DAHANCA 35

A national randomized trial of proton versus photon radiotherapy for
the treatment of head-neck cancer

Version 1.10
26/03/2019
# Indhold

- Study organisation ............................................. 3
- Introduction ......................................................... 4
- Background ............................................................ 4
  - Morbidity of head and neck cancer radiotherapy .................. 5
  - Highly conformal radiotherapy ...................................... 6
  - Proton therapy .......................................................... 6
  - Normal Tissue Complication Probability (NTCP) modelling ............. 7
- Aims ................................................................. 7
  - Primary endpoints ...................................................... 8
  - Secondary endpoints ................................................... 8
- Study design .......................................................... 9
  - Type of randomization ................................................. 9
  - Selection Criteria ...................................................... 9
  - Statistical considerations ............................................. 10
  - Interim report .......................................................... 11
  - Data collection and management ..................................... 11
  - Inclusion ............................................................ 11
  - Randomisation .......................................................... 12
  - Treatment details ....................................................... 12
- Radiotherapy Quality Assurance (QA) ...................... 13
- Patient recruitment and clinical investigations prior to treatment ......................................................... 14
- Pilot phase .............................................................. 15
- Translational studies .............................................. 15
- Health economics study ............................................. 15
- Timetable ............................................................... 15
- Side effects ............................................................. 16
- Radiation safety ......................................................... 17
- Publication of results ................................................ 17

- Ethical account ......................................................... 17
- Guidelines for participant information and written informed consent ....................... 18
- Informed Consent ......................................................... 18
- Financial plan ............................................................. 19
- Reimbursements to the patients ........................................ 19
- Abbreviations .............................................................. 20
- References ............................................................... 22
- Appendices .............................................................. 26
Study organisation

DAHANCA secretariat
Department of Experimental Oncology
Aarhus University Hospital
Palle Juul-Jensens Blvd. 99, 8200 Aarhus
Denmark
Tel +45 78462620,
Fax +45 86197109

Radiotherapy Quality Assurance
DAHANCA QA group/
Cai Grau professor
Christian Rønn Hansen physicist

Primary investigator
Jeppe Friborg MD
The Danish Center for Particle Therapy
Aarhus University Hospital
and
Department of Clinical Oncology
Rigshospitalet
Blegdamsvej 9, 2100 Copenhagen
Denmark
Tel +4535458189
Email jeppe.friborg@regionh.dk

Translational co-chair
Jens Overgaard MD, Professor
Department of Experimental Oncology
Aarhus University Hospital

Participating departments (local investigators)

The Danish Center for Particle Therapy
Aarhus University Hospital
Kenneth Jensen MD
Christian Rønn Hansen physicist

Department of Oncology
Herlev University Hospital
Elo Andersen MD
Eva Samsøe physicist

Department of Oncology
Aalborg University Hospital
Maria Andersen MD
Martin Nielsen physicist

Department of Oncology
Zealand University Hospital Næstved
Mohammad Farhadi MD

Department of Oncology
Odense University Hospital
Jørgen Johansen MD
Christian Rønn Hansen physicist

Department of Clinical Oncology
Rigshospitalet
Bob Smudlers physicist

Department of Oncology
Aarhus University Hospital
Jesper Eriksen MD, Professor
Jørgen Petersen physicist
Introduction
Radiotherapy is, together with surgery, the primary treatment of head-neck cancer, and approximately 75% of patients are estimated to benefit from irradiation as part of their initial treatment. Radiotherapy represents a compromise between the desire to deliver a high dose to the tumor while sparing the adjacent normal tissue. Current therapy is effective but inflicts a significant burden of symptoms that can have profound implications for quality of life. Proton therapy represents the latest development in radiation therapy, and the past decade has seen a steady increase in centers worldwide. Due to the specific energy deposition of protons, it offers a theoretical advantage compared to photon therapy, especially considering sparing of normal tissue and reducing morbidity. This advantage is especially important in the head-neck area, where an abundance of critical organs limits the therapeutic window. The efficacy of proton therapy in reducing side effects of head-neck cancer treatment has been documented in planning studies and several phase one trials; however, given the physical properties of the beam, proton treatment is more sensitive to set-up errors, changes in anatomy and organ motion, resulting in potentially significant dosimetric and biological uncertainties. It therefore remains unknown whether the expected benefit can be reproduced in a clinical setting, and as proton therapy also comes at a substantial financial cost, and with frequent inconveniences for the patient as treatment is only available at one institution in Denmark, the benefit needs to be verified in clinical trials. As the prediction models supporting the benefit of proton therapy are associated with a significant degree of uncertainty a randomized trial constitutes the best design.

