior- or three-/four fields technique have been used until recently, but now intensity-modulated radiotherapy (IMRT) has gradually emerged as a further optimization. Currently computed tomography-based three-dimensional treatment planning is more common with delineation of target
volumes. An initial course of approximately 45 Gy delivered by external beam radiotherapy (EBRT) have commonly been used, often supplemented by a boost to the tumour either by EBRT or and brachytherapy.

2.3.3 Chemoradiotherapy

In 1974 Nigro et al. published a notable preliminary report on the effects of CRT that would prove to be highly influential [24]. The preliminary report describes three patients with squamous cell carcinoma of the anal canal treated with preoperative CRT. EBRT to a total dose of 30 Gy was combined with one concomitant course of 5-Fluorouracil (5-FU) day 1-4 in combination with Mitomycin C (MMC) day 1. APR was performed about 6 weeks after completion of CRT in two of the three patients, and no tumour was found in the operative specimens. The third patient refused surgery and one year later had no evidence of tumour. This successful experience led to further investigation both by the group of Nigro [25] and others [23, 26]. The CT regimen is still used, but a second course of CT has become customary.

2.3.3.1 The role of chemotherapy

The role of chemotherapy was unsettled until the two randomised trials in the mid-nineties stated that concurrent CRT was superior to RT alone [27, 28]. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) [27] conducted a trial, ACT I, where 585 patients with anal carcinoma were randomised between RT alone and CRT. The RT consisted of a primary course of 45 Gy. After a six weeks break, further treatment depended on tumour response. If there was ≥ 50 % tumour response, a boost of 15-25 Gy was given, otherwise the patient underwent salvage surgery. The CRT consisted of the same RT regimen concurrent with one course of 5-FU day 1-4 and MMC day 1 (MMC/5-FU) and a second course of 5-FU during the last week of RT. Patients in ACT I treated with CRT had significantly lower rate of local failure (36 % vs. 59 %) and
better 3-year cancer-specific survival (CSS) (72 % vs. 61 %), but no significant difference in 3-year overall survival (OS) (65 % vs. 58 %). Early morbidity was significantly more common in the CRT group.

The European Organisation of Research and Treatment of Cancer (EORTC) published results from a similar study one year later (EORTC 22861) of 110 anal cancer patients, with locally advanced tumours (T3-4N0-3 or T1-2N1-3) [28]. All patients had an initial course of 45 Gy. A boost of 15 or 20 Gy was given in cases of partial or complete response after a six weeks break, or salvage surgery in cases with poor response. The CT regimen was approximately similar to the ACT I trial. Patients treated with CRT had significantly lower local failure rate and higher colostomy-free survival after five years, but there was no significant difference in 5-year OS (56 %). Regarding severe toxicity in skin or diarrhoea, there was no significant difference between the groups.

2.3.3.2 5-Fluoruracil

5-FU belongs to the antimetabolite group of chemotherapy that interferes with the DNA/RNA synthesis by interacting with enzymes responsible for nucleotide synthesis. Bone marrow toxicity and symptoms from the gastrointestinal tract as nausea, vomiting, diarrhoea and mucositis are the most common adverse effects [29]. It has been used in cancer treatment for more than 40 years and is commonly used in combination with radiotherapy to enhance cytotoxic effect by synergism.

2.3.3.3 Mitomycin

MMC is an antibiotic with cytotoxic effect. It is activated by bioreduction and acts like an alkylating agent producing DNA cross-linking [30]. Bone marrow toxicity is common and haemolytic uremic anaemia, interstitial pneumonitis and heart failure are potentially serious side effects [29].
To determine the role of MMC in the treatment, the Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) conducted a trial where 310 patients with anal cancer were randomised to either RT in combination with 5-FU or RT in combination with MMC/5-FU [31]. The RT consisted of a primary course of 45 Gy. The superior border was lowered at 30.6 Gy and further reduction at 36 Gy to include only the macroscopic tumour. If there was a palpable residual tumour at 45 Gy, an additional 5.4 Gy was delivered. In case of histologically confirmed residual disease four to six weeks after completion of CRT, additional 9 Gy were given and salvage surgery was performed if a biopsy was still positive six weeks after the boost. One group received two cycles of MMC/5-FU while the other group received two cycles of 5-FU, both during the first and fifth week of RT. Patients in the MMC/5-FU group had significantly higher colostomy-free survival (71 % vs. 59 %) and disease-free survival (73 % vs. 51 %) after four years, but there was no significant difference in OS. Severe toxicity was more common among patients in the MMC/5-FU group.

### 2.3.3.4 Cisplatin

As MMC was associated with severe acute toxicity, other chemotherapy combinations were considered. Cisplatin (CDDP) as a radiation sensitizer had proved to be an essential component of combined modality treatment of cancer in oesophagus [32] and cervix [33]. The mechanism of action is through inhibition of DNA synthesis by the formation of DNA cross-links. Nausea is common and requires antiemetic medication. Nephro- and neurotoxicity are dose limiting side effects [29].

Replacement of MMC with CDDP in curative CRT was encouraged by promising results in several small (retrospective and phase II) studies [34-38]. As locally advanced tumours had adverse outcome, neoadjuvant chemotherapy (NACT) to downstage tumour before radical CRT was tested as a possible optimization [39]. With the purpose of
determining whether MMC or CDDP in combination with 5-FU was the best regimen of CRT and to investigate the effect of NACT in anal cancer treatment, the Radiation Therapy Oncology group (RTOG) conducted a large randomised study in 1998 (RTOG 98-11). Two courses of NACT and further two courses concurrent CT using CDDP in combination with 5-FU (CDDP/5-FU) were compared to RT with two courses of concurrent MMC/5-FU the first and fifth week. All patients received a minimum dose of 45 Gy. After 30.6 Gy, the superior border was placed at the bottom of the sacroiliac joints with an additional field reduction of node-negative inguinal nodes after 36 Gy. Total RT dose was dependent on tumour stage: 45 Gy to T2 tumours while patients with T3, T4, N+ or T2 residual disease after 45 Gy received a boost up to 55-59 Gy. The results, published in 2008, concluded that CDDP-based therapy failed to improve DFS compared to MMC-based therapy, but CDDP-based therapy resulted in a significantly worse colostomy rate (19 % vs. 10 %). Severe haematological toxicity was worse in the MMC group [2].

2.3.4 Inguinal lymph node irradiation

The role of prophylactic inguinal lymph node irradiation is controversial. RTOG published a contouring atlas in 2009 recommending routinely the inclusion of the inguinal regions in the treatment fields for patients with anal cancer [40]. Two years later, the Australian Gastrointestinal Trial group published guidelines and atlas for IMRT supporting inclusion of inguinal regions in the elective nodal volumes [41]. There has been reports of inguinal recurrences when excluding elective inguinal irradiation [42, 43], while others have suggested reducing the fields for selected cases [44, 45]. Retrospective studies of patients without inguinal metastases treated without elective inguinal irradiation have shown groin recurrences in less than 10 % of the patients [46, 47]. A reduced radiation dose of 36 Gy was routinely given in the large randomised RTOG-98-11 trial [2].
2.3.5 Treatment time

Previously, a planned treatment interruption of 4-6 weeks was common due to severe acute toxicity during CRT [27, 28, 31]. Gradually, data emerged reporting tolerability of shortened radiation regimen [48] and inferior results of split-course regimens [49]. It is now recommended to avoid split course regimens [50, 51].

