Proton versus photon therapy in anal squamous cell carcinoma

Swedish anal carcinoma study (SWANCA)

Sponsor: The anal carcinoma study group
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- Version 1.2, 2020-11-10 (Non-substantial amendment)
- Version 1.1, 2020-09-30 (Non-substantial amendment)
- Version 1.0, 2020-06-23 (Initial Protocol)

Protocol Signature Sheet

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On behalf of the study group

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Protocol Amendment and Version History

Protocol Version	Date	Reason for change	Change type
1.0	2020-06-23	Initial version	N/A
1.1	2020-09-30	Administrative changes and changes to visits in sections 11 and 22	Non-substantial
1.2	2020-10-10	Administrative changes and clarifications to sections 10, 11, 16, 18 and 22	Non-substantial
1.3	2021-01-26	Correction to section 12.11	Non-substantial

List of Changes from previous version 1.2		
Section	**Change**	**Change Type**
Section 12.11	Removed item 6 due to being irrelevant. Listing corrected.	Non-substantial

1 Synopsis

Protocol title	Proton versus photon therapy in anal squamous cell carcinoma – Swedish anal cancer study
NCT number	NCT04462042
Development phase	Phase II
Study population	Patients with squamous cell anal carcinoma aimed for radical radiotherapy with concomitant chemotherapy.
Endpoints	**Primary endpoint** • Grade ≥3 acute GI and haematological side-effects during therapy and up to three months after the end of treatment. **Secondary endpoints** • Other acute side-effects than GI and hematologic assessed during and up to three months after the treatment. • Late side effects 1, 2 and 5 years after completion of treatment • Patient reported quality of life during and after treatment up to 5 years • Tumour response rate at 3-6 months after completion of treatment • Locoregional failure • Disease free survival • Overall survival • Health economic analysis • Feasibility
Study design	The study is an open label, multi-centre, randomised phase II study. 100 evaluable patients with anal squamous cell carcinoma as defined above will be randomised in a 1:1 ratio to treatment consisting of • Arm 1: Radiotherapy delivered with protons • Arm 2: Radiotherapy delivered with photons
Eligibility criteria	**Inclusion criteria** 1. The patient must be at least 18 years old. 2. Histologically confirmed squamous cell carcinoma of anal canal or distal rectum with known p16/HPV status. 3. The patients may have TNM-stage T2(≥4 cm)-4, N0-1c,M0 (UICC 8th edition). 4. WHO/ECOG performance status 0-1. 5. Hb >100 g/L 6. ANC >1.5 x 10^9/L 7. Platelets >100 x 10^9/L 8. Creatinine <1.5 x ULN 9. Bilirubin <3 x ULN 10. ALAT <3 x ULN 11. The patient must be expected to tolerate the treatment (radiotherapy with concomitant capecitabine and mitomycin C)

12. The patient must be able to understand the information about the treatment and give a written informed consent.

Exclusion criteria

1. Patients with cancer of the perianal skin without involvement of the anal canal (ICD-O-3 C44.5) are not eligible.
2. Patient judged to have any other treatment than radiotherapy with concomitant chemotherapy as the preferred treatment
3. Concomitant or previous malignancies. Exceptions are, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin or, other previous malignancy with a disease-free interval of at least 5 years.
4. Two or more synchronous primary cancers in the pelvic region at time of diagnosis
5. Previous radiotherapy, surgery or chemotherapy that may interfere with the planned treatment for the present disease, as judged by the investigator.
6. Co-existing disease prejudicing survival (expected survival should be >2 years).
7. Pregnancy or breast feeding
8. When prosthetic materials (e.g. hip prostheses) are present close to the target volume it must be considered if this may introduce uncertainties in dose calculations that precludes especially, proton therapy.
9. Patients with pacemaker/ICD are not eligible.

Stratification

To avoid imbalance between treatment arms patients the minimisation method will be used to achieve balance between sex (F/M), p16/HPV status (+/-) and colostomy before treatment.

Duration of treatment

Approximately six weeks

Radiotherapy

The prescribed doses to different target volumes will be equivalent to those recommended in the Swedish National Care program for anal carcinoma. For the patients in this study it means, 57.5 Gy(RBE) in 27 fractions (2.13 Gy(RBE)/fraction). Any lymph node metastases equal to or greater than 2 cm in its largest dimension will be treated with the same dose and fractionation as the primary tumour. Lymph node metastases with a diameter less than 2 cm will be treated with 50.5 Gy(RBE) in 27 fractions (1.87 Gy(RBE)/fraction). Prophylactic treatment of clinically uninvolved lymph nodes consists of 41.6 Gy(RBE) in 27 fractions (1.54 Gy(RBE)/fraction). Treatment is given once daily, 5 days per week.

Chemotherapy

The Swedish national care program for anal cancer recommend concomitant chemotherapy during radiotherapy. In the present study, chemotherapy will be administered according to the national guidelines irrespective of treatment arm. In this study, the

	treatment with a combination of mitomycin C and capecitabin (CAPMI) will be used.
Efficacy control	Local and regional failure Disease free survival Overall survival
Safety evaluation	Acute and late side effects; Adverse events and side effects graded according to CTCAE v5.0 QL; Patient scored morbidity and QL
Statistical methods	**Efficacy**: Stratified Cox regression analysis, Kaplan-Meier and Breslow methods. For locoregional failure the Fine-Gray regression will be considered. **Shift in distributions of side effects**: Mann-Whitney U-test
Criteria for evaluation	**Per protocol**: Patients that have started the assigned study treatment.
Intention to treat:	All correctly randomised and included patients
Planned sample size	100 evaluable patients (patients completing primary treatment)
Analysis plan	The primary end point will be analysed when all patients have finished treatment and when median follow-up is two years. Further analyses when all patients have been followed for at least two years.
Duration of the study	Two to four years inclusion, five years follow-up after inclusion of the last patient.

2 Abbreviations

AC	Anal carcinoma
AE	Adverse event
AJCC	American Joint Committee on Cancer
ANC	Absolute neutrophil count
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical tumour volume
DCE	Dynamic contrast enhanced
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
GI	Gastro-intestinal
GTV	Gross tumour volume
Gy	Gray
Gy(RBE)	"Biological" or "photon equivalent" dose
Hb	Haemoglobin concentration
HPV	Human papilloma virus
ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
IMPT	intensity modulated proton therapy
IMRT	Intensity modulated radiotherapy
MFO	Multifield optimization
MRI	Magnetic resonance imaging
MV	MegaVolt
NTCP	Normal tissue complication probability
OS	Overall survival
PET	Positron Emission Tomography
PRV	Planning organ at Risk Volume
PTV	Planning target volume
QA	Quality assurance
QL	Quality of life
QLQ	Quality of Life Questionnaire
RBE	Relative biological effectiveness
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SCC	squamous cell cancer
SFO	Single field optimization
SFUD	Single field uniform dose
SIB	Simultaneously integrated boost
TLV	Dental and Pharmaceutical Benefits Agency
TNM	Tumour Node Metastasis classification
V_d	Volume (of an organ) receiving $\geq$d Gy(RBE)
WBC	White blood cell count
VMAT	Volumetric modulated arc therapy
WHO/ECOG	World Health Organization/Eastern Cooperative Oncology Group

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Innehållsförteckning

4 Background and introduction

4.1 Study rationale

Dosimetric studies suggest that radiotherapy with protons has a potential to reduce side effects compared to treatment with photons for patients with anal carcinoma (AC). There are so far no studies comparing these treatment techniques in a randomised setting. The aim of this study is to compare side effects following photon therapy versus proton therapy within the framework of a randomised controlled trial.

4.2 Background

Recent data suggests that close to 200 patients with AC are diagnosed each year in Sweden and the trend is increasing. AC is approximately twice as common in women as in men. There is a strong association between human papilloma virus (HPV), especially the subtypes HPV 16 and 18 and AC. The median age for AC patients is about 65. The overall survival after 5 years is approximately 70%. Radiotherapy is usually the first line treatment and given in combination with chemotherapy as recommended in the national care program.

Virtually all clinical studies have been performed with conventional photon techniques (3-D conformal or intensity modulated radiotherapy (IMRT/VMAT)). These techniques have gone through a strong development during the last 1-2 decades. Advanced proton radiotherapy with intensity modulated proton therapy (IMPT) and spot scanning has been available for a little more than a decade. The main difference between proton and photon techniques consists of the resulting dose distribution due to the physical properties of protons. Protons often allow for lower radiation doses in structures at a distance from the target while the target dose remains similar. For treatment of large volumes in the pelvis the absorbed dose in organs such as intraperitoneal bowel, urinary bladder and pelvic bone marrow will differ between the two techniques.