The Danish Center for Particle Therapy (DCPT) will open in January 2019, providing Denmark with an excellent opportunity to initiate the much-needed trials and clarify the value of proton therapy. We therefore propose a national prospective randomized trial to test whether proton therapy reduces the morbidity of head-neck cancer radiotherapy. The trial will have the following objectives:

1) To test whether proton therapy reduces the prevalence and severity of xerostomia and dysphagia compared to photon therapy (primary endpoints)
2) To compare additional acute toxicity, late toxicity and QoL associated with both treatments (secondary endpoints)
3) To examine loco-regional control and overall survival for both treatments (secondary endpoints)
4) To validate existing normal tissue complication probability (NTCP) models for identification of patients with potential benefit from more conformal radiation techniques.
5) To examine the economic consequences of proton therapy

Background
Cancer of the head and neck is a frequent malignancy associated with significant mortality and morbidity. Overall incidence rates in Denmark and worldwide are increasing [1, 2] with
approximately 1200 new patients diagnosed per year in Denmark [3]. Predominantly squamous cell carcinomas, head-neck cancers are characterized by a tendency to early regional, but late distant spread and treatment of head-neck cancer has therefore traditionally been delivered with aggressive loco-regional surgery and radiotherapy as the primary treatment modalities. Tumors of the pharynx and larynx, which constitutes the majority of cases, are almost exclusively treated with primary radiotherapy, as surgery at these sites is associated with a risk of unacceptable morbidity.

As a result of successive randomized clinical trials, the intensity of radiotherapy has increased stepwise since the 1970ties, with corresponding gains in local control [4-6]. While local control rates are approaching an impressive 70%, the treatment is associated with significant short- and long-term side-effects, among these dysphagia, xerostomia, weight loss and fatigue [7]. This has brought an increased focus on efforts to decrease morbidity while maintaining efficacy [8].

Within the last decade human papilloma virus (HPV) has evolved as a risk factor for head-neck carcinoma, especially in the oropharynx, and HPV-positive oropharynx cancer now constitutes >30% of all HNSCC, with incidence rates expected to increase significantly the coming decades [9]. HPV-positive oropharynx cancer patients are generally characterized by having a good performance status with minimal co-morbidity and superior overall survival and loco-regional control compared to HPV-negative patients [10, 11]. This translates into a steep increase in numbers of survivors, many of them younger, emphasizing the importance of minimizing long-term morbidity [12].

**Morbidity of head and neck cancer radiotherapy**

Radiotherapy induced morbidity can be divided into acute or long-term toxicity, depending on the latency from irradiation to clinical signs of injury. The degree of acute toxicity is often treatment limiting and is characterized by the epithelial reactions such as mucositis and dermatitis, resulting in significant dysphagia and pain, which resolves within weeks to months after treatment. Severe dysphagia, defined as liquid food only or worse occurs in 40-50% of patients during conventional radiotherapy, but increases up to 70-80% in combined chemo-radiotherapy, with two-thirds of patients in need of a feeding tube during treatment [13, 14]. The degree of mucositis is directly associated to the radiation dose, and steps towards reducing dose or irradiated volumes will reduce the acute toxicity [15].

Long-term morbidity is characterised by damage to slowly proliferating tissue such as muscles, nerves and glands, and develops gradually months to years after treatment, often resulting in permanent dysfunction. The most frequent complaints are xerostomia and dysphagia. The degree of xerostomia is correlated with dose to the salivary glands, and randomised trials have verified the value of lowering doses to the salivary structures [16, 17]. The severity of dysphagia ranges from mild grades to severe dysphagia with need for permanent feeding tubes and a significant impact on quality of life. Persistent dysphagia of any degree is found in 25% after radiotherapy alone [18], and late severe dysphagia have been reported in up to 30% after chemo-radiotherapy [19]. The condition is potentially debilitating, as some patients require life-long feeding tubes and have an increased risk of aspiration pneumonia. Detailed work by several groups have revealed that the pharyngeal constrictor muscles constitute, organs at risk, and that the risk of dysphagia is closely associated with dose to these structures [20-23], leading to predictive models for swallowing dysfunction following head-neck cancer radiation [24, 25]. The effect of lowering dose
to swallowing structures on the risk of dysphagia has been confirmed in observational studies [26]. The significance of dysphagia and xerostomia is also reflected in the quality-of-life experience post-treatment [27-29], emphasizing the importance of minimizing the risk.