2.3.6 Salvage surgery

Surgery has since the emergence of CRT been reserved for persistent residual tumours or locoregional recurrences. Long-term survival is obtained in a substantial part of patients [52-56]. A Swedish study from 2002 of 35 patients reported a five-year survival rate of 52 % after salvage APR. There were no postoperative deaths, but considerable morbidity related to the perineal wound [52]. A more recent Danish study of 49 patients who underwent anal cancer salvage surgery reported a five-year survival of 61 % and a low rate of perineal complications. Involved margins were associated with adverse outcome [53]. A lower five-year OS of 29 % was reported in a Canadian study of 51 patients with local failure treated with salvage surgery [54].

2.4 Prognosis

The prognosis of anal cancer is generally quite good. As distant metastases seldom are present at initial presentation, the majority of the patients are considered for curative treatment. However, among these there are elderly patients with major comorbidities that are not candidates for intensive curative treatment. Five-year OS rates in the range of 58-78 % are reported [5-7, 10, 19, 57, 58]. Unselected cohorts tend to have lower rates compared to randomised trials where patients with severe comorbidity or high age often are excluded. CSS gives additional information of the prognosis as many elderly patients die from other causes during the five-year follow-up.
2.5 Late effects

Injury to DNA is the primary mechanism by which ionizing radiation kills cells. In most cells, the cell death after radiation occurs when the cell goes to mitosis, and not from the initial response to damage. The radiation exposure to normal tissue is unavoidable despite optimized radiation techniques. Malignant tumours may infiltrate microscopically into normal structures. Normal tissue within the tumour or in proximity to the tumour is exposed to the full tumour dose. As the name external beam indicates, the beams are delivered from outside the body to reach the target volume. Normal structures near the target volume may be exposed to clinically relevant doses in the entrance and exit of the beams.

Early side effects occur during or shortly after radiotherapy. Late effects become clinically manifest after latent times of months to years. The pathophysiological processes are complex involving changes in organ-specific parenchymal cells, fibroblasts and vascular endothelial cells. The incidence and severity of late effects is influenced by multiple factors among them dose per fraction, total dose, volume, tissue tolerance and patient-related factors as comorbidity [17, 30].

The small bowel, rectum, bladder, internal genital organs, and the pelvic skeleton including the hips are exposed to irradiation in varying degree in pelvic radiotherapy. The intestines are radiosensitive and susceptible for late toxicity such as diarrhoea, obstruction, ulceration, fistulae, perforation, and bleeding [59, 60]. Late effects in the rectum may include stricture, ulceration, fistulae, diminished rectal compliance, and decreased storage capacity [60-62]. Late effects from the bladder include dysuria, increased urinary frequency, urgency, contracture, spasm, reduced flow, and incontinence as a result of global bladder injury, and haematuria, fistulae, obstruction, ulceration, and necrosis as a result of focal injury [63]. In an effort to
provide guidance, the group of Quantitative Analysis of Normal Tissue Effects in the Clinic (Quantec) has published several organ specific papers with recommendations of dose-volume constraints [64-66].

Fine, hair-line cracks known as pelvic insufficiency fractures may occur in the pelvic skeleton, and also occasionally acetabular protrusion and avascular necrosis of the femoral head after radiotherapy. Dose constraints are not well established, but a tolerance dose of 52 Gy is proposed [67]. An increased risk of pelvic fractures after pelvic irradiation was found in a large population-based study of older women with pelvic malignancies [68].

Increased serum levels of gonadotropins and reduced serum testosterone are reported after pelvic radiotherapy in male rectal cancer patients [69]. A mean dose to the penile bulb below 50 Gy is recommended in Quantec`s organ specific paper for radiation-induced erectile dysfunction [70]. In females, the risk of ovarian failure after radiotherapy increases with aging, and a dose of 14.3 Gy has been claimed to result in infertility for women at the age of 30 years [71].

There is limited knowledge about late effects after radiotherapy for anal cancer and the results vary. Two previous studies reported moderate to severe late effects in 15-16 % [72, 73]. Minor late toxicity was found in a German retrospective analysis published in 2008 [74]. The large American study of thirty years experience reported significant late complication in approximately 25 % of the patients [75]. A recent Australian retrospective review of twenty-five-years experience with radical CRT for anal cancer reported 8 % severe late toxicity [45].
2.5.1 Reporting of late effects

There is no gold standard for documentation and assessment of late effects. Which tool is best suited to evaluate late effects depends on what one wants to measure. In some contexts, it is interesting to measure objectively the damage of the disease and treatment. In other contexts, it is more relevant to evaluate subjective patient information of symptoms and impairment of function. Several scoring systems exist, among them The US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [76], Late Effects in Normal Tissue (LENT) [77]/ Subjective, Objective, Management and Analytic (SOMA) classification [78] and Toxicity Criteria of the RTOG/EORTC [79].

A distinction has been advocated between mechanistic and biology centred research which is often doctor-reported and based on objective findings, unlike the pragmatic and patient-centred studies where the patient’s experience is the primary source of information [80]. An objective sign will not necessarily result in a symptom, and the threshold for morbidity may differ among patients according to several factors among them comorbidity and lifestyle.

Figure 4: Various dimensions of normal tissue effects (S. Bentzen, Semin Rad Onc 2003 with permission)
In recent years, there has been more focus on patient involvement. Patient-reported outcomes (PROs) are often questionnaires based on subjective information collected directly from the patient. There is an increased emphasis on patient’s perception to capture the most relevant features for the patient. Along with this, there is a growing awareness that there is a risk of toxicity underestimation by physicians [81]. As a consequence, this has led to a greater use of PRO. A development of a Patient-Reported Outcomes version of CTCAE (PRO-CTCAE) has been initiated by the NCI.

2.6 Health-related quality of life

Quality of life (QOL) is a poorly defined term which means different things to different people [82]. It is a subjective construct which is challenging to measure using quantitative methods. To distinguish between QOL in its more general sense and for matters related to health care, the term “health-related quality of life” (HRQOL) was introduced. HRQOL measures are made up of scales that assess symptoms and activity limitations. The concept incorporates multidimensionality and subjectivity [83]. At least four domains are included in the concept: physical-, disease-related or treatment-related symptoms, psychological- and social functioning. The patient, as the primary source of information, ensures the subjectivity, and enables the clinicians to gain insight into the patients’ perspectives of their condition and treatment [84].

There are limited data of long-term HRQOL in anal cancer survivors. So far, most available data come from small patient samples. Diarrhoea, faecal incontinence, and sexual dysfunction are commonly reported [85-89].

2.6.1 Assessment of HRQOL

A great number of questionnaires have been developed to measure HRQOL. The choice of questionnaire depends on who will be investigated and for what purpose. The
questionnaires can be classified based on intention for utilization.

Generic instruments are intended for general use, regardless of condition. An advantage with these instruments is that they allow comparison across different groups of patients independent of disease. On the contrary, there is a risk that the questions are not fully relevant to all participants in the group. The Medical Outcome Study 36-Item Short Form (SF-36) [90] and EuroQol (EQ-5D) [91] are commonly used generic questionnaires.