The standard treatment of AC T2($\geq$4 cm) - 4,N0-1c,M0, according to the Swedish care programme for anal carcinoma, is radical radiotherapy of known tumour tissue and prophylactic radiotherapy to pelvic lymph nodes concomitant with chemotherapy (RCC 2020). A substantial proportion of side effects emanates from structures in proximity to the site of the tumour, i.e. rectum/anal canal and perineal skin surfaces. Since these structures are part of the tumour volume the doses will be similar regardless of treatment technique. Thus, the side effects from these sites may be assumed to be similarly severe after proton or photon therapy.

Haematological toxicity is particularly relevant in the case of combined radio- and chemotherapy. Radiotherapy of the pelvic region alone seldom causes major haematological complications. Chemotherapy frequently does. The combined haematological toxicity from radiotherapy and chemotherapy may lead to dose reduction of chemotherapy with a potentially detrimental effect on treatment outcome (Bazan et al.2012). It has been shown that a mean dose to the pelvic bone marrow of more than 32 Gy progressively increases the risk of grade $\geq$3 haematological toxicity in intensity modulated photon radiotherapy with concurrent chemotherapy (Franco et al 2016). Septic complications as a consequence of haematological toxicity may also cause serious problems for the patients. Furthermore, severe acute side effects may lead to treatment interruptions due to patient compliance and/or a compromised general condition. The pelvic bones harbour up to 40% of the haematopoietically active bone marrow (Ellis, 1961). It is known that grade $\geq$3 haematological toxicity is reported to occur in well over 50% of patients treated for AC with photons and chemotherapy (Franco et al. 2016). In the photon case, virtually all pelvic bone marrow is exposed to radiation, due to the treatment technique and the properties of photon radiation. In silico simulations of proton therapy shows that, at least, 50% of the pelvic may be completely spared from radiation dose. It may thus be assumed that proton therapy only to a limited extent will add to the

haematological toxicity of chemotherapy. The incidence of haematological toxicity grade >3 may then be assumed to decrease substantially to a reported level of 20% (Franco et al. 2016). The situation is different regarding dose-volume parameters that determine dose constraints for intraperitoneal bowel. Data are comparatively sparse and the proposed normal tissue complication probability (NTCP)-models are therefore not validated and not robust enough for predictive purpose (Jadon et al 2019). Published studies have used different organ-at-risk definitions and different end-points which makes the interpretation of results even more difficult (Jackson et al 2010). An unpublished study of 170 patients performed retrospectively the frequency of at least grade 3 toxicity was 34% after VMAT (personal communication: Martin Nilsson, Skåne University hospital, Lund, Sweden). This is probably a relevant figure to use since it is derived from a population receiving similar treatment as the population in the present study. Similar frequencies have been reported by others (e.g. Devisetty et al 2009). These results reflect the difficulties to reach the optimisation objectives with photon techniques. At least in advanced tumour cases.
In summary, AC is a disease in which modern therapy is reasonably successful in achieving tumour control/cure. Both acute and late side effects are substantial. Proton radiotherapy is hypothesised to have the potential to decrease the incidence/severity of some acute side effects from certain organs at risk e.g. bone marrow and intraperitoneal bowel. By sparing the dose to these organs it is also possible that late effects might be less evident. Sparing of the bone marrow may lead to fewer septic events and dose reductions of chemotherapy which may, as a consequence, improve tumour control. The primary aim of this study is to find ways to decrease acute side effects primarily to alleviate some discomfort from the patient during and after a usually painful treatment experience. It has also been concluded by others that reduction of acute side effects is a relevant aim and end point for the evaluation of new treatment techniques and both patient reported and physician reported data are recommended for assessment (Glynne-Jones et al 2017).

4.3 Organisation

Presently, in Sweden all patients aimed for curative intent chemo-radiotherapy are treated in one of four university hospitals (in Göteborg, Lund, Umeå and Uppsala) according to an agreement on a national level. Before start of therapy, all patients are discussed at a national multidisciplinary board. This ensures that all patients that may be eligible for a clinical trial are reviewed before treatment.

4.4 Radiotherapy

Radiotherapy techniques have developed rapidly during the last decades with the introduction of intensity modulated therapy and automated computer optimisation of treatment plans. These techniques have contributed to the reduction of side effects and increased the tolerance to radiotherapy of large volume. These techniques are considered a prerequisite for modern radiotherapy and are thus, in this context considered as the conventional treatment.

4.4.1 Proton therapy

From a clinical point of view the main difference between photon and proton radiation can be attributed to the proton Bragg-peak that deposit the main part of the energy in a small spot/volume. This leads to a different dose distribution compared with photons and, perhaps most important, a very rapid fall at depth. On the other hand, the penumbra of protons at depth is usually wider than that of photons. This may be a disadvantage of protons if critical organs are situated close to the tumour target. In radiotherapy of anal carcinoma some sensitive structures are situated within the volume of high dose and can thus not be spared by either photons or protons. Other organs at risk such as small bowel and bone marrow are

predominantly quite distant from the target and could therefore be spared to some degree by protons. It is therefore justified to investigate if protons will give a clinically detectable reduction of the frequency and/or severity of side effects from these organs

5 Objectives of the trial

5.1 Primary objective

- To study the acute side effects during, and in the first three months after radiotherapy with proton therapy versus photon therapy of localised anal cancer stage T2 (≥4cm)-T4 and/or N0-1c and M0.

5.2 Secondary objectives

To compare:

- Other acute side-effects than GI and hematologic
- The frequency of late side effects up to 5 years after treatment
- Patient reported quality of life during and after treatment up to 5 years
- Tumour response rate at 3-6 months
- Locoregional failure
- Disease free survival
- Overall survival
- Health economic between the treatment groups
- Feasibility

6 End points

6.1 Primary end point

- Grade ≥3 acute GI and haematological side-effects during therapy and up to three months after the end of treatment.

6.2 Secondary end points

- Other acute side-effects than GI and hematologic assessed during and up to three months after the treatment.
- Late side effects 1, 2 and 5 years after completion of treatment
- Patient reported quality of life during and after treatment up to 5 years
- Tumour response rate at 3-6 months after completion of treatment
- Locoregional failure
- Disease free survival
- Overall survival
- Health economic analysis
- Feasibility

7 Study design

The study is an open label, multi-centre, randomised phase II study. 100 patients with anal carcinoma (including carcinoma of the perianal skin) will be randomised in 1:1 ratio to treatment consisting of

- Arm 1: Radiotherapy delivered with protons
- Arm 2: Radiotherapy delivered with photons

Randomisation will be stratified by sex, presens of colostomy and p16/HPV-status using the minimisation method (Pocock 1983).

8 Study period

The inclusion is estimated to be 2-4 years. The study ends five years after inclusion of the last patient

9 Overview of study treatment

Radiotherapy with concomitant chemotherapy is the recommended curative treatment for anal carcinomas T2(>4cm)-T4/N+M0. The recommended treatment is described in detail in (RCC 2020). The treatment in this study does in all aspects follow the national recommendations. The treatment in both treatment arms will be identical in all aspects except the fact that in the experimental arm will consist of proton radiation. The care program suggests a few alternative possibilities concerning the choice of radiotherapy dose and fractionation and chemotherapy prescription. In practice only one radiotherapy schedule and one alternative for chemotherapy are frequently used. In the present study these dominating alternatives should be used.

9.1 Radiotherapy

This means for radiotherapy that it is delivered in 27 fractions with five fractions per week during an overall treatment time of 5.5 weeks. 57.5 Gy(RBE) in 27 fractions is the planned dose for the primary tumour and lymph nodes with a greatest diameter of at least 2 cm will receive the same dose as the primary tumour (corresponding to PTVT_57.5 and PTVN_57.5). Lymph node metastases less than 2 cm are prescribed 50.5 Gy(RBE) in 27 fractions (corresponding to PTVN_50.5). Elective treatment of clinically uninvolved nodes will be delivered to a total dose of 41.6 Gy(RBE) in 27 fractions (PTVN_41.6).
It is implied that photon therapy is given with intensity modulated radiotherapy (IMRT)/volumetric arc therapy (VMAT)/helical tomotherapy (HTT). Proton plans will be produced by single field optimization (SFO)/single field uniform dose (SFUD) or multifield optimization (MFO)/intensity modulated proton therapy (IMPT) depending on which technique that renders the best result regarding target coverage, radiation doses to organs at risk and plan robustness. SIB will be used in all cases to reach the intended dose for each target volume in 27 fractions.
For converting proton dose from physical dose (Gy) to “biological” or “photon equivalent” dose Gy(RBE) a factor of 1.1 is used.