Highly conformal radiotherapy

Over the past few decades head-neck radiotherapy has evolved from 2D-planning to a highly conformal treatment on linear accelerators [30]. In parallel with the development in treatment delivery, planning systems and set-up verification have co-evolved and the result has been a reduction in side effects of the treatment while maintaining or improving treatment efficacy for most patients. The value of Intensity-Modulated Radiotherapy (IMRT) has specifically been in lowering dose to normal organs with a reduction in the prevalence of xerostomia as the most evident outcome. Early results from patient series from many institutions verified the safety of IMRT and documented the reduction in morbidity [21, 31-40], but these results were not reproduced in randomised controlled trials (RCTs) until very late when three studies corroborated the results [17, 41, 42]. The randomised trials also elucidated unknown side effects not identified in earlier phase one/two trials, e.g. the detection of an association between treatment-related fatigue and the extended low-dose area in IMRT [43], underlining the importance of randomised trials in the assessment of new technology.

Despite the development, IMRT is still limited by the physical properties of the photon beam and although conformity has increased, a significant amount of normal tissue is irradiated, and toxicities remain a serious concern.

Proton therapy

Proton therapy for clinical use has been known for decades [44], but only recently, the development in technology and beam delivery has enabled the technology to become more accessible. Although the number of proton centers worldwide is rapidly increasing, it remains a very large investment and is significantly more expensive than photon therapy per treatment fraction.

The specific energy deposition of the proton is responsible for the advantages of proton therapy. While photons deposits maximum dose just beneath the skin with an exponential fall-off in dose throughout the body, protons deposits maximum dose in a sharp point (The Bragg peak) with negligible dose to tissues beyond that point. By modulating beam energy, the Bragg peak can be spread out to produce a highly conformal radiation plan with very little dose beyond the target structures. Numerous dosimetry (planning) studies covering most tumor sites have shown a theoretical benefit of proton therapy over photon technologies, particularly regarding normal tissue sparing [45-48].

Although the theoretical advantage seems clear, several aspects of proton therapy may limit the clinical value. The relative biological effectiveness (RBE) of protons compared to photons is not precisely known, and the uncertainty, especially at the end of the Bragg peak, may influence the clinical outcome [49]. The very confined area of proton dose deposition also means that even small anatomical changes, target movement, set-up errors and physical proton stopping power
estimate may have significant influence on target coverage and subsequent treatment result [50, 51]. These potential pitfalls are especially important in the treatment of head-neck cancer, due to the close proximity of many critical organs, including the spinal cord, brain, salivary glands, constrictor muscles, larynx and optic structures.

While tumors of the pharynx and larynx constitute the majority of head-neck cancers most of the clinical experience in proton treatment has been in tumors close to the skull base or salivary gland carcinomas. In a review from 2014 only 1 of 18 clinical studies contained data from the pharynx or larynx [45]. Slater et al described 29 oropharyngeal cancer patients treated with photons and a supplementary proton boost to achieve a high dose, leading to good local control rates without increased toxicity [52]. Later studies have focused on reducing toxicity, and a reduction in both acute and long-term toxicity, while maintaining very high local control rates, were seen in 50 patients treated with protons for oropharyngeal carcinoma [53]. However, 98% of patients in that study were HPV-positive indicating a highly selected group, with a much better prognosis, than the average head-neck cancer patients in an ordinary (Danish) clinic. Compared to photon IMRT at the same center, proton therapy seemed to be associated with reduced rates of feeding tube dependency and severe weight loss [54], however, the burden of symptoms measured by patients reported outcome (PRO) did not show any clear difference between modalities [55].

With substantial experimental data, but only two observational studies supporting the benefit, randomized prospective studies are needed to establish the value of proton therapy in the treatment of the most commons forms of head-neck cancer. The risk of only marginal clinical benefit combined with the uncertainties of target coverage, makes high-quality clinical studies a necessary step in establishing evidence-based guidelines for proton treatment.

Normal Tissue Complication Probability (NTCP) modelling

Only patients with an expected benefit of proton therapy on the risk of dysphagia and xerostomia can participate in the study. The selection of patients with an expected benefit of proton treatment is performed using an NTCP model based on comparison of proton and photon dose plans for the individual patient. NTCP models often result from multivariate analysis of large datasets containing information on radiation dose to organs and morbidity and can be used to predict the risk of a side effect or complication. To select patients, we will use published NTCP models on dysphagia [24] and xerostomia [56]. If updated models with an increased ability to identify patients at risk of these endpoints become available later, these can be used to select patients for the study. However, the endpoints will remain the same.

A randomised prospective study, like the proposed, will also enable formal testing of the generalizability of other NTCP models from photon to proton therapy and thereby support the demonstration of clinical utility of such model-based selection of treatment modality.