Disease-specific instruments are intended to assess HRQOL in a group of patients with a specific disease. An advantage is that the questions are tailored to the particular disease group. On the other hand, comparisons across different groups are more difficult. Among others EORTC has developed multiple questionnaires to assess HRQOL in cancer patients, which are in widespread use. There exists a core questionnaire, QLQ-C30 [92] and different disease-specific modules that are supplementary. Another example of a disease-specific instrument to be used in evaluating HRQOL in cancer patients is The Functional Assessment of Cancer Therapy – General (FACT-G) [93].

Condition-specific instruments are designed to address one specific aspect of HRQOL. If it is beneficial to explore an aspect in depth, a condition-specific questionnaire could be useful. However, as these are intended for general use, the questions may become less relevant for use with cancer patients. Commonly used condition-specific questionnaires are Hospital Anxiety and Depression Scale (HADS) [94], Multidimensional Fatigue Inventory (MFI) [95] and McGill Pain Questionnaire (MPQ) [96].

In a health economic perspective, the assessment will include other factors. A combination of life length and QOL will often be emphasized. A quality adjusted life
year (QALY) is one such health economic term. As a basis for the concept, it is assumed that a life year with symptoms, illness or disability in varying degree has reduced QOL compared to a life year without similar problems. For the time being, this is not a concept used in the daily clinical practice. However, the daily clinical practice depends on funding from the politicians and bureaucrats who often consider the health benefits in such terms.

2.7 Neurotoxicity

Neurotoxicity is a well known dose-limiting side effect of Cisplatin. Several studies have described long-term chemotherapy-induced neurotoxicity after Cisplatin-based treatment for testicular cancer [97, 98]. There are several instruments available. Some of them use common toxicity criteria scales while others use functional assessment or QOL assessment. So far, there exists no gold standard for assessing chemotherapy-induced neurotoxicity [99]. Of the functional assessment instruments, Scale for Chemotherapy-Induced Long Term Neurotoxicity (SCIN) is a brief self-reported scale and suitable for screening. It is proposed to reflect an overall neurotoxicity based on three subscales: neuropathy, Raynaud’s phenomenon and ototoxicity [100].

2.8 Faecal incontinence

Faecal incontinence is the involuntary passage of faecal content. The definitions of the condition vary. Some include both unintended leakage of gas and stool in the definition while others distinguish between faecal- and anal incontinence of which only the latter includes both the unintended leakage of gas and faeces. Prevalence rates differ, probably due to different definitions, but also because faecal incontinence is a tabooed issue which is often under-reported. In population-based surveys, prevalence of unintended leakage of stool from 1 % to 6 % has been reported [101-103]. The prevalence rises with increasing age [101, 102] while female gender as a risk factor is
Faecal incontinence may occur after pelvic radiotherapy [61]. The rates vary widely, ranging from 3 to 55% [105]. In anal cancer survivors, the estimates of faecal incontinence are limited, and the faecal incontinence rates differ [38, 74, 87, 89, 106]. Various types of instruments for measurement are used. Some studies report only serious degrees of faecal incontinence while others emphasize all degrees as significant. In most studies, faecal incontinence has not been evaluated as a primary endpoint.

2.8.1 Assessment of faecal incontinence

The method used for assessment of faecal incontinence will affect the prevalence measured. Anorectal manometry and ultrasound could be useful in a context evaluating the sphincter function emphasizing physical measurements like pressure and rectal compliance. However, considering faecal incontinence as a symptom, a subjective assessment is required [107]. There exist several self-reported scales, among them different scoring systems. However, none of these is disease-specific for anal cancer patients. The St. Mark`s score for faecal incontinence [108] has been found to reflect patients` perceptions quite well and is considered reliable regardless of the type of incontinence, age and sex, and it provides an assessment of the degree of the incontinence [109, 110]. Unlike other established scales such as Pescatori [111] and Wexner [112], the St. Mark`s score includes information about faecal urgency and the use of constipating drugs.
3 AIMS OF THE THESIS

The aims of this thesis were to investigate the outcome of anal cancer patients treated with curatively intended chemoradiotherapy in Norway. By studying a complete, unselected national cohort, we aimed at analyzing the treatment results in terms of local control, recurrence, and survival. Furthermore, we aimed at assessing whether the national guidelines for treatment were followed and to identify areas that need improvement. Additional aims were to evaluate the patient-reported outcomes in the follow-up, with special focus on health-related quality of life, symptom burden and function of pelvic organs. Since faecal incontinence was assumed to be one of the most stressful disabilities, the aim was to evaluate the prevalence and severity of this in anal cancer survivors.

Specifically, the aims were:

- To analyze the treatment results on local control, recurrence and survival obtained with the national treatment guidelines, and to identify areas that need improvement.

- To evaluate the health-related quality of life in the long-term follow-up of anal cancer survivors after treatment with curative CRT compared to results obtained from a reference group from the normal population.

- To evaluate the prevalence and severity of faecal incontinence in the long-term follow-up of anal cancer survivors previously treated with curative CRT compared to results obtained from a reference group from the normal population.
4 METHODS AND MATERIALS

This study consisted of three parts. Patients in the first part formed the basis for the later surveys of survivors.

4.1 Patients

The patient cohort included all patients treated with curative intended RT or CRT for non-metastatic, squamous cell carcinoma of the anal region in Norway during a seven-year period between July 2000 and June 2007. As part of a Nordic collaboration, the five university hospitals registered patient-, tumour-, and treatment characteristics (Appendix 1). Treatment results were recorded during the follow-up and were subsequently collected in a national database. Patients with distant metastasis and patients treated with palliative intention were excluded. If surgery was the only treatment, the patient was excluded from the analysis. Inclusion of patients in paper I is shown in figure 5.
4.2 Treatment principles in Norway 2000-2007

Based on the promising results which at the time existed on CDDP [34, 36-38] and NACT [39] as part of multimodal treatment of anal cancer, the Norwegian Gastrointestinal Cancer Group (NGICG) recommended the following national guidelines for curative intended treatment from 2000 and throughout the study period:

- Patients with well or moderately differentiated T1N0 tumours < 1 cm without muscular invasion were treated with surgery with local excision.
Patients with more advanced T1N0- or T2N0 tumours were recommended EBRT 54.0 Gy to tumour and one course of MMC/5-FU concomitantly at the start of RT.

Patients with locally advanced T3-4N0 or T1-4N+ tumours, were recommended a more intensified treatment with two courses of NACT with CDDP/5-FU and a third course concomitant at the start of RT, 58.0-60.0 Gy to tumour and pathological lymph nodes.

Figure 6: Recommended treatment guidelines of NGICG in Norway 2000-2007.

Chemotherapy regimens:

- 5-FU: 5-Fluorouracil 1000 mg/m²/24h
- MMC: Mitomycin C 10 mg/m²
- CDDP: Cisplatin 60-100 mg/m²
Radiotherapy planning and treatment technique:

Previously, the field borders were set from bony landmarks in the pelvis. Computed tomography-based 3D treatment technique was gradually introduced in Norway during the first years of the study period and delineation of target volumes became the standard. RT was mostly delivered with a two- to four-field technique and 6- to 18 MV photon beams.

Elective treatment volumes:

Lateral border of radiation fields:
- At 1.5 cm lateral to the pelvic brim if the primary tumour did not extend below the internal sphincter (pelvic lymph nodes included).
- At 2.5 cm lateral to the pelvic brim if the primary tumour extended below the internal sphincter (pelvic and medial part of the superficial inguinal lymph nodes included).