9.2 Chemotherapy

The national care program recommends two similar alternatives as first choice of chemotherapy. One is the combination of mitomycin C and 5-flurouracil (FUMI). The other is mitomycin C and capecitabin (CAPMI). Presently, in Sweden the latter combination is predominant. To avoid possible sources variation, CAPMI will be the combination used in the present study. The dosage and administration of drugs shall follow the national care program, irrespective of treatment arm. This is also the case regarding instructions for dose reduction and/or discontinuation of drug delivery. A schedule for dose-reduction of chemotherapy components that is in use at the Uppsala Akademiska hospital is enclosed (in Swedish) as Addendum 3 for guidance.

10 Patient selection criteria

10.1 Inclusion criteria

1. The patient must be at least 18 years old.
2. Histologically confirmed squamous cell carcinoma of anal canal or distal rectum with known p16/HPV status.
3. The patients may have TNM-stage T2(≥4 cm)-4, N0-1c,M0 (UICC 8th edition).
4. WHO/ECOG performance status 0-1.
5. Hb >100 g/L
6. ANC >1.5 x 10^9/L
7. Platelets >100 x 10^9/L
8. Creatinine <1.5 x ULN
9. Bilirubin <3 x ULN
10. ALAT <3 x ULN
11. The patient must be expected to tolerate the treatment (radiotherapy with concomitant capecitabine and mitomycin C)
12. The patient must be able to understand the information about the treatment and give a written informed consent.

10.2 Exclusion criteria

1. Patients with cancer of the perianal skin without involvement of the anal canal (ICD-O-3 C44.5) are not eligible.
2. Patient judged to have any other treatment than radiotherapy with concomitant chemotherapy as the preferred treatment
3. Concomitant or previous malignancies. Exceptions are, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin or, other previous malignancy with a disease-free interval of at least 5 years.
4. Two or more synchronous primary cancers in the pelvic region at time of diagnosis
5. Previous radiotherapy, surgery or chemotherapy that may interfere with the planned treatment for the present disease, as judged by the investigator.
6. Co-existing disease prejudicing survival (expected survival should be >2 years).
7. Pregnancy or breast feeding
8. When prosthetic materials (e.g. hip prostheses) are present close to the target volume it must be considered if this may introduce uncertainties in dose calculations that precludes especially, proton therapy.
9. Patients with pacemaker/ICD are not eligible.

11 Study procedure

11.1 STUDY ENTRY

1. Written informed consent is needed before any study-specific procedures are performed. Treatment should start within 3 weeks after registration.

11.2 Baseline evaluations

1. Recording of toxicity according to CTCAE v5.0
2. Adequate clinical assessment with a TNM (UICC 8th edition) classification (MRI and CT/MR-PET of the pelvis and thoracic CT/pulmonary X-ray, and histology showing squamous cell carcinoma).
3. Medical history
4. ECOG perfomance status

5. Haematology: Hb,WBC, WBC differential, ANC, platelets
6. Blood chemistry: Bilirubin, ALP, ALAT, ASAT, creatinine, Na, K, Ca, albumin and Mg
7. p16/HPV analysis of the primary tumour
8. Digital photo of perianal area (saved into patient's clinical files)
9. Body weight and height
10. Questionnaires (see addendum 5)

11.3 Evaluation during therapy (weekly)

1. Recording of toxicity according to CTCAE v5.0
2. Haematology; Hb, WBC, WBC differential, ANC, platelets
3. Blood chemistry (only week 4 of radiation); Bilirubin, ALP, ALAT, ASAT, creatinine, Na, K, Ca, albumin and Mg
4. Daily Questionnaires (see addendum 5)
5. Digital photo of perianal area (saved into patient's clinical files)

11.4 Evaluation 1, 2 and 3 weeks after end of treatment

1. Hb, WBC differential, ANC, platelets
2. Questionnaires (see addendum 5)

11.5 Evaluation 1-2 months after end of treatment

1. Recording of toxicity according to CTCAE v5.0
2. Digital rectal examination
3. ECOG performance status and weight
4. Hb,WBC, WBC differential, ANC, platelets
5. Bilirubin, ALP, ALAT, ASAT, creatinine, Na, K, Ca, albumin, Mg
6. Digital photo of perianal area (saved into patient's clinical files)
7. Questionnaires (see addendum 5)

11.6 Evaluation 4-6 months after end of treatment

1. Recording of toxicity according to CTCAE v5.0
2. Digital rectal examination
3. CT-PET
4. Response evaluation
5. ECOG performance status and weight
6. Haematology; Hb,WBC, WBC differential, ANC, platelets
7. Blood chemistry; Bilirubin, ALP, ALAT, ASAT, creatinine, Na, K, Ca,albumin and Mg
8. Questionnaires (see addendum 5)

11.7 Every 3 months for the first 2 years and then every 6 months until 5 years

1. Recording of late toxicity (Late toxicity according to CTCAE c 5.0, except for late skin toxicity which will be graded according to RTOG)
2. Digital rectal examination
3. ECOG performance status and weight
4. CT thorax and abdomen once yearly for the first 3 years
5. MRI of the pelvis / CT-PET if clinically indicated
6. Questionnaires (see addendum 5)

11.8 Side effects during radiotherapy

The most common acute side effects from radiotherapy of anal carcinoma are varying degrees of fatigue, diarrhoea, nausea and radiation dermatitis.
Dermatitis is common in skin of the gluteal cleft, peri-anal area, groins and external genitalia. It occurs usually during the third week of treatment and increases during therapy. Normally it subsides after therapy (often the improvement starts a couple of weeks after cessation of therapy. The restitution process is gradual and may go on for several months. The skin reaction is graded into 5 grades (0-4) by the CTCAE 5.0. Recommendations for treatment of reactions are listed in the Swedish Care Program (RCC 2020) which should be followed. Other side effects are also graded according to CTCAE 5.0 and treated as indicated.

Skin care is a major problem for patients undergoing radiotherapy for anal carcinoma. Different routines are used at different centres. It is recommended that the skin care program produced by the department of oncology in Skåne university hospital is used as a general recommendation for patients in the present study. A copy of the protocol (in Swedish) is enclosed as an addendum (Addendum 6)

11.9 Evaluation after completion of radiotherapy

At two to three months after completion of therapy an assessment of tumour control and morbidity must be made. Tumour control is assessed as judged by the responsible physician, national and local routines. Side effects are graded according to CTCAE 5.0 using CTC terminology.

11.10 Follow up

Patients should be seen every three months for two years after completion of radiotherapy and a full clinical assessment should be made. During this time, it is recommended that an oncologist sees the patient with at least 6 months intervals. Information on locoregional and distant tumour control should be recorded. After two years, evaluation of locoregional control should be made every 6 months up to 5 years. During this time the follow-up is done according to the National Care program.
Late side effects should be monitored according to the CTCAE 5.0 from three months and up to five years after completion of radiotherapy.

Questionnaires as per section 13 should be administered at 1, 3, 6, 9, 12, 24, 36 months and 5 years after randomisation.

Patients should be monitored for local recurrence and if symptoms arise that are suspicious of distant metastases appropriate investigations must be carried out to confirm or exclude their presence. Also, if a locoregional recurrence is found, an MRI and a PET-CT for documentation is mandatory and screening for distant metastases should be performed. If distant metastases develop but there is no evidence of local recurrence within the irradiated volume, effort should be made to continue to monitor the primary site. If possible, histological confirmation should be performed in all cases.

11.11 End of treatment or follow up

Follow-up by the protocol ends when any of the events below occurs:

- If 5 years of follow-up is reached
- If residual tumour or a locoregional recurrence is diagnosed. Survival will then be followed by the Swedish population registry

- In cases of other serious medical conditions, follow-up ends as judged by the investigator. Survival will then be followed by the Swedish population registry
- If the patient dies before 5 years' follow up
- Withdrawal of consent

12 Radiotherapy

Radiotherapy must start within three weeks from the date of study entry (randomisation). Prolongation of overall treatment time should be avoided. In cases of unplanned treatment breaks or of a Bank Holiday, the overall treatment time may be kept by giving the patient two fractions per day with 7 h interval (the interval may be longer, but never shorter than 6 h) for maximum four days. The overall treatment time is ideally 37 days and must not exceed 40 days.