Aims

The primary aim is to investigate whether the prevalence of

1) Observer-rated dysphagia >= grade 2 (grade 2-4) measured by the DAHANCA late toxicity score
2) Patient-rated xerostomia >= moderate xerostomia (moderate-severe) patient rated xerostomia (EORTC HN 35 questionnaire)
can be reduced by proton radiotherapy compared to photon radiotherapy in the treatment of squamous cell carcinoma of the head-neck.

**Primary endpoints**
Primary endpoints will consist of observer-reported dysphagia measured by the DAHANCA late toxicity score (assessed at 6 months) and patient-reported xerostomia measured by the EORTC HN 35 questionnaire (assessed at 6 months).

**Secondary endpoints**
QoL: HN35 swallowing and social-eating scale and specific HN35 items related to eating and pain, and specific C30 items related to fatigue, nausea and vomiting.

Acute toxicity: DAHANCA toxicity scoring (see appendix)

Late toxicity: DAHANCA toxicity scoring (see appendix), stimulated whole mouth salivary flow and swallowing test (Modified Barium Swallowing). Observer-rated dysphagia and patient-rated xerostomia at 12 months.

Secondary endpoints will also include loco-regional tumor control, disease-specific survival and overall survival.

1. Loco-regional tumor control will be measured from date of randomisation to the first documented loco-regional failure. The following will be considered loco-regional failures:
   a. Histological verified persistent tumor in the head-neck region documented at least two months after end of radiotherapy. Persistent tumor less than two months after radiotherapy is not considered treatment failure.
   b. Local or regional disease progression at any time.
   c. Local or regional failures are registered separately.
2. Overall survival (all causes) will be measured from date of randomisation to date of death.
3. Disease-free survival will be measured from date of randomization to date of death (all causes), loco-regional failure or distant failure, whichever comes first.
4. Disease-specific survival will be measured from date of randomization to date of death (by loco-regional or distant failure).
5. Quality-adjusted life-years (QALY) comparison (with EQ-5D)
Study design
A randomized trial of proton versus photon therapy in head-neck cancer patients selected to have an expected benefit of proton therapy in the reduction of late morbidity.

Type of randomization
Included patients will be randomised in a 2:1 ratio, in which the probability that a patient is assigned to the experimental treatment arm is 2/3 (figure 1). The 2:1 randomization is chosen for two reasons a) to provide more statistical power to the proton NTCP model and b) to ensure a sufficient sample size for a proxy comparison of the experimental arm with a historical cohort of photon treated patients for secondary endpoint analysis of loco-regional control. Regarding (b), we choose this design as a formal non-inferiority trial with loco-regional control as primary endpoint would require a prohibitive number of patients in each arm. However, the 2:1 randomization will allow for a historical comparison to detect differences in loco-regional control and pattern of failure.

Stratification will include P16 status (P16+ oropharynx/P16−), tumor stage (T1-2/T3-4), N stage (N0/N+) and treatment center.

The randomization will be performed centrally by DAHANCA. Except for the intervention (radiotherapy modality) both groups will be treated identically in all aspects of the follow-up and evaluation.

Selection Criteria
Inclusion criteria:

- Patients with histologically proven squamous cell carcinoma of the pharynx or larynx planned for primary radiotherapy with curative intent
- A predicted clinical significant reduction in the risk of any of the two primary endpoints (>= grade 2 observer-rated dysphagia or moderate-severe patient-reported xerostomia) after proton therapy compared to photon therapy based on comparison of the individual patient dose plans
- No current or earlier malignancies, which may influence treatment, evaluation or outcome of the head-neck cancer
- Informed consent as required by law
- The patient cannot participate in conflicting protocols
- Above 18 years of age

Exclusion criteria:

- Patient with cancers of the glottic larynx (stage I/II), nasopharynx, skull base, sino-nasal area, unknown primary tumor and prior malignancies.
- Patients with contraindications for proton therapy. Per January 2019, this includes pacemakers, implanted defibrillators and tracheostomy
- Inability to attend full course of radiotherapy or follow-up visits in the outpatient clinic
- Distant metastasis
• Previous radiotherapy of the head and neck
• Previous surgery for the primary cancer with curative intent

Statistical considerations

Power calculation
The power calculation is based on a 10% absolute reduction* in the prevalence of >= grade 2 dysphagia (graded 0-4) and >= moderate xerostomia (none, slight, moderate, severe). The same cut-off is used in non-randomised studies of proton versus photon therapy [57]. Using data from the published models approximately 25% of Danish patients are at risk of >=grade 2 dysphagia and 38% of moderate-severe xerostomia [58]. With the proposed 2:1 randomization (proton:photon) a reduction in dysphagia prevalence from 25% to 15% will require 246 patients using a two sided alpha of 5% and a power of 80%. A reduction in the prevalence of xerostomia from 38% to 28% will require 390 patients with the same design parameters.