Superior border of radiation fields:
- At the sacral promontory if the primary tumour extended into the rectal mucosa.
- At the lower border of the sacroiliac joint if the primary tumour did not extend into the rectal mucosa.

Inferior border of radiation fields:
- 2 cm below the primary tumour or 1 cm below the perineum.
Figure 7: Radiotherapy treatment plan of a female cancer patient with a locally advanced T3 tumour with regional lymphatic metastasis to perirectal lymph node. The tumour extended from the anal verge to just above the dentate line. Frontal, lateral and axial view of radiation fields. Blue line: Clinical target volume (CTV). Pink line: Inguinal clinical target volume. Orange line: Planning treatment (PTV). Yellow lines: Radiations fields. Colour wash: 95 % and 90 % of the prescribed dose in red and blue shades.

4.3 Evaluation of treatment and definitions of endpoints

Evaluation of treatment results was based on clinical and radiological evaluation of treatment response after 4-6 weeks and finally after 3 months. Patients with persisting residual tumour were considered for salvage surgery. Primary treatment control was defined as no residual tumour after CRT supplemented with salvage surgery when necessary. Disease-free patients entered a follow-up program with visits every 3 months the first 2 years, then every 6 months up to 5 years, thereafter annually. Recurrence was defined as the first event of any tumour relapse. Locoregional recurrence was defined as any tumour recurrence in the pelvic or inguinal regions, with or without the presence of distant metastasis. Distant failure was defined as any
distant metastasis outside the pelvic or inguinal regions, independent of locoregional status. Survival analyses of recurrence-free survival (RFS), OS, and CSS were calculated after three and five years of follow-up. Paper I is based on the results of evaluation of these endpoints.

4.4 Survivors

All recurrence-free survivors from the national cohort of anal cancer were invited by mail to participate in a cross-sectional study to evaluate HRQOL and faecal incontinence. At the time of analysis of treatment results for paper I, 111 patients had died. Further four patients had died by the start of the follow-up study of long-term late effects. Based on an assessment by the physician who knew the survivor from the follow-up, five survivors were considered to be unable to participate due to dementia and severe psychiatric disease. The invited survivors had a minimum follow-up of two years after diagnosis and were without comorbidity incompatible with participation.

The eligible survivors were invited to the follow-up study for evaluating late effects. The invitation was sent by mail and the survivors could choose whether they wanted to participate in both the questionnaires and the telephone interview or just one or the other. Most of the participants accepted to take part in the whole study. Survivors with a stoma were excluded from the analysis regarding faecal incontinence (paper III). Details about the inclusion of survivors are shown in figure 8. Survivors who signed informed consent received questionnaires to assess HRQOL and went through a telephone interview for an evaluation of the prevalence and severity of faecal incontinence.
328 patients treated with curatively intended (chemo) radiotherapy

115 dead

69 dead due to anal cancer
46 dead to other causes

213 anal cancer survivors

2 survivors with current anal cancer

4 survivors under investigation for recurrence

207 survivors without any sign of anal cancer

8 survivors not offered participation

3 dementia

4 severe psychiatric/ physical diseases

1 language incompatibility

199 survivors offered participation

51 non-responders

12 negative response paper II

136 signed informed consent

8 did not return the questionnaires

128 anal cancer survivors participated in the study evaluating HRQOL

17 negative response paper III

131 signed informed consent

24 excluded due to stoma

107 anal cancer survivors participated in the study evaluating faecal incontinence

Figure 8: Inclusions of survivors in paper II and paper III.
4.5 Volunteers

The symptoms and dysfunction we expected to find among survivors exist to some extent in the general population. Since we did not have normative data for faecal incontinence or the colorectal module, we established an age- and sex-matched reference group from the general population. This enabled better interpretation of the survivors’ responses. Participants to this reference group were randomly drawn from the National Population Register and invited to participate by mail. History of cancer in the pelvis or abdomen excluded participation. Details about inclusion of volunteers are shown in figure 9.

Figure 9: Inclusion volunteers paper II and paper III.
4.6 Assessment of long-term effects

4.6.1 HRQOL and neurotoxicity

HRQOL was evaluated with the EORTC core questionnaire (QLQ-C30) [92]. This validated cancer-specific 30-item questionnaire contains five functional scales assessing physical, role, emotional, cognitive, and social function, three symptom scales assessing fatigue, nausea and vomiting, and pain, six single items assessing symptoms commonly reported by cancer patients, and a global health-status during the last week. The questionnaire is available in a Norwegian version (Appendix 2). As far as we know, there exists no disease-specific questionnaire to assess HRQOL in anal cancer patients. The EORTC module for colorectal cancer CR29 (QLQ-CR29) was used as it contains questions that were considered relevant for this patient group [113]. This 29-item questionnaire incorporates four scales assessing urinary frequency, faecal seepage, stool consistency, and body image, and single items including urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, anxiety, flatulence, faecal incontinence, sexual interest, impotence, and dyspareunia. This questionnaire is also available in a Norwegian version (Appendix 3).

All items had response categories with four levels, from “not at all” to “very much”, except the two items for global quality of life (QOL), which used seven-point items ranging from “very poor” to “excellent”. A raw score was estimated by the average of the items that contributed to a scale. The score was standardised by linear transformation into a score ranging from 0-100 according to the EORTC scoring manual [114]. A high score on the global QOL/functional scales represents a high QOL or a high/healthy level of functioning, and a high score for the symptom scale/items represents a high level of symptoms. The results from the anal cancer survivors and the age-and sex-matched volunteers were compared to evaluate the impact of anal
cancer on HRQOL. The interpretation of HRQOL scores was done according to Osoba where a 10 points difference in a 0-100 point score was interpreted as a moderate clinical difference and a 20 point difference as a large clinical difference [115].

Normative data of QLQ-C30 from the general population are available in different countries [116-119], but as far as we know there are currently no reference data of QLQ-CR29. The Norwegian normative data of QLQ-C30, published in 1998, were obtained from a randomly selected sample of 3000 persons from the National Registry aged 18 to 93 years [116]. More recent normative data are available from the Dutch population published in 2011 [117]. To evaluate whether the group of volunteers was a representative sample of the normal population, a comparison between the QLQ-C30 scores of the volunteers and the Norwegian and Dutch normative data was performed.

Chemotherapy-induced neurotoxicity was assessed by the Norwegian version of Scale of Chemotherapy-Induced long-term Neurotoxicity (SCIN), which is a brief self-reported scale recommended as a screening instrument. It consists of six questions covering peripheral sensory neuropathy, Raynaud’s phenomenon, and ototoxicity [100]. All questions had four categories similar to those in the EORTC QOQ above (Appendix 4).

Paper II is based on the results of evaluation of long-term HRQOL obtained from these questionnaires.

4.6.2 Faecal incontinence

To evaluate the occurrence and degree of faecal incontinence, the participants were questioned by a structured telephone interview, performed by trained health personnel. (Appendix 5). The interview included the St. Mark’s score of faecal
incontinence, which is a validated instrument to score the frequency and degree of faecal incontinence during the last four weeks [108]. It consists of seven questions exploring the frequency of involuntary leakage of gas, liquid stool, solid stool and alteration in lifestyle; need to wear a pad or plug; use of constipating drugs; and the ability to defer defecation for 15 minutes as an indication of urge. The three items of type and frequency of incontinence and the item of alteration of lifestyle are scored on a 4-point scale: never = 0, rarely (1 episode) = 1, sometimes (>1 episode) = 2, weekly (≥1 episodes a week) = 3, and daily = 4. The two items regarding use of pad/plug or constipating drugs are binary: no = 0 and yes = 2. The last item regarding urgency is binary: no = 0 and yes = 4. The incontinence score ranges from 0 (completely continent) to 24 (completely incontinent).