12.1 Patient position and immobilisation

The patient should preferably be treated in supine position, adequately positioned and immobilised according to the Skandion routines. If the patient has not been randomized when treatment planning imaging is performed, the preparations **must** be performed according to the Skandion routines described for proton treatment (described in Addendum 7).

The patient should be instructed to void the bladder and drink 3 dl of liquid 30 min before treatment planning imaging and each fraction. If applicable and possible, the patient should also empty the bowel.

12.2 Patient data acquisition

Treatment planning CT-imaging (slice thickness $\leq$ 3mm) should be performed with the patient in treatment position and according to proton treatment routines except for patients that have already been randomized to photon treatment. If the rectum is distended to a diameter of >5 cm by scybala and/or gas, the patient is asked to use a laxative before the procedure is repeated. If the rectum still is distended, it is assumed that the state is habitual and thus may serve as a base-line for planning. A co-registered MRI- or PET-scan is recommended to facilitate tumour delineation. MRI-only procedures are not allowed since the method is not verified for protons.

12.3 Target volumes

12.3.1 Tumour volumes

Gross Tumour Volume(s) (GTVT_57.5, GTVN_57.5, GTVN_50.5) of the primary tumour (GTVT) and metastatic regional lymph nodes (GTVN) are outlined based on available information (clinical examination, endoscopy, diagnostic MRI/PET). GTVT and GTVN should always be delineated as separate volumes.

Clinical Target Volume(s) (CTVT_57.5, CTVN_57.5, CTVN_50.5) CTVT_57.5 consist of GTVT with a 10-15 mm margin, depending on anatomical borders, tumour growth pattern etc. Wider margins allowed when indicated. CTVN_57.5/50.5 consist of corresponding GTVN with a 5-10 mm margin, depending on size and appearance. CTVT and CTVN should always be delineated as separate volumes.

Planning Target Volumes (PTVs) PTVT_57.5 and PTVN_57.5/50.5 are CTVT_57.5 and CTVN_57.5/50.5 with a 7 mm margin in all directions. Imaging (CBCT or orthogonal images) should be performed daily for set-up verification. PTVT/N should generally not be

delineated closer than 4mm to the skin surface. However, if there is tumour closer than 4 mm to the skin surface, PTV should extend to (or outside) the skin surface and a bolus should be used during photon treatment (see also section 12.6 "Treatment planning"). PTVT and PTVN should be delineated as separate volumes.

12.3.2 Elective lymph node volumes

CTVN_41.6 is an adjuvant lymph node volume and consists of regional lymph nodes at risk for subclinical spread of the tumour at a distance. The lymph nodes/sites relevant elective for treatment of anal carcinoma are the following (in accordance with the National care program)

- Presacral, mesorectal, obturator and internal iliac lymph nodes (in all cases).
- External iliac nodes
- Inguinal nodes, may be omitted only if the tumour is entirely located in the rectum
- The ischiorectal fossa if the tumour engages the external sphincter or levator muscle
- The anus with a margin of 20 mm circumferentially and distally.

CTV should not extend more than 10 mm into the urinary bladder and not more than 1 mm into bone or muscle if these structures are not engaged by tumour growth.

PTVN_41.6 consists of the CTVN_41.6 with an isotropic margin of 7 mm. The PTV_41.6 should not be delineated closer than 4 mm to the skin surface (See also 12.7 "Treatment planning")

12.4 Organs at risk

The following organs at risk (OAR) must be delineated

- Urinary bladder
- Intestine (operationalised by the volume named "Bowel bag")
- Skin
- Pelvic bone marrow
- Femoral heads

12.5 Structure names in the treatment planning system

All structures should be named according to the Swedish standard nomenclature in radiotherapy (Strålsäkerhetsmyndighetens rapport 18:2016). The following structure names should be used:
"GTVT_57.5", "GTVN_57.5", "GTVN_50.5", "CTVT_57.5", "CTVN_57.5", "CTVN_50.5", "CTVN_41.6", "PTVT_57.5", "PTVN_57.5", "PTVN_50.5", "PTVN_41.6", "Bladder", "BowelBag", "Skin", "BoneMarrow", "FemoralHead_L", "FemoralHead_R"
Other OARs should be delineated when relevant according to local routines. For delineation guidelines, see Ad 1. For dose limitations, see dose-volume objectives/constraints below.

12.6 Treatment technique

Radiation treatment with photons should be delivered with external photon beam therapy with IMRT/VMAT/HTT.
Radiation treatment with protons should be delivered with scanned proton beam therapy with either SFO/SFUD or MFO/IMPT.
The position of the patient should be verified with electronic kV or MV portal imaging or x-ray volumetric imaging (cone beam CT) according to local routines at each treatment centre, and included in the quality assurance (QA) report (see below). Patients undergoing proton therapy will perform repeated CT-scans according routines at the Skandion clinic, and

patients treated with photons will be re-scanned according to local routines at each treatment centre. The monitor units (dose) used for verification of position should be considered if MV portal imaging is used.

12.7 Treatment planning

The clinician should assess the imaging and ascertain whether the tumour is adequately bolused by the surrounding buttocks ie. 5mm of tissue surrounding GTV. If there is not 5mm of tissue around whole GTV, tailored wax or sheet bolus should be considered in patients in whom additional bolus is required.

12.7.1 Photon plans

Treatment planning should be performed using IMRT/VMAT/HTT software. Corrections for heterogeneities should be performed. The international Commission on Radiation Units and Measurements (ICRU) report number 83 should be considered.
Maximum allowed voxel size for the dose calculation grid is 3 mm in the transversal plane. A size equal to the CT slice thickness is recommended.
During treatment planning in order to achieve the appropriate radiation dose close to the skin surface a "planning bolus" or extended fields outside the skin should be used. In order to evaluate dose homogeneity in overlapping target volumes, separate "optimizing planning volumes" may be created according to local routines. During treatment planning it must be ensured that the different CTVs are delineated as separate, not overlapping, volumes. PTVs can be replaced by robust treatment plan evaluation of the corresponding CTVs. If robust treatment plan evaluation is employed, this must be included in the QA report. The use of bolus in the inguinal region is normally required only if skin is invaded by tumour.

12.7.2 Proton plans

Proton plans can be produced as SFO/SFUD or MFO/IMPT using proton software of the Skandion clinic. The international Commission on Radiation Units and Measurements (ICRU) report number 78 should be considered. Maximum allowed voxel size for the dose calculation grid is 3 mm in the transversal plane. A size equal to the CT slice thickness is recommended. Artifacts in the tissue, such as implants, ports, teeth, clips, shunts etc. must be contoured and overridden with appropriate HU, according to the routines at the Skandion clinic. This should be done prior to optimization. When necessary, in superficial targets, a range shifter should be used. During treatment planning it must be ensured that the different CTVs are delineated as separate, not overlapping, volumes. PTVs can be replaced by robust treatment plan evaluation of the corresponding CTVs according to routines at the Skandion clinic. If robust treatment plan evaluation is employed, this must be included in the QA report. Proton plans are to be recalculated to physical dose using the RBE value 1.1.

12.8 Beam qualities

Photon beam quality is chosen to optimise the individual dose distribution but should be no less than 6MV.
Proton treatment will be delivered with pencil beam spot scanning, with beam energies up to 240 MeV.

12.9 Photon and proton beam dose calibration

In order to check the reference dosimetry of the accelerators used in the study, it is recommended that participating centres take part in external dosimetry audits.

12.10 Dose specification and fractionation

The prescribed target doses 57.5/50.5 Gy(RBE) to tumour volumes and 41.6 Gy(RBE) to adjuvant volumes) shall be given as homogeneously as possible to each target volume (see dose-volume constraints/objectives below).

Radiotherapy is given daily, 5 days/week, with 27 fractions of 2.13 Gy(RBE) (PTV_57.5), 1.87 Gy(RBE) (PTV 50.5) and 1.54 Gy(RBE) (PTV_41.6). Overall treatment time is thus optimally 37 days. Maximum allowed treatment time is 40 days.
Dose recording and reporting shall be performed as described below in the QA section.