As some patients will qualify for both endpoints we estimate that a total of 500 patients are needed. Accrual will, however, continue for both endpoints until 246/390 evaluable patients are accrued.

The inclusion/exclusion criteria stated will allow approximately 600 potential candidates for inclusion in Denmark per year [3]. By a conservative estimate we anticipate that 60% of patients (360/year) would be interested in participating in the study and proceed to a dose plan comparison between photons and protons. Of these patients 30% (108/year) will be expected to have an NTCP gain of more than 10% [59, 60], and thus, will be offered inclusion into the randomised trial (figure 1).

*The cut-off value (10%) chosen for the power analysis represents the initial value in the phase two feasibility study. If only few patients are selected based on this criterium, a lower cut-of value can be applied if the risk reduction is clinically significant

Statistical analysis
The following statistical analyses will be applied:

The primary endpoints will be analysed by the Kaplan-Meier method with time to occurrence of the first event of dysphagia/xerostomia and using the log-rank test for comparison. Further, 2x2 contingency tables of 12-month incidences will be supplied, supported by Fisher’s exact test for difference.

The primary QoL analysis will include all completed questionnaires. Mean changes in EORTC QoL questionnaire item scores from baseline between groups will be compared by two-sample t tests. We deem differences in EORTC QoL scores of 10 points or more clinically significant in line with EORTC guidelines and use p<0.01 as significance level as a pragmatic compensation for the multiple (but related) tests.
Actuarial rate of overall survival, cause-specific survival and loco-regional control will be reported. Cox proportional hazards regression models will be used for multivariable analyses of survival-related endpoints. Cause-specific survival and loco-regional control will be analysed using a competing risk model. The loco-regional control of the experimental arm and recurrence pattern will be compared to the expected rates in the DAHANCA database after adjusting for P16 status, disease site, UICC stage, performance status and smoking status. Here the expected Kaplan-Meier curve for the patient cohort using the DAHANCA database will be plotted with CI together with the observed curve in the experiment as descriptive statistics without formal significance testing.

**Interim report**
To ensure loco-regional control, two interim analyses are planned. The first after 99 patients or 30 failures, and the second after 198 patients or 60 failures. Expecting a loco-regional control around 80% after 1½ years of follow-up, a significance level of 0.10 and a power of 80%, a difference in hazard ratios of 1.4 and 1.25 can be detected. A significant difference in loco-regional control favouring the photon arm will lead to a study halt and a detailed failure analysis to clarify reasons for the higher number of recurrences in the proton arm. Resumption of the study will be depending on this analysis and would require unanimous approval by the study group.

**Data collection and management**
The DAHANCA database will serve as the central database in the study. The database has been refined for research purposes the past 20 years and has been used in numerous DAHANCA studies. Data will be entered only by investigators or individuals authorized by the investigators. Data entry is possible online from all Danish head-neck cancer centers, and a study specific interface will be added for the present study with the necessary protocol parameters, questionnaires, morbidity and outcome registrations. The digital radiotherapy treatment plans incl. diagnostic imaging will be collected in the Danish dose plan bank which has been approved for use in clinical trials. A Data Management Plan (DMP) will outline the necessary requirements of data collection and management, including how data will be stored and analysed. The DMP will be based on the obligations and requirements from the Danish Data Protection Agency, The Act on Processing of Personal Data (lov om behandling af personoplysninger) and the National Research Ethics Committee.

All authorities who need to access data by law will be permitted data access from the database. If other research groups wish to access any of the data, they may contact the primary investigator for a data agreement. The trial will be registered at ClinicalTrials.gov and clinicaltrialsregister.eu.

**Inclusion**
At the multidisciplinary conferences eligible patients are informed of the protocol and the possibility to perform comparable proton/photon plans. If the patient accepts, comparable plans will be performed and data collection from functional tests and questionnaires will begin.
Delineation of target structures and organs-at-risk (OAR) on the local planning CT following the guidelines described in DAHANCA. A proton and a photon doseplan will be produced. The proton doseplan can be conducted locally or at the DCPT following a pre-specified template. Based on dose to swallowing structures and salivary glands the risk of dysphagia, and xerostomia will be estimated from the chosen NTCP models. The dose plans are presented at the national proton conference. In case of comparable target coverage and an estimated NTCP advantage that is clinically relevant the patient is offered inclusion into the trial.