Paper III is based on the results of evaluation of long-term faecal incontinence obtained from this score.

4.7 Statistics

In the analyses of treatment results in paper I, OS, CSS and RFS were estimated by Kaplan-Meier methods. Cox proportional hazards regression analysis was performed to identify significant prognostic variables of CSS and RFS. Age and all univariable significant variables were entered into the multivariable models. The proportional hazard assumption was verified by inspection of log minus log survival curves. A two-sided p-value < 0.05 was considered as statistically significant.

Differences between responders and non-responders in assessment of HRQOL and faecal incontinence in paper II and III were analysed using Chi-square tests for categorical variables and Student t-tests for continuous variables.
Analyses of the HRQOL scores including handling of missing values were performed according to the EORTC scoring manual [114]. Mean scores of HRQOL were compared between survivors and volunteers. The HRQOL symptoms considered relevant in the pre-specified hypothesis were dichotomised as “not at all/a little” (no/mild) vs. “quite a bit/very much” (moderate/severe) in analyses of frequency of symptoms. Conditional logistic regression was used to compare survivors vs. volunteers with regard to mean score of HRQOL and the percentage distribution of dichotomized symptoms due to the use of age- and sex-matched volunteers. Chi-square tests were used in comparisons of subgroups of survivors in analyses of neurotoxicity.

In analyses of St. Mark’s faecal incontinence score, conditional logistic regression was used to compare scores and symptoms between survivors and volunteers. Subgroup analyses of St. Marks score among the survivors were performed by the Mann Whitney U test. The faecal incontinent factors were dichotomised as never/rarely/sometimes vs. weekly/daily, or never vs. rarely/sometimes/weekly/daily based on what we considered being clinically relevant. Dichotomised faecal incontinence factors were used as dependent variables in logistic regression models to assess the associations with sex, age and tumour stage in subgroups of survivors. Both crude and multivariable models (with all three independent variables included) were assessed.
5 SUMMARY OF THE RESULTS

5.1 Paper I

Chemoradiotherapy of anal carcinoma: Survival and recurrence in an unselected
national cohort.

This paper presents the treatment results of the 328 patients who were treated with
curatively intended CRT for anal cancer in Norway in the current time period. The
national guidelines were to a great extent followed, although individual adjustments
due to comorbidity and frailty were made if considered required.

Complete response after CRT was obtained in 87% of the patients, rising to 93% after
salvage surgery. Full treatment with chemotherapy, elective irradiation of the groins
and salvage surgery, were performed to a lesser extent in elderly patients, mainly due
to frailty and comorbidity. Recurrence occurred in 73 patients (24%), predominately
locoregional, resulting in a 3- and 5-year RFS of 79% and 74%, respectively. Most
locoregional recurrences were in the primary tumour site, within the previous
radiation fields. Inguinal recurrences occurred in six patients for whom prophylactic
radiation of the groins had been omitted despite recommendations. Recurrence was
treated with curative intent in 45% of the cases. The 3- and 5-year OS were 79% and
66%, and CSS were 84% and 75%, respectively. Patients with localized (T1-2N0)
tumours had significantly higher RFS and CSS compared to patients with locally
advanced (T3-4N0/T1-4N+) tumours as shown in figure 10. The 5-year RFS in patients
with localized tumours was 81% vs. 68% in patients with locally advanced tumours (p
< 0.05 log rank). For 5-year CSS, the rates were 87% vs. 66% (p<0.05 log rank),
respectively. Females had significantly higher RFS and CSS compared to males as
shown in figure 11. The 5-year RFS in females was 77% vs. 65% in males (p<0.05 log
rank). For CSS, the rates were 79% vs. 67% (p < 0.05 log rank).
In conclusion, there is a clinical dilemma associated with this intensive treatment, balancing the risk of acute toxicity against the risk of insufficient treatment with adverse outcomes. Deviations to reduce toxicity may be appropriate in some cases, but ideally everyone, regardless of age, should be considered for the full treatment. The survival rates are good, but recurrence is a major problem.
Figure 10: Recurrence-free survival (above) and cancer-specific survival (below) according to tumour stage.
Figure 11: Recurrence-free survival (above) and cancer-specific survival (below) according to sex.
5.2 Paper II

*Impaired health-related quality of life after chemoradiotherapy for anal cancer: Late effects in a national cohort of 128 survivors.*

A systematic survey of symptoms and dysfunction formed the basis for the follow-up study. This paper describes the long-term HRQOL in anal cancer survivors. The response rate was 64%. The responders were in general younger than the non-responders, and had less comorbidity, but there were no significant differences in TNM stage, radiotherapy dose, or chemotherapy. The median follow-up time after diagnosis was 66 months (range 25-112). Anal cancer survivors reported significant impairment of function, especially social and role function, compared to age- and sex-matched volunteers, with a difference of ≥ 20 points in mean scores in QLQ-C30 (p<0.001). Furthermore, survivors had markedly more fatigue, dyspnoea, insomnia and diarrhoea, with a difference of ≥ 15 points in mean scores in QLQ-C30 (p<0.001). The quality of life was significantly reduced among survivors with a mean score of 68 vs. 83 in volunteers, p<0.001 (figure 12). Anal cancer survivors had increased stool frequency, more buttock pain, flatulence, faecal incontinence, impotence (male), dyspareunia and reduced sexual interest (females), with a difference of ≥ 15 points in mean scores in QLQ-CR29, p<0.001 between the groups (figure 13). A subgroup analysis of survivors who had received cisplatin as part of their treatment, revealed increased tinnitus compared to survivors not treated with cisplatin, p<0.01.

In conclusion, this paper clearly shows that survivors after CRT for anal cancer have significant long-term impairment of HRQOL. Reduced social, role and sexual function, and increased diarrhoea, incontinence for gas and stools, and buttock pain were commonly reported. There is generally no systematic evaluation of HRQOL in routine follow-ups. An increased awareness and greater efforts to identify and alleviate problems in survivorship of anal cancer are required.
Figure 12: EORTC QLQ-C30 mean scores. Data from anal cancer survivors compared to age- and sex-matched volunteers.

Figure 13: EORTC QLQ-CR29 mean scores. Data from anal cancer survivors compared to age- and sex-matched volunteers.
5.3 Paper III


Due to the tabooed nature and the lack of systematic assessment of failing faecal continence in the follow-up of anal cancer survivors, more knowledge about the extent of this problem is needed. In this paper, the frequency and severity of faecal incontinence in long-term survivorship after curatively intended CRT for anal cancer is described. Informed consent was obtained from 131 of the 199 invited survivors (66 %). Of these 24 were not eligible in this part of the study due to stoma, leaving 107 survivors for the analysis. The median follow-up time after diagnosis was 66 months (range 25-111). The responders were in general younger than the non-responders, and had less comorbidity, but there were no significant differences in TNM stage, radiotherapy dose, or chemotherapy. Measurement of faecal incontinence by the St. Marks score of faecal incontinence revealed 43 % suffering from faecal incontinence of any degree during the last four weeks. Anal cancer survivors had significantly higher St. Mark`s score than the age- and sex-matched volunteers (mean 9.7 vs. 1.1, p<0.001). Faecal incontinence was primarily associated with leakage of liquid stool and to a lesser extent leakage of solid stool. Urgency was reported by 64 %, alteration in lifestyle and gas incontinence (daily/weekly) was reported by 54 % and 55 % of the survivors, respectively. Only 29 % of those with unintended leakage of liquid stool used constipating drugs. Survivors of locally advanced tumours had higher incontinence score.