12.11 Dose-volume constraints/objectives

Since photon plans and proton plans will not have the same dose distributions to OARs, every effort should be made to keep radiation doses as low as possible to OARs even if constraints/objectives already are met.
Objectives and constraints in the table below are grouped according to their priority in priority group 1. In priority group 2 there is no ranking between the volumes in the priority group. Group 3 is for data collection purposes and is thus not used for optimisation. The numbering in the list is for data management purposes only. For each patient, the responsible physician decides how the priority between the structures within this priority group should be employed during treatment plan optimization.

Priority	Volume	Objective (all doses given in Gy(RBE))	Constraint (all doses given in Gy(RBE))	Description
Priority group 1				
1*	PTVT_57.5, PTVN_57.5	$D_{98\%} \geq 54.6$		The "near minimum dose" to PTVs_57.5 should be equal to or higher than 54.6 Gy(RBE)
2*	PTVN_50.5	$D_{98\%} \geq 48.0$		The "near minimum dose" to PTV_50.5 should be equal to or higher than 48.0 Gy(RBE)
3*	PTVN_41.6	$D_{98\%} \geq 39.5$		The "near minimum dose" to PTV_41.6 should be equal to or higher than 39.5 Gy(RBE)
4*	PTVT_57.5, PTVN_57.5	$D_{2\%} \leq 60.4$		The "near maximum dose" to PTVs_57.5 should be equal or lower than 60.4 Gy(RBE)
5*	PTVN_50.5	$D_{2\%} \leq 53.0$		The "near maximum dose" to PTVN_50.5 should be equal or lower than 53.0 Gy(RBE)
6	BowelBag		V30 <450 cc V45 <195 cc	The volume of Bowel bag receiving 30 Gy(RBE) should be smaller than 450 cc and the volume receiving 45 Gy(RBE) should be smaller than 195 cc
7	BoneMarrow	$D_{mean} \leq 32$		The mean dose to the pelvic bone marrow should preferably not exceed 32 Gy(RBE)

8	Femoral heads	$D_{2\%}$ <52		The "near maximum dose" in one femoral head should be kept below 52 Gy(RBE)
9	Bladder	D_{mean} <45		The mean dose in the urinary bladder not included in the PTV (Bladder-PTV) should be less than 45 Gy(RBE)
Priority group 2				
10	Z_Skin	D0.1 cc ≤50		The dose to 0.1 cc of Z_skin (the skin (1-5 mm depth) outside of the CTVs volumes (including a 9 mm margin) should be equal to or less than 50 Gy(RBE)
11	Testes	D_{mean} <2		The mean dose to the testes should preferably not exceed 2 Gy(RBE)
Priority group 3 (for data collection only)				
12	Genitals			Defined for dose monitoring purposes

* Dose objectives and constraints for PTVs can be replaced by robust treatment plan evaluation of the corresponding CTVs. The geometric and dosimetric uncertainty parameters employed in the robust evaluation must correspond to the margins added when expanding from CTV to PTV.

12.12 Radiotherapy, quality assurance (RT-QA)

The purpose of the QA protocol is to ensure uniformity of all radiotherapy data for all patients. A working group will be assigned in order to collect treatment and verification data to ensure compliance to the study protocol.

Radiotherapy related treatment information and other relevant documentation for each patient shall be sent to the QA group at completion of radiotherapy (see below). Patient data stored digitally in the DICOM format, such as CT-images, dose plans, and dose distributions, should be sent to Michael Blomquist, Centrum för medicinsk teknik och strålningsfysik, Strålningsfysik, Norrlands Universitetssjukhus, Umeå, according to Ad 2.

Dummy runs, including both delineation of structures and treatment planning will be performed and there will be individual patient checks. When ten patients in each treatment arm have been included, structure delineation and dose-volume constraints/objectives will be evaluated. Quality audits may be performed.

In order to maintain the quality of the treatment, each participating centre should strive to include a minimum of 5 patients per year. If a centre includes less than 2 patients per year, this centre should be considered for closing.

12.13 Dummy run procedure

A dummy run should be performed before the start of the patient trial. CT and MR images of an anal cancer patient will be sent to participating centres from the QA group. Delineation of target volumes and OARs according to the study protocol will be performed at each centre, as well as a proton and photon treatment plan according to the study protocol. Evaluation of

target delineation and treatment plans will be performed by the QA group before the centre starts to include patients.

12.14 Individual patient checks

A detailed description how to prepare and process the data needed for the QA process is presented in Addendum 2. Additionally, the treatment plans for the first 5 patients from each centre will be reviewed at the weekly national multidisciplinary conference.

13 Quality of life and patient reported symptoms

The patient reported outcomes (PRO) will be a main source of the assessment of treatment related side effects. The patients will be asked for a written consent to take part in both the present study and the ongoing "ProtonCare"-study. The reported data will be used for evaluation of the questions specific to both studies. The data will thus be shared for dual purposes. A common patient information document will be presented for the patients in order to make it easier for the patient to understand how their personal data will be used for answering study questions.

PROs will be collected during and at the start of RT, after 3 weeks, end of treatment, 1, 3, 6, 9, 12, 24, 36 and 60 months after the termination of RT. The timing for data collecting is chosen to capture the expected maximum increase in symptom burden after treatment. All PROs will be collected by paper questionnaires.

The forms specific for the present study are the following:

- HRQoL will be investigated with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the QLQ-C30, version. This is a generic cancer-specific questionnaire covering physical, social and psychological functioning, as well as cancer-specific symptoms. The instrument consists of 30 items covering five functioning scales (*physical, role, emotional, cognitive* and *social function*), three symptom scales (*fatigue, pain and nausea/vomiting*) and two *global health/QoL* items. Six single items address additional symptoms commonly reported by cancer patients (*loss of appetite, insomnia, dyspnea, diarrhea* and *constipation*) and *financial difficulties* are also included. The QLQ-C30 will be supplemented with the disease specific module (anal-cancer) QLQ-ANL27.
- Fatigue will be measured with the Multidimensional Fatigue Inventory (MFI-20). This questionnaire consists of 20 items that assess five dimensions of fatigue based on different modes of expression: (1) general fatigue (2) physical fatigue (3) reduced activities; (4) lack of motivation; and (5) mental fatigue. A total score is calculated for each scale by summation of the individual item scores, that range from 4 to 20.
- Anxiety and depression will be measured with the Hospital Anxiety and Depression Scale (HAD).The questionnaire is a 14-item screening questionnaire, with seven items respectively relating to anxiety (HAD-A) and depression (HAD-D). Ratings are made on a four-point scale with scores ranging from 0 to 21 for each item. HAD scores are classified as follows: 0-7 = non-cases, 8-10 = doubtful cases and 11-21 = cases
- Sleep disturbance was measured with the seven-item Insomnia Severity Index (ISI). The ISI uses a five-point Likert scale to rate difficulty with sleep onset, sleep maintenance and early morning awakening, as well as interference with daytime functioning, how noticeable sleep problems are to others, distress caused by

problematic sleep and overall sleep satisfaction. Total scores range from 0 to 28, with higher scores indicating greater severity.

- EuroQol (EQ-5D) is a generic QoL instrument designed for self-administration. The result could be expressed as a weight with values between zero and one (0-1). Together with information about survival the QoL weight can be expressed as quality-adjusted life-years (QALYs). EQ-5D is a validated instrument available in many different languages. The instrument is frequently used in a variety of diagnoses in both Swedish and international studies which makes comparisons across studies and patient populations possible.
- During radiotherapy, daily reported symptoms will be investigated by a newly developed symptom scale, Radiotherapy related symptom assessment scale (RSAS). The questionnaire includes 13 items specific for current diagnose. The RSAS is a validated instrument for assessing symptom intensity and distress in patients with different cancer disease undergoing radiotherapy, with psychometric properties within the expected range. Answering categories ranges from not at all to a great deal (1-4).

14 Cost-utility analysis

A health-economic evaluation of interventions could provide important information to aid decision making in health care. The evaluation is a tool to assess the benefits and consequences and costs of different treatment options.

Since quality of life is a central issue in the present study, a cost-utility analysis is most appropriate, i.e. costs and quality of life as well as clinical outcome measured as survival time will be considered. The results of the health-economic part of the study will be expressed as cost per quality adjusted life years (QALYs) saved of one intervention in comparison with the other.