The patient is informed of the results of the plan comparison and offered inclusion into the trial. If the patient accepts, randomization is performed centrally.

1. Randomisation to the photon arm - start of photon treatment locally (standard arm)

2. Randomisation to the proton arm
   a. For patients randomized to proton therapy a second planning process will take place at DCPT in Aarhus, including a proton-specific planning CT. Contours from the first planning will be transferred to the new planning CT.
   b. Start of proton treatment
   c. At the end of treatment, the patients will continue follow-up at the local center.

Randomisation
At inclusion the DAHANCA 35 inclusion form (appendix 2) is completed and faxed to the DAHANCA secretariat (fax nr +45 86197109), where the randomisation procedure will take place with regard to the stratification variables. Subsequently, a randomisation number and the corresponding treatment will be returned.

Treatment details
Photon arm: Photon radiotherapy using VMAT/IMRT delivery to a total dose of 66-68 Gy in 33-34 fractions, six fractions per week to the high dose CTV (CTV1). Doses to the intermediate dose CTV CTV2 and the elective CTV (CTV3) are 60 and 50 Gy, respectively. Alternatively, hyperfractionated, accelerated radiotherapy to 76 Gy in 56 fractions, 10 fx/week, with 66 Gy and 56 Gy to intermediate and low dose volumes, respectively. Concurrent medical treatment with nimorazole and weekly cisplatin (locally-advanced disease). Details of the radiotherapy and medical treatment can be found in the effective DAHANCA guidelines at the time of inclusion (www.dahanca.dk).

Proton arm: Proton radiotherapy to a total dose of 66-68 Gy in 33-34 fractions, six fractions per week to the high dose CTV (CTV1). Doses to the intermediate dose CTV CTV2 and the elective CTV (CTV3) are 60 and 50 Gy, respectively. Alternatively, hyperfractionated, accelerated radiotherapy to 76 Gy in 56 fractions, 10 fx/week, with 66 Gy and 56 Gy to intermediate and low dose volumes, respectively. Concurrent medical treatment with nimorazole and weekly cisplatin (locally-advanced disease). Details of the radiotherapy and medical treatment can be found in the effective DAHANCA guidelines at the time of inclusion (www.dahanca.dk).
The concurrent medical treatment (weekly cisplatin and nimorazole) are prescribed according to the national treatment guidelines in both arms of the study, and are not part of the experimental treatment.

3.5 Functional tests
The above-mentioned evaluation will be supplemented by functional tests. These will include

a) Stimulated whole-mouth salivary flow measurement (see appendix). The saliva samples will be used to assess the salivary flow and will be disposed of immediately after measurement (within minutes) (saliva will not be stored afterwards).

b) Modified Barium Swallowing Test (MBS). The MBS test allows for the identification of normal and abnormal anatomy and physiology of the swallowing function by using a radiograph and can therefore be externally validated. This examination involves fluoroscopy of oral and pharyngeal phases of swallowing food and liquids of varying consistencies mixed with barium contrast. The MBS will also be quantified using a penetration-aspiration score.

3.6 Follow-up program
All patients will be followed for at least ten years after treatment. Acute toxicity during treatment will be registered at DCPT (protons) or the local centers (photons), and late toxicity at the local centers. The DAHANCA toxicity registration is mandatory and follow national guidelines.

Acute toxicity:
DAHANCA: Baseline, weekly during treatment, end of treatment, 14-days post-treatment, 8 weeks post-treatment.

Late toxicity:
DAHANCA: 6, 12, 18, 24, 36, 48, 60 months after treatment
EORTC QLQ-C30, HN35, EQ 5D baseline, EOT, 2, 6, 12, 18, 24, 36, 48, 60, 72, 96, 120 months after treatment

Functional evaluations (MBS, stimulated whole mouth salivary flow): Baseline (MBS), 6, 12 (MBS), 24, 60 months after treatment.

Radiotherapy Quality Assurance (QA)

In a clinical radiotherapy trial, QA is of pivotal importance, and subpar QA has been shown to impact treatment outcome significantly [8]. Thus, external quality review of the individual treatment doseplans in both trial arms is a necessary component of the trial. Traditionally, this time-consuming task has been performed post-treatment, with no possibilities to correct doseplans before delivery. In order to streamline the process and enable pre-treatment review, we will use an online QA platform, utilizing the well-established national treatment plan bank. With this platform the QA oncologist and QA physicist can review the individual treatment plans using a secure web browser and expedite the evaluation within days. The individual plan review will automatically be send back to the planning center with approval or comments for improvement. The review experience will be evaluated and shared in a yearly national workshop to ensure a conscious improvement in doseplan quality across the centers.
This national online QA process is a novel concept with implications reaching outside Denmark. The experience and workflow will be analysed and published independently of the trial.