In conclusion, moderate to severe faecal incontinence is common among survivors after CRT for anal cancer. As this is a huge problem for many anal cancer survivors, post-treatment follow-up should include evaluation of continence. There might be an underconsumption of even simple measures such as pads or constipating drugs.
Treatment of faecal incontinence, which has shown an effect in other patient groups, should be considered.

**Figure 14:** St. Marks score for incontinence for liquid stool and lack of ability to defer defecation for 15 minutes (urge) in anal cancer survivors compared to age- and sex-matched volunteers.
6 DISCUSSION

6.1 Methodological considerations

6.1.1 Paper I

This is a large and complete national cohort. It included all patients treated in Norway during seven years. To best ensure the completeness, the numbers were checked against the corresponding numbers from the Cancer Registry of Norway. Overall, there were more cases of anal cancer in the current treatment-based database compared to the National Cancer Registry. A recent publication reported that approximately 82% of patients registered with rectal-, sigmoid- and anal cancer in the Norwegian Patient Register were recorded in the Cancer Registry of Norway in 2008 [120].

The extensive national collaboration and loyalty to the guidelines enabled an overall evaluation of the entire group. Since the study population was unselected, it reflects daily practice to a greater extent than a randomized study with strict inclusion- and exclusion criteria. On the other hand, the non-randomized design and the fact that treatment regimens differed according to the stage of the disease, comparisons between treatment groups were not possible to do, and conclusions about optimal radiation doses and chemotherapy regimens cannot be drawn. In subgroup analyses of treatment deviations, temporary interruption or premature ending of RT or not receiving CT, was not significantly associated with treatment outcome. Due to small numbers in subgroups, there is a risk of false negative conclusion (type II error).

The median follow-up after diagnosis for outcome analyses was 49 months (range 1-108), and 57 months (range 10-108) in survivors. A longer follow-up might influence the endpoints. However, other publications on long-term results [75, 121] indicate that the majority of recurrences are detected within the first two years.
6.1.2 Papers II and III

The present study of late effects after CRT was performed with a cross sectional design which resulted in variable length of time since diagnosis. This might have implications for the prevalence reported as time plays an essential role in development of late effects [30]. A prospective design could enable analysis of development of late effects with time.

The choice of instruments is crucial. A strategy based on objective toxicity scales performed by physicians will be quite different from a strategy emphasising the patient’s subjective perception [80, 122]. In order to evaluate HRQOL and to focus on patient perceived aspects relevant in cancer survivorship, a subjective approach was needed. PROs are a preferable method. Cancer-specific instruments provide questions suitable for cancer patients. In the present study, EORTC QLQ-C30 [92] and QLQ-CR29 [113] were chosen as these were validated, well-known and translated into Norwegian. Furthermore, normative data of QLQ-C30 from the Norwegian population and several other European countries exist [116-119]. This enabled a possibility to compare results from the reference group in the study to population studies. If the reference group was considered to be representative, it would also serve as a reference for the other measures, such as QLQ-CR29, SCIN and St. Marks.

As we hypothesized, survivors presented symptoms and dysfunctions related to late effects after curative CRT. To examine all areas thoroughly would be beyond the scope of the current study. In addition, the study revealed other symptoms such as increased fatigue, which could be hypothesis generating. QLQ-C30 and QLQ-CR29 used in the current study provide a quantitative overview of HRQOL. A subjective evaluation of symptoms and dysfunctions, and the importance of these are obtained from the patient.
The assessment of chemotherapy-induced neurotoxicity was a small part of the study. To be performed, we needed a short and simplified questionnaire including the essential variables. SCIN [100] was chosen as an adequate screening instrument in this setting since it had been used for other patient groups who had received cisplatin.

HRQOL scales do not necessarily address issues of primary concern to the patient. An adaption to a distressing symptom by avoidance of situations in which the symptoms are exposed, or replacement of roles compatible with the condition, could be a beneficial coping strategy to maintain quality of life. To determine the full extent of the symptoms could be difficult when these strategies have been implemented [123]. In some contexts, it may be relevant to gain more knowledge about a symptom that particularly stands out as a problem. In that setting, a condition-specific instrument could be more appropriate when evaluating the symptom burden [124].

![Diagram](https://via.placeholder.com/150)

**Figure 15**: Symptoms are not synonymous with HRQOL. Burkett in Cancer Surviv 2007 with permission.

In general, faecal incontinence is claimed to be a stressful dysfunction [125, 126]. Since we hypothesized that faecal incontinence would have a high prevalence in anal cancer survivors, we decided to select this symptom specifically for further evaluation. Faecal incontinence was also assessed in one of the symptoms scales in EORTC QLQ-CR29 by questioning unintended leakage of flatulence or stool. This disease-specific HRQOL questionnaire may provide an impression of this symptom and how it impacts on the survivor’s life in the context of cancer survivorship. However, to understand the
magnitude and severity of faecal incontinence, more specific knowledge is necessary.
To get more detailed information, a condition-specific grading system was required.
The St. Mark’s incontinent score is a well-known, validated score taking into account
faecal urgency and constipating drugs [108]. For better understanding of the problem,
a scale describing the components of faecal incontinence, and grading the severity,
provides much more detailed information.

Evaluation of faecal incontinence by two different approaches revealed how results
may vary according to the instrument used. In assessment by the St. Mark`s score, 43 %
of the anal cancer survivors reported faecal incontinence of any degree, while in
assessment by the EORTC QLQ-CR29, the rate was 57 %. The difference may be
explained by several factors. The St. Mark`s score evaluated incontinence during the
last four weeks, and QLQ-CR29 requested incontinence during the last week. Time for
completion of the telephone interview and for responding to the questionnaire was not
necessarily coinciding, and the wording was not exactly identical. The most
fundamental difference is probably the ability to guide the respondent during an
interview to ensure correct perception of the question. This may be an expression of
information bias.

To aid interpretation of HRQOL scores of the anal cancer survivors, the mean scores
were compared to corresponding average score within the normal population. The
comparison of mean scores between groups may facilitate the meaning of a score as
the norms may be used as reference values. A single value without references to other
scores may not be informative if one is unfamiliar with the tool. Although these data
are primarily qualitative and clinical significance subjective, it may be useful to
quantify them to obtain an overview of the situation for the whole group. In the
current study, interpretation of HRQOL scores was performed according to Osoba using
the concept of clinically meaningful difference [115]. There exists other methods such as the use of Cohen`s effect size, but to clinicians we believe moderate and large differences in scores are more familiar.

An obvious limitation in the study is that there is a risk of selection bias both among survivors and in particular in the reference group of volunteers. Elderly people and survivors with comorbidity were more reluctant to participate. It is impossible to conclude whether this could have influenced the results in any directions, but tumour- and treatment characteristics were fairly similar.