According to Swedish guidelines for health-economic studies the analysis should be performed from a societal perspective, i.e. all relevant costs irrespectively of where they occur should be identified, quantified, and valued. A societal perspective includes indirect costs, i.e. costs related to loss of production when patients cannot work due to their disease. Specifically, not only the costs of the two interventions will be assessed but all type of resources associated with the two treatment arms during the total follow-up time should be considered. That includes, e.g. costs for treatment of side-effects, costs for surgery when performed, and travelling costs for patients. Costing will be performed at the end of the study. For evaluation and analysis of the study results, a relatively simple health-economic model will be developed. This model will be used for evaluation of the two treatment arms from inclusion into the study until 5 years of follow up or death

15 Statistical plan

15.1 Sample size determination

Based on previous reports of acute side effects from photon therapy, (Mauch et al. 1995, Mell et al. 2008, Franco et al 2016), in silico planning during study preparation, and current knowledge about acute and late side effects after VMAT treatment in this patient group we assume that acute bone marrow side effects will decrease with proton therapy. The assumption is that we the conventionally treated patients will have at least 50% risk of grade 3 or higher haematological toxicity. With proton therapy the corresponding toxicity is assumed to be reduced to 20%. If these proportions are assumed, based on Fishers exact test with two-

sided level of significance of 0.05 and an allocation of 1:1 between control and interventions groups, 100 randomised and evaluable patients will give the statistical power of 0.85. It is assumed that a proportion of patients will be unevaluable due to e.g. withdrawal of consent or inability to complete the treatment. For that reason a maximum number of 120 patients will be randomised. If 100 evaluable patients complete the treatment before 120 are randomised, the randomisation will close.

The statistical power may potentially be increase for several secondary end points when combinations of side effects and patient reported outcomes are taken into consideration. Other end points (e.g. bowel, skin or urinary side effects) are less studied and the magnitude of the effects are less predictable. However, it is planned to investigate possible shifts in the distribution of side-effect grades between the two treatments, which may strengthen the inference.

15.2 Statistical methods

Stratification will be made for sex, HPV/p16 positivity and colostomy before treatment start. Primary end points will be analysed using the Fishers exact test for inference of proportions. Shifts in distributions of side effects will be analysed by using the Mann-Whitney U-test, in this test the stratification is not used. For efficacy analysis, survival curves will be computed using both the Kaplan-Meier and the Breslow method. Cumulative incidence of failure of locoregional control together with mortality will be performed. Cox regression analysis adjusted for all eligible covariates will be applied for efficacy analyses. For failure of locoregional control, Fine-Gray regression will also be considered. . Baseline data will be tabulated and illustrated graphically if appropriate.

The analyses will be based on received treatment and will include eligible patients, but analyses will also be performed on the intention-to-treat analysis set (see below). Every effort will be made to collect survival data on subjects, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. OS is defined for each patient as the time between randomization date and death. If a patient has not expired, the patient will be censored at the time of last contact (last known alive date). Loco-regional failure will also be analysed by methods accounting for death as acompeting risk. DFS is defined for each patient as the time between randomisation and the time of first recurrence, locoregional, systemic or death. If a patient has residual disease after treatment, the time of recurrence will be defined as end of radiotherapy.

The analyses will be made according to stratification and/or a combination of stratification and other adjustments.

15.3 Subject populations(s) for analysis

Intention to treat population: All correctly randomised and included patients.
Protocol-compliant population: Patients that have started the assigned study treatment .

16 Reporting of adverse events

16.1 Definition

Safety will be reported as adverse events as per ICH-GCP.
An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product (or receiving a treatment) and

which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (such as rash), symptom (such as nausea or pain), laboratory finding, or disease temporally associated with the use of a medicinal (investigational) product (or a treatment), whether or not related to the medicinal (investigational) product.
A Serious Adverse Event (SAE) is an adverse event that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

16.2 Reporting procedure

Side effects related to given treatment should be reported and graded according to CTCAE v5.0 using CTC terminology and noted in the eCRF. Adverse events clearly associated to disease progression should not be reported as AE, however, if there is any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported.

Hospitalization due to investigations or planned surgical procedures should not be classified as SAEs. Hospitalization due to pain, GI symptoms, need of nutritional support or infections, which is regarded as expected and common side effects during chemo and radiotherapy of AC patients, should not be classified as SAEs.

- All SAEs during the study must be reported to the sponsor within 24 hours after notification by the study personnel using provided SAE-forms
- SAEs will be reported until 30 days after completion of radiotherapy.

17 Quality assurance

For quality assurance of radiotherapy, see above.

17.1 Control of data consistency

All patients included in the study are identified by the patient identification number. Identification code lists that links patients' names to the patients' identification number must be stored in the Investigator File.
Study data will be recorded via electronic Case Report Forms (eCRF). Study data may be recorded directly into the eCRF, i.e. the eCRF may be the source data, or be transcribed by the site from the paper source documents onto the eCRF according to the local source-data list. Prior to study start, the Investigator and the Monitor must identify and document the expected source location of every CRF data. Expected source locations are for example the subject's medical record, laboratory reports and the CRF itself.
Accurate and reliable data collection will be assured by verification of the eCRF against the investigator's records and medical records by a study monitor, as well as study integrity, compliance with the protocol and applicable regulations.

17.2 Site monitoring

In consistency with the principles of ICH-GCP, the sponsor takes responsibility for monitoring of the study. As external monitor for the study each treatment centre will appoint a research nurse, or equivalent, not involved in any aspects of the study. The external monitor

should be experienced in clinical trials and monitoring. The site monitoring reports will be sent to the Data Centre for further evaluation.
During the study, there will be regular contacts with the study sites, including on-site visits in order to ensure that the study is conducted and documented properly in compliance with the protocol, ICH-GCP and applicable regulatory requirements.
The trial will be monitored consistent with the demands of the trial and site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP and all applicable regulatory requirements.

17.3 Legal aspects

Investigators of participating centres agree to co-operate with any quality assurance visit undertaken by third parties.
The study will be performed according to ICH-GCP guidelines and after approval of the Swedish Ethical Review Authority. Changes in the protocol must be communicated with the Swedish Ethical Review Authority.

17.4 Direct access to data/documents

The sponsor has the responsibility to maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Investigators files and subjects clinical source documents must be kept for at least 10 years after completion or discontinuation of the study.

18 Data management

18.1 Patient registration/randomisation procedure

Subject eligibility will be established before treatment randomisation. Subjects will be randomised strictly sequentially, as subjects are eligible for enrolment/randomisation.
If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.
The randomisation list will be created by an independent statistician at RCC Norr. When a patient is found to be eligible and has signed a written informed consent, randomisation will be performed electronically.

18.2 Case report forms

Study data will be recorded via the eCRF. During study treatment the eCRF should be filled in weekly, and after completion of treatment the eCRF should be filled in at each time point for follow-up.
The investigator at the enrolling site is responsible for collection of source data if patient visits are decentralized to other clinics.

18.3 Quality of life forms and Questionnaires

Questionnaires will be administered to the subjects as described in sections above. The questionnaires will be sent directly to the subjects or to the participating centres by the Proton Care Study group in order to be forwarded to the patient. The questionnaires will be enclosed with postage-paid, pre-addressed envelopes to be returned by the patient directly to the Proton

Care study group. Proton Care are responsible for entering the answers of the questionnaires into their specific data base.

19 Ethical considerations

19.1 Patient protection

The study is to be performed in accordance with the ethical recommendations of the Helsinki declaration and the ICH-GCP guidelines, or the laws and regulations of the country, whichever provides the greatest protection of the patient.

19.2 Patient integrity

The investigator must assure that the patient's anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents collected in this study patients will only be identified by their identification code, year and date of birth.

19.3 Informed consent

All subjects will receive written and oral information about the aims of the study, possible hazards, and the mechanism of treatment allocation. They will be informed about the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.
It will be emphasized that the participation is voluntary and that the patient is allowed to decline further participation whenever he/she wants. If the patient wishes to withdraw from the study, he or she will be offered the standard treatment at the clinic.
A signed, informed consent must be obtained from the patient before study entry. In the cases were the patient declines to participate in the study the conventional treatment according to local practice should be offered.
If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

19.4 Independent ethical review

This protocol and any accompanying material provided to the patient, such as written patient information used to obtain informed consent, will be submitted by the investigator to the Swedish Ethical Review Authority. Approval from the authority must be obtained before starting the study and should be documented in a letter to the investigator specifying the date on which the authority granted the approval.