**Patient recruitment and clinical investigations prior to treatment**

The multidisciplinary conference

Newly diagnosed eligible patients with head-neck cancer requiring radiation therapy will be informed of the study trial aims and randomisation at the first multidisciplinary consultation by a clinical oncologist. The information will in broad terms cover the study, including rationale, possible treatment in Aarhus and the selection criteria with dose plan comparisons. It will be emphasised that in case of a potential benefit of protons the patient will receive a more thorough information and an offer to participate in the study, and in case of no benefit of proton therapy the patient will continue the photon planning and treatment locally (which is the standard treatment).

First planning

Delineation of target structures and organs-at-risk (OAR) on the local planning CT following the guidelines described in DAHANCA. A proton and a photon doseplan will be calculated using the same prioritization of target structures and OARs. The proton doseplan can be conducted locally or at the DCPT. Based on dose to swallowing structures and salivary glands the risk of dysphagia, and xerostomia will be estimated from the chosen NTCP models. The dose plans are presented at the national proton conference. In case of comparable target coverage and an estimated NTCP advantage $\geq 10\%$ the patient is offered inclusion into the trial.

Information

The patient is informed of the results of the plan comparison and in case of an expected clinical benefit as described, the patient will be offered inclusion into the trial. Written information will be provided to the patient and 24 hours of time for reflection offered. If the patient accepts, written informed consent will be obtained and randomization performed centrally.

1. **Randomisation to the photon arm**
   a. QoL questionaires (EORTC QLQ-C30, HN35, EQ-5D) and DAHANCA baseline data
   b. Saliva samples and modified barium swallowing
   c. Start of photon treatment locally

2. **Randomisation to the proton arm**
   a. QoL questionaires (EORTC QLQ-C30, HN35, EQ-5D) and DAHANCA baseline data
      (local center)
   b. Saliva samples and modified barium swallowing (local center)
   c. For patients randomized to proton therapy a second planning process will take place at DCPT (in Aarhus), including a renewed planning CT. Contours from the first planning will be transferred to the new planning CT. Patients randomized to photon therapy will be treated at the local center using the plan generated in the first planning process.
d. Start of proton treatment at DCPT

e. At the end of treatment, the patients will continue follow-up at the local center.

**Pilot phase**

In order to ensure feasibility and workflow at least twenty patients with head-neck squamous cell carcinoma needs to have been treated in a phase II study before the randomised trial can be initiated. At each individual center at least five patients with head-neck squamous cell carcinoma needs to have been treated with proton therapy before the randomised trial can be initiated at the center. The separate phase II trial resembles the proton arm in the DAHANCA 35 with parallel model-based selection, baseline investigations, treatment delivery and follow-up program, including functional tests. However, the functional swallowing test (MBS) will not be mandatory in the pilotphase. Recruitment of patients in the phase II study is contingent on completed QA dummy runs be each individual treatment center.

**Health economics study**

Particle therapy is a financially demanding technology, and still with uncertainty about its impact on patients’ outcome relative to the cost. It is thus important to investigate whether the investment is worthwhile, whether and for which patients it is cost-effective, and what is the expected impact on health care budget [61]. We plan to collect and analyse the relevant health economy parameters for all patients included in the randomized trial, including type, number and cost of equipment and personnel, patient population and treatment indications, time requirements, use of health-related resources, disutility of care, return to work life, etc. as described in detail in [61]. The data will form the basis of a cost accounting model, which together with the outcome data (morbidity, local control, quality of life, survival) will be used to estimate the cost-effectiveness of proton vs. photons in head and neck radiotherapy. The study will be planned and conducted in collaboration with health economists in Denmark and Europe, through the European Particle Therapy Network. The data in DAHANCA 35 will be supplemented by registry information. The health economics study will be described in a separate protocol, and permissions will be obtained separately.

**Timetable**

Jan-April 2019: Development of the online QA platform. QA dummy runs to ensure compliance and cohesion of the individual treatment centers. In this period the first head-neck cancer patients will be treated in a phase II trial to confirm treatment delivery, logistics and set-up. Treatment of the first head-neck cancer patients in the phase II trial.

August 2019: Start of the randomised trial. Centers will begin to recruit patients contingent on treatment of patients in the phase II trial.

August 2021: First interim report

August 2022: Second interim report. First interim analysis (depending on recurrence rate).