Regarding the reference group the concern for bias is greater due to the low response rate, which may lead to a healthier group with a more positive attitude than the actual normal Norwegian population. As an attempt to assess whether our reference group was representative for the normal population, the scores were compared to four different normative data sets. Before the comparison was performed, the scores of the normative datasets were converted to age- and sex-distribution in our reference group of volunteers. This comparison is illustrated in figure 16.
Figure 16: EORTC QLQ-C30 mean scores. Data from age- and sex-matched volunteers, compared to Dutch, Swedish, German and Norwegian normative data corrected according to age- and sex-distribution among volunteers.

There are some differences between the groups, both in-between the normative population data and between the normative population data and the reference group.
of volunteers. Regarding pain and fatigue, the difference between the data from the group of volunteers and the Norwegian normative data are quite dissimilar. The data of mean score for these symptoms were even higher for the Norwegian normative data than the data from the anal cancer survivors. On the other hand, regarding constipation and diarrhoea, both the data from the group of volunteers and the Norwegian normative data diverged from the other groups. It is possible that normative data have limited validity over time because of life, values and expectations of life may change with time.

But largely, the data from the group of volunteers and the normative data followed the same pattern. With certain reservations and based on this comparison, the group of volunteers was considered sufficiently representative for the normal population.
6.2 Discussions of results

CRT is an effective treatment with a 5-year CSS of 75% in this unselected cohort. However, approximately one quarter experience recurrence, mostly locoregional and most commonly in the primary tumour site. The results are still quite discouraging for the patients with locally advanced tumours, and male gender increases the risk for poor outcome. An exact comparison with other similar studies is difficult because the reported staging and endpoints varies. Given this reservation, the results from the current study seem to be in line with results in other unselected cohorts.

6.2.1 Optimization of chemoradiotherapy regimen

In order to optimize the treatment and outcome, different approaches have been explored. A possible replacement of MMC with CDDP was evaluated both in the RTOG 98-11 and the more recent multicenter study in United Kingdom, ACT II. In long-term update of RTOG 98-11, the patients in the MMC-group had significantly better DFS and OS compared to the patients in the CDDP-group [57]. ACT II, is the largest randomised trial with more than 900 anal cancer patients randomised to either MMC/5-FU or CDDP/5-FU concurrent with RT and a further randomisation to adjuvant CT after CRT or not. The preliminary results in an abstract concluded that there were no differences in the primary endpoint of complete response rate or the secondary endpoint of colostomy for none of the four arms [127]. It has been concluded that MMC is not inferior to, and possibly better, than CDDP, and with less toxicity.

The efficacy of dose escalation of radiation boost and NACT was explored in a recent French trial, ACCORD 03. Patients with locally advanced anal cancer (tumour ≥ 40 mm or N1-3M0) were randomised to receive either two cycles of CDDP/5-FU neoadjuvant followed by EBRT (45 Gy) with two concurrent cycles of CDDP vs. no NACT and the
same CRT regimen, and a further randomisation of high dose irradiation boost (20-25 Gy) vs. standard irradiation boost (15 Gy). No significant differences were found regarding 5-year colostomy-free survival or OS [58]. This supported that neither NACT nor increased radiation dose was superior to standard treatment.

Other CT combinations have been tested in phase II trials. In the EXTRA study, replacement of 5-FU by capecitabine was well tolerated [128]. The feasibility of MMC in combination with CDDP in concurrent CRT was assessed in the EORTC phase II study 22011-40014. The authors concluded that the results were promising, but haematological toxicity leading to limited compliance [129]. A triplet chemotherapy combination, CDDP/MMC /5-FU, was used in a recent published phase II study from UK. This regimen resulted in significant toxicity and low compliance [130].

In Norway, like much of the rest of the world, it was believed that an approach with NACT and by replacing MMC with CDDP, would improve the treatment results. However, these trials demonstrated that definitive CRT with concurrent MMC/5-FU is still considered as the standard care, although CDDP may be an alternative instead of MMC in patients with increased risk of haematological toxicity. CDDP-related nevrototoxicity was except to tinnitus, not more common in the current study. The support of NACT is lacking and there is no obvious benefit of increasing the radiation dose. On the basis of this, the Norwegian guidelines were revised in 2010. CDDP is replaced by MMC, and the NACT regimen is abandoned. Localized (T1-2N0) tumours are recommended EBRT 54 Gy with one course of MMC/5-FU concomitant during the first week of the radiation. Locally advanced (T3-4N0/T1-4N+) are recommended EBRT 58 Gy with two courses of MMC/5-FU concomitant, during the first and fifth week of radiation. Elective irradtiation of the negative groins are now recommended if the
tumour extend below the dentate line or invades the distal vagina, but not for small tumours located above the dentate line.

6.2.2 Targeted therapy

Targeted therapy has gained an important place in medical cancer treatment in recent years. Within the group of targeted therapy, is the EGFR inhibitor, Cetuximab. The clinical utility was first demonstrated in metastatic colorectal cancer and the benefit was linked to the mutation status of K-ras gene in the tumour [131]. Efficacy of Cetuximab in combination with RT has been proven in locally advanced head and neck squamous cell carcinoma [132]. Mutation of the K-ras gene is infrequent in anal carcinoma [133] and Cetuximab may represent a possible way of improvement. So far, there are limited data, but Cetuximab in combination with CT and RT are investigated in several ongoing trials, including one from the Nordic anal cancer group (NOAC), the NOAC 8 study.

6.2.3 Prognostic and predictive factors

The extent of the disease is reported as the most important prognostic factor in several studies [4, 5, 9, 19, 21, 45, 134, 135], and this was reflected in the present study. We found a significant increased risk of recurrence and cancer-specific death in patients with more advanced tumour stage at diagnosis despite intensified treatment. Furthermore, less favourable outcome in males compared to females was found in the current study. This trend has been reported by several other groups [5, 21, 28, 45, 135, 136]. Whether male gender is a risk factor resulting from biology or confounding factors is still unknown. Worse prognosis in the elderly has been reported [5, 7, 9]. In the current study, high age significantly increased the risk of CSS, but no significant association with RFS. This probably reflects the fact that elderly to a certain extent received less intensive primary treatment and to a lesser extent underwent salvage surgery. Several retrospective studies with split course RT have reported clinical
response to RT as an independent predictor of treatment outcome [6, 137, 138].

To find a way of optimizing treatment of patients with increased risk is challenging. Several strategies are being tested. A possible correlation between high-grade acute organ toxicity during CRT and increased OS and locoregional control was found in a small retrospective study [139]. MRI features have been shown not to predict clinical outcome in a small retrospective study [140]. The role of positron emission tomography (PET) in prediction of outcome in anal cancer has recently been evaluated in studies. Persisting metabolic response in the tumour after CRT seemed to be negatively associated with survival [141, 142]. Several studies have investigated the role of molecular biomarkers [143-145], but so far this knowledge has not been taken into daily clinical practice in treatment of anal cancer. More knowledge is warranted to be able to optimize treatment of patients with increased risk while balancing the effect and the toxicity.