19.5 Risk benefit analysis

Patients with AC have a good prognosis with standard treatment consisting of radiotherapy delivered with photons combined with chemotherapy. Proton therapy has been performed for more than 20 years in many countries, and although there are no studies directly comparing photon and proton treatment in this patient group, there are no indications that treatment results should be inferior with proton therapy. In silico studies suggest that side effects will be reduced with proton therapy.
Benefit for patients included in the study is thorough surveillance during and after treatment and guarantee of high-quality radiotherapy. Benefit for the patient group is enhanced knowledge about the treatments in the study.
The Skandion clinic is situated in Uppsala, which means that some patients receiving proton therapy will have to travel longer distances and spend more time away from home during

their treatment period. However, this is often the case for patients not included in this study since AC therapy is centralised to four Swedish hospitals. Travelling expenses for the patients will be reimbursed according to the routines at each treatment centre.
The patients in the study are covered by the Swedish Patient Insurance.

20 Participating centres

The four Swedish hospitals engaged in the treatment of AC patients will be invited to take part in the study.
Each centre must expect to include a minimum of 5 patients per year. If a centre includes less than 2 patients per year, that centre should be considered for closing. Previously included patients will then be followed according to the protocol, but no further inclusion is accepted from that centre.
Centres from other European countries may be accepted as participants in the study as decided by the study group.

21 Ownership of data

The data are owned by the Study Group consisting of the investigators at the participating centres. The patient material of the individual centre cannot be extracted for publications to answer the questions of this study. Future research projects utilising data from the present study must be approved by the Study Group.
Data collected using questionnaires by ProtonCare is regulated per a separate agreement. ProtonCare remains responsible for safe keeping the data collected under their supervision. The agreement regulates data sharing between the Study Group and ProtonCare during and after this study

21.1 Meetings

Regular meetings with representatives from all participating centres (Study Group) will be held once per year or when considered necessary. The Study Steering Committee will also have separate regular meetings. In the time between Study Group meetings, the members of the Study Steering Committee shall act as contact persons and will have an executive role. Decisions taken shall be discussed at the meetings of the Study Group. The Study Steering Committee shall prepare and arrange the meetings of the Study Group.
The Study Group will invite a pre-selected member from the Proton Care study Group at each meeting as regulated in a separate agreement.

21.2 Reporting

All presentations of data from the study should only be made after agreement within the Study Group. The results of the study will be submitted to an internationally recognized scientific medical journal. Apart from the Study Group, each participating centre with at least 10 patients included will be guaranteed co-authorship for one person. In addition to this, persons with special responsibilities within the study may become co-authors. The Vancouver declaration will be followed in all publications based on this study. See also separate agreement between the Study Group and Proton Care study group regarding data responsibilities and publication rights.

22 Flow chart of study procedures

Flow chart for patient reported data is presented in Addendum 5

	Baseline	Weekly during RT and at treatment completion	1, 2 and 3 w After treatment	1-2 months after treatment	4-6 months after treatment	Every 3 months for 2 years	Every 6 months until 5 years	End of study at 5 year or prematurely
Physical examination (physician/registered nurse)	X	X		X	X	X	X	X
Medical History	X							
Performance status (ECOG)	X			X	X	X		X
Length, weight	X	weight		weight	weight	weight	weight	weight
Biopsy including p16 analysis	X							
Haematology (Hb, WBC differential, ANC, platelets)	X	X	X *	X	X	As needed		
Blood Chemistry (Bilirubin, ALP, ALAT, ASAT, creatinine, Na, K, Ca, albumin and Mg)	X	X**		X	X			
Informed consent	X							
Randomization	X							
Side effects and adverse events	X	X		X	X	X	X	X
*** Photography (optional)	X	X		X				
Tumour control (including measures if applicable)					X	X	X	X
Biopsy + MRI+PET/CT if recurrence					X	X	X	X
Questionnaires	According to Addendum 5							

* Blood samples to be taken once weekly up to 3 weeks.

** Only week 4

*** Photography only for local use as reference, to be stored in patient clinical records.

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Addendum 1 - Organs at risk

The following organs at risk must always be delineated:

- Urinary bladder
- Intestine (operationalised by the volume named "Bowel bag")
- Skin
- Z_Skin
- Pelvic bone marrow
- Femoral heads
- Genitals

Delineation Guidelines

Urinary bladder	The outer wall of the bladder is contoured as it appears on treatment-planning CT
Bowel bag	The bowel bag is contoured superiorly from 1.5 above the most superior part of the PTV. Anteriorly to the inside of the abdominal wall. Laterally, it is delineated from bowel edge to bowel edge. The posterior limit is the most posterior bowel edge. The most inferior limit includes the most inferior bowel that is not rectum or rectosigmoid junction (Devisetty et al. 2009)
Skin	The skin should be delineated from 1 to 5 mm depth inside the patient (structure Body), i.e. have a thickness of 4 mm, and cover at least all the irradiated patient surface.
Z_Skin	should be based on the Skin structure, but exclude all intersecting CTV volumes, including and margin of 9 mm.
Pelvic bone marrow	The external contour of the PBM is delineated on the planning CT using bone windows. Pelvic BM is divided into three subsites: (*1*) iliac BM (IBM), extending from the iliac crests to the superior border of the femoral head, (*2*) lower pelvis (LP), consisting of the pubes, ischia, acetabula, and proximal femora, extending from the superior border of the femoral heads to the inferior border of the ischial tuberosities, and (*3*) lumbosacral spine (LS), extending from the superior border of the L5 vertebral body to the coccyx but not extending below the superior border of the femoral head. (Mell et al.2008).
Femoral heads	Femoral heads as they appear on CT
Genitals	Males: Penis and testes. Penis and testes are defined separately (since testes have a dose restriction) Females: Clitoris, major and minor labiae defined as a single volume.

Addendum 2 - Radiotherapy QA reporting

Radiotherapy related data should be collected and reported by each centre for every patient and transferred to the QA-centre. The data transfer is handled through the Sharefile service provided by Skandionkliniken (https://skandionibasa.sharefile.eu/). Each participating centre has access to a Sharefile folder named "SWANCA NNN", where NNN is the name of the centre.

Sharefile reporting

For each patient a subdirectory to "SWANCA XX" should be created and named "XX-YYY", where XX-YYY is the patient number (XX identifies each participating centre and YYY is a running patient number).

- From the TPS, DICOM export and save under the directory "XX-YYY":
  - CT-images
  - Structures
  - Treatment plan
  - Total dose distribution (in Gy) in DICOM-RT format
  - co-registered MR or PET images, when applicable
- Create a document (Word, Excel, Text or pdf) stating the date of the first and the last treatment fraction. Name the file "XX-YYY history" and save it under the directory "XX-YYY".

Data to RT-QA office

Notify the RT-QA office that patient data has been uploaded by sending an e-mail to or call:
Michael Blomquist, Medical physicist
E-mail: michael.blomquist@regionvasterbotten.se

Phone: +46 (0)90 785 8460

Addendum 3 - Dosreduktionsschema för radio-kemoterapi av analcancer från Akademiska sjukhuset, Uppsala

Dosreduktion Mitomycin ej aktuellt inför Dag 1.

Dosreduktion Capecitabin:
Tox grad
0 Neutrofila >= 2.0 TPK >= 100 ges Capecitabin 100%
1 Neutrofila >= 1.5-< 2.0 TPK >= 75-< 100 ges Capecitabin 100%
2 Neutrofila >= 1.0-< 1.5 TPK >= 50-< 75 ges Capecitabin 75%
3 Neutrofila >= 0.5-< 1.0 TPK >= 10-< 50 Uppehåll tills återhämtning
4 Neutrofila < 0.5 TPK <10 Uppehåll tills återhämtning
Dosreduktion för patienter med sänkt kreaclearence <50 ml/min enl. FASS.

Dosreduktion Diarreér:

Tox grad 0,
Ingen diarré, och ingen ökning av avf.frekvens, ges Capecitabin 100%, Strålbehandling- Fortsätt

Tox grad 1,
< 4 avföringar per dag, ges Capecitabin 100%, Strålbehandling- Fortsätt

Tox grad 2,
4-6 avföringar per dag, eller måttliga kramper , Strålbehandling- Fortsätt (1,2,och 3;e gången) och administrera Loperamid
Uppehåll tills grad <= 1, sen
1 gången: ges Capecitabin 100%
2 gången: ges Capecitabin 75%
3 gången: ges Capecitabin 50%

Tox grad 3
7-9 avföringar per dag eller inkontinens (om pat var kontinent före beh), eller svåra kramper
Uppehåll tills grad <= 1, sen
Strålbehandling- Uppehåll tills diarrén är grad <= 2
1 gången: ges Capecitabin 75%
2 gången: ges Capecitabin 50%

Tox grad4
>=10 avföringar per dag, eller melena eller behov av parenteral support.- Avbryt Capecitabinbeh.
Strålbehandling- Avbryt tills diarrén är <= grad 2 (om det tar > 2 veckor ska strålbeh. avbrytas permanent)

Addendum 4 – Photography

The perineal area should, if possible, be documented by a digital photo weekly during radiotherapy and further at the scheduled physical examinations thereafter. The purpose is to document the external tumour component and the skin reaction in short and long terms.