August 2024: Estimated end of recruitment. Follow-up and evaluation continues.
August 2025: Primary endpoint assessment.

Side effects
Photon radiotherapy is the standard treatment in Denmark, and information is given in accordance with the normal procedure for these patients. The range of side-effects of photon and proton treatment during and after radiation therapy are comparable, although proton therapy may induce more skin toxicity, both acute (dermatitis) and late (fibrosis). The severity of late effects, dysphagia and xerostomia, are expected to be lower after proton therapy.

Side-effects during or after head-neck radiation in general can be acute or chronic (short or long term) and include:

- Inability to consume any solid food – liquids only (acute)
- Mouth sores or fungal infection (acute)
- Dental problems (acute / chronic)
- Pain during swallowing (acute / chronic)
- Dry mouth or throat - loss of saliva partially or almost totally (acute / chronic)
- Sore and swelling of the throat (acute)
- Miscoloured, red irritated skin (acute /chronic)
- Difficulty swallowing (acute /chronic)
- Loss or major changes to sense of taste and/or smell (chronic)
- Problems with opening of the mouth due to stiff jaw muscles and joint (chronic)
- Tension of the skin of the throat (chronic)
- Fatigue (acute/chronic)
- Reduced production of thyroid hormones (chronic)

Rare complications include: Osteoradionecrosis
Very rare complications include injury of the spinal cord resulting in numb areas and pain in arms and legs.

Side-effects to the radiotherapy will be registered in accordance with the DAHANCA guidelines. During therapy on a weekly basis (use of analgesics, dysphagia, use of feeding tube, tracheostomy, degree of mucositis and dermatitis, nausea and other possible side-effects. In follow-up side-effects and late complications will be registered at 2, 6, 12, 18, 24, 36, 48 and 60 months, including use of feeding tube, degree of xerostomia and dysphagia, hoarseness, oedema, fibrosis, osteoradionecrosis, neurological symptoms, tracheostomy or other late effects. Death and the cause of death (primary cancer, other cancer, accident, treatment-related, suicide or unknown) is also registered in the DAHANCA database.

The primary investigator should be notified of any occurrence of late adverse events >= grade 4 according to the Common Terminology Criteria for Adverse Events (CTCAE) suspected to be related to the radiotherapy until five years post-treatment. The notification will be communicated
through the DAHANCA follow-up form. Late adverse events develop after the treatment most often within the first 3 years.

**Radiation safety**  
Patients requiring proton therapy needs to undergo a second head-neck CT planning scan at the proton center in Aarhus, and up to six additional CT scans of the head-neck region during proton treatment. A head-neck CT will expose the patient to approximately 8 mSv, compared to the approximately 70,000 mSv they receive from the radiation therapy. As the low-dose area in proton therapy is considerably lower compared to photon therapy, proton treated patients will in total receive less radiation, even with the extra CT scan.

MBS is presently not part of the routine follow-up programme for head-neck cancer in Denmark. An MBS examination is estimated to equal extra 1 mSv of radiation, thus, 2 mSv extra radiation in total. This is several thousand times less than the combined radiation from the treatment and the added risk neglectable.

**Publication of results**  
When the study is completed positive, negative and inconclusive results will be published in international scientific journals. The publication of results will take place in agreement among the collaborators and will be coordinated by the primary investigator. When all data have been analysed and the results published, study participants can be informed about the results by contacting the investigators. As soon as possible after end of the study the results will be reported in Clinicaltrials.gov. Following this, data will be published on www.clinicaltrialsregister.eu.

**Ethical account**  
The standard treatment for inoperable head-neck cancer is primary photon radiotherapy. This treatment is often effective but associated with a significant degree of short- and long-term side effects, among these long-term xerostomia and dysphagia. In theoretical studies and small clinical series proton radiation therapy seems to provide a safe treatment with less long-term side effects. There are no randomised trials comparing photon to proton radiation treatment, and the proposed national study will therefore provide important future evidence to help selecting the best treatment for these patients. All included patients in the randomized study will be treated according to the randomization key and followed as described in the protocol. The study will be conducted according to current legislation and the Helsinki declaration.

All data is treated confidentially, and each recruiting centre is responsible of managing the data safe and in compliance with the Data Protection Act (databeskyttelsesloven) and the General Data Protection Regulation (databeskyttelsesforordningen). The study will be registered on the internal list of research projects in Region Midtjylland.
Guidelines for participant information and written informed consent

Newly diagnosed eligible patients with head-neck cancer requiring radiation therapy will be informed of the study trial aims and randomisation at the first multidisciplinary consultation by a clinical oncologist. The information will in broad terms cover the