6.2.4 Colostomy

CRT replaced surgery primarily because it was a more effective treatment regarding survival and recurrence. An additional benefit for the patient was that the sphincter was preserved and thus the stoma avoided. Colostomy rate and colostomy-free survival are common endpoints in trials of anal cancer [2, 28, 58]. CRT is referred to as a sphincter preserving treatment. In this perspective, a stoma is an expression of a non-successful sphincter-preservation treatment. However, the term needs clarification. In the Norwegian study, 84 patients (26 %) had a colostomy. Even though the majority was due to locoregional failure, as much as 25 % was due to complications and 19 % had persisting pre-treatment stoma. Cause-specific colostomy rates are proposed as a concept by division into tumour-related colostomy and treatment-related colostomy [146]. A third group of baseline pre-treatment-colostomy has also been proposed.
Stomas prior to CRT often become permanent [148]. In the Norwegian study only five patients had their pre-treatment stomas reversed.

6.2.5 Salvage surgery

In patients with persisting primary tumour after CRT or in patients with locoregional recurrence, salvage surgery is an important additional modality. In the present study, 43 patients (13%) had persisting residual tumour after CRT of whom 24 (7%) underwent salvage surgery. The remaining patients with residual tumours, 19 (6%), were not considered candidates for extensive surgery primarily due to comorbidity and high age and to a lesser extent due to tumour extension. This is possibly due to adequate patient selection for major surgery. In addition, this illustrates a dilemma in clinical practice. The threshold for modifying treatment to avoid high toxicity is naturally lower if the patient has comorbidity and high age. At the same time, adequate CRT for these patients may be the only possibility for disease control and cure. However, the fear of toxic therapy is real, and the risk assessment is dual. In the present study, three patients died during treatment and another two within three months after treatment, possibly influenced by treatment toxicity. Still, it is important to consider treating with adequate radiation fields, including inguinal fields, even in elderly patients.

R0 resection was achieved in 20 of the 24 patients who underwent salvage surgery due to persistent residual tumour. Probably due to a more aggressive biology of the cancer, the prognosis of these patients was less favourable. In the present study, 55% of the patients who underwent salvage surgery due to residual tumour had a recurrence, of these none achieved long-term survival. Surgical resection was performed in 44% of patients with recurrence, in most cases salvage surgery due to locoregional recurrences. Similar to results from other studies [52], the long-term prognosis of
patients after salvage surgery due to recurrence was more favourable compared to surgery for residual tumour.

6.2.6 Identification, prevention and treatment of late effects

The effective treatment of anal cancer leaves many long-term survivors. Unfortunately in many cases, the treatment results in unavoidable late effects. Measures to identify, prevent and minimize late effects should be a priority. Promising results have emerged regarding reduction of acute toxicity by IMRT technique [149-151]. Hopefully, this will reduce the long-term effects as well.

Follow-up of survivors treated for anal cancer should include evaluation of HRQOL and symptom burden. By introducing evaluation of late effects as a regular part of the follow-up, the problem is on the agenda both for the patient and the doctor. An important tool for implementation would be to create guideline or flowcharts for management of late effects. Collaboration in multidisciplinary teams will often be required as the symptoms could be complex. Knowledge about treatment of late effects is limited and is not in proportion to the extent of the problem. As illustratively pointed out by a British gastroenterologist: “Nearly every hospital has at least one gastroenterologist with expertise in Crohn’s disease compared to barely a handful of gastroenterologists worldwide profess expertise in radiation-induced problem even though this is far more common” [152]. These survivors are a shared responsibility. References to a gastroenterologist should probably be performed more often. Attempts to treat late effects are worthwhile. A practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment of cancer was published in 2012 [153]. Although there are limited data from this group, treatment results of late effects in other pelvic malignancies could help. Survivors with faecal incontinence may benefit from conservative approaches such as dietary advice, pelvic floor exercises, biofeedback, medication to improve stool consistency, and
constipating drugs [154, 155]. Results from studies using hyperbaric oxygen therapy in
treatment of late radiation tissue injury are promising regarding refractory pain and
radiation proctitis [156, 157]. Sacral nerve stimulation may be a viable treatment
option for radiation-induced faecal incontinence [158]. Sexual dysfunction is also a
problem for many survivors after pelvic radiation [159, 160]. Documentation of
treatment is sparse [161], but hormone replacement in premenopausal women, vaginal
dilators, lubrication cream, or medication for erectile dysfunction should be
considered.

6.2.7 Increased focus on late effects and HRQOL

The total burden of dysfunctions and symptoms is high for many of these survivors and
correlates to some extent with a reduction of global health score. However, neither
QOL nor HRQOL solely reflect the symptom burden, but includes factors not directly
related to disease-related or treatment-related effects [124]. A cancer survivor
expressed: “It is not just the big problems like bleeding, it is all the little things put
together that wear us down”. From the patient’s perspective, more information,
better preparation and the importance of recognition and acknowledgement of
symptoms was emphasised [162]. In a recent paper from the English National Cancer
Survivorship initiative, the authors concluded that a systematic approach to
prevention, detection and management of some treatment-related consequences could
significantly improve the ability of patients to manage their condition [163]. Support
for this statement was found in a randomised trial showing that routine assessment of
HRQOL improved communication and patients’ well-being [164]. Systematic knowledge
is essential during the follow-up of survivors. This is an underlying premise for the
ability to understand, to confirm, to promote discussion, and to attempt treatment. It
is important not only to alleviate their symptoms and dysfunctions, but also to gain
knowledge of what these survivors suffer from, as this is crucial to be able to meet this
group with insight and understanding. To experience understanding and to obtain confirmation is necessary in a coping strategy.
7 CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, CRT of anal cancer is an effective treatment leaving many long-term survivors. The overall survival is good, and comparable with other studies. Still, the local recurrence rates are challenging, and the risk is increased in male patients as well as in patients with locally advanced tumours. Late effects are a problem in cancer survivorship. The study confirmed the pre-specified hypothesis that anal cancer survivors suffer from symptoms after CRT with impaired anorectal, urinary, and sexual function and more pelvic pain resulting in reduced HRQOL. Several of these symptoms should be investigated further to assess severity and impact of quality of life.

Based on the results of this thesis, further perspectives for improvement of treatment and care of patients with anal cancer could be achieved:

- Further research in order to optimize treatment results is required. It is necessary to improve local control and to obtain more knowledge of prognostic and predictive factors in order to provide a more individualized treatment.

- Better understanding of the mechanisms and development of late effects, as well as optimization of treatment of late effects, is necessary to reduce symptom burden and to maintain HRQOL. Implementation of existing knowledge and use of available treatment must be included in follow-up. Due to symptom complexity, a multidisciplinary approach will be required.

- An increase focus on late effects may contribute to improving QOL. Improved patient information, and acknowledgement of symptoms and dysfunction, may help the anal cancer survivors to reorientation and to achieve better symptom management.
REFERENCES


130. Sebag-Montefiore D, Meadows HM, Cunningham D, Plowman PN, Hurman DC, Davidson N et al. Three cytotoxic drugs combined with pelvic radiation and as maintenance


ERRATA

The following errors have been found in the thesis:

- Paper I: Under section Methods and Material, Treatment:
  
  o Patients with local (T1-2N0) tumours (TN-group 1) were recommended external beam radiotherapy (EBRT), 54.0 Gy in 27 fractions to tumour and pathological lymph nodes and one course....... This is a writing error. It should have been written: .... to tumour and one course....

- Paper I: Table I: One of the patient classified T1N0M0, should been classified TXNXM0.
PAPER I
APPENDICES 1-5