1. The choice of camera is free but it should, if practically possible, be the same camera for all patients at the same clinic.
2. A ruler should be included in the images
3. The images are stored in the patient's clinical records.

Addendum 5 - Flow chart of Patient Reported Data

Questionnaire	Baseline – prior RT treatment start	Daily during RT treatment	3 w - after RT treatment start	End of treatment	1 month	3 months	6 months	9 months	12 months	24 months	36 months	60 months
QLQ-C30	X		X	X	X	X	X	X	X	X	X	X
QLQ – ANL27	X		X	X	X	X	X	X	X	X	X	X
MFI-20	X		X	X	X	X	X	X	X	X	X	X
HAD	X		X	X	X	X	X	X	X	X	X	X
ISI	X		X	X	X	X	X	X	X	X	X	X
EQ5D	X		X	X	X	X	X	X	X	X	X	X
RSAS		X										

RT = Radiation Therapy
w = weeks
EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-ANL27= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (diagnos specific)
MFI-20 = Multidimensional Fatigue Inventory
ISI = Insomnia Severity Index
HAD = Hospital Anxeity and Despression Scale
EQ5D = EuroQol
RSAS = Radiotherapy Related Symptoms Assessment Scale

Addendum 6 – Skin Care Guidelines

Below information is an excerpt from addendum 5 and 6 from the document "Analcancer – Specific Omvårdnad vid strålbehandling" version 1.0 date 1880409 issued by Skånes Universitetssjukhus, VO Hematologi, onkologi, och strålningsfysik.

The text below is intended to serve as a guideline in caring for radiated skin in the study.

Bilaga 5: Användning av barriärservetter

Egenskap
Servetterna behandlar och skyddar med Dimethicone (silikon), är allergivänliga och ger en transparant skyddsbarriär som andas.
Servetterna underlättar rengöring och ersätter andra produkter o moment dvs. inga tvättlappar, tvål, lotion mm.

Barriärservetter ger ett allt-i ett skydd som förebygger och lindrar hudirritation.
Servetterna kan delas i 4 delar första tiden och längre fram brukar patienten själv ha en uppfattning vilken storlek som passar bäst. Servetten kan även klippas till och läggas i hudveck och mellan hud och kläder för undvika skav.

Används vid varje toalettbesök och i början efter mjukt toapapper men när huden är ansträngd direkt och utan toapapper först.
Undvik tvätta med vatten då det är uttorkande. Man kan vid behov skölja behandlingsområdet max 1 gång/dag med vatten/NaCl.

Hudstatus, slemhinna och yttre genitalier görs i början 1 gång i veckan och vid mer besvär tätare. Servetterna ger en tunn hinna och är steg 1 behandling. Vid ökade besvär finns Barriärsalva som Steg 2. Steg 3 är Cavilon spray eller att man penslar på samma substans för att få lite mer barriär. Servetterna används fortsatt för att rengöra och lägga ett basskydd.

Bilaga 6: Gemensamma riktlinjer slemhinna GI & Gyn

Gemensamma riktlinjer GI & Gyn: hud och slemhinna vid RT

	GI	Gyn
Mottagningsbesök	Kontaktssk vid cytbeh Onkmott2 vb Slutsamtal	2 v efter RT start gynmott, 1ggr/v & vb Slutsamtal
	GI & Gyn	**Gynmott**
Information/följs under RT Hud/slemhinna Nutrition kostråd (vikt/kg) Illamående Elimination Ev. dietist Smärta (VAS 0-10) RTOG bedömning/åtgärd Recept-kit gyn/GI	• Undvika vatten hud/ slemhinna. Skölj med vatten max 1 ggr/dag • Hålla rent • Lufta • Undvika skav • Servetter: Tvättservett Cavilon 3M • Senare: barriär kräm Chiron • Vb smärtlindrande (lokalt och per os) Dokumentation Melior: • RTOG bedömning/åtgärd hud/slemhinna • Nutrition kostråd (vikt/kg) • Illamående • Elimination • Ev. dietist • Smärta (VAS 0-10) • Recept-"kit" gyn/GI	
Prevention Hud/slemhinna	• Undvika vatten hud/ slemhinna. Skölj med vatten max 1 ggr/dag • Hålla rent • Servetter: Tvättservett Cavilon 3M • Lufta	
Hud/slemhinna RTOG 0 -1 opåverkad/rodnad hel hud	• Undvika vatten hud/ slemhimma –risk för att torka ut • Hålla rent • Lufta • Servetter: Tvättservett Cavilon 3M • Hud/slemhinna: Dokumentation melior: RTOG bedömning/åtgärd	
Hud/slemhinna RTOG 2-3 fläckvis sårighet/ sammanflytande sårighet	• Vatten/NaCl-skölja rent max 1 ggr/dag • Servetter: Tvättservett Cavilon 3M kan läggas i hudveck (ljumskar, klinkor) för att undvika skav. • Lufta dagligen • Smörj med barriär kräm Chiron Barrier Cream+ vb Xylocain gel eller morfin gel. Morfin gel enbart på öppna sår för bäst effekt. • Komplettera med smärtlindrande per os – recept, RTOG 3 (narkotika) • Hud/slemhinna: Dokumentation melior: RTOG bedömning/åtgärd • Smärta: Dokumentation melior VAS 0-10	
Hud/slemhinna RTOG 4 Sår, blödning, nekroser	• Ev inneliggande patient • NaCl-skölja rent max 1 ggr/dag • Daglig omläggning • Servetter: Tvättservett Cavilon 3M kan läggas i hudveck (ljumskar, klinkor) för att undvika skav. • Lufta dagligen • Smörj med barriär kräm Chiron Barrier Cream + vb Xylocain gel eller	

Addendum 7 – Skandion Patient position and immobilisation

Skandionkliniken

20140701

Fixationsmall Bäcken

UserOrigin i lasermarkering i patienten

Observera att Skandions fixeringsrutiner inte tillåter någon madrass under patienten.

Dessa fixationer kan fästas i bordet med indexeringspinne (Lock-bar) och positionerna anges i mallen.

Indexering Bord: Klicka här för att ange text.

Nackkudde Civco: Välj ett objekt.

Civco Kneefix 3: ☐

Civco Elevation Block: ☐

Civco Feetfix 3: ☐

Scanflex Armstrap: Armstrap 60: ☐ Armstrap 70: ☐

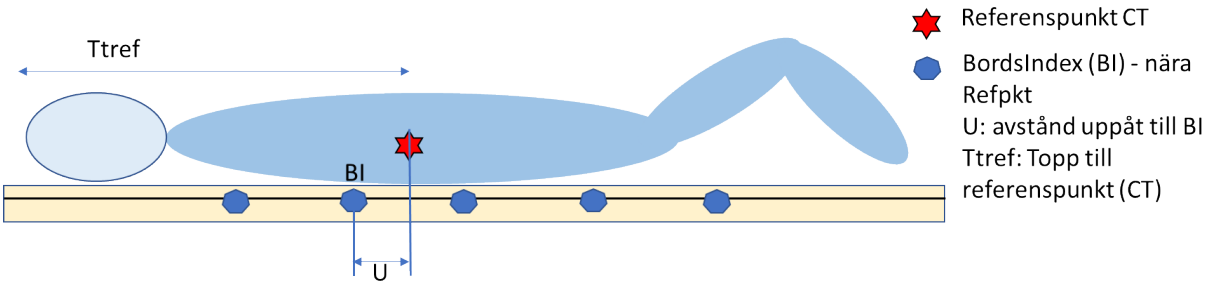
Civco Rectangle: ☐

Civco Head Support: ☐

Övriga upplysningar: Klicka här för att ange text.

OBS Nyhet 2020-02-12
Information om position av referenspunkt - se nästa sida!

Positioner som anges nedan underlättar bedömning av behov av bordsförlängning samt gör andra simuleringar av behandlingen möjliga innan patienten kommer till Skandionkliniken.



Ange:

Ttref (cm): Klicka här för att ange text.

BI (ovanför Refpunkt (CT)): Klicka här för att ange text.

U (cm): Klicka här för att ange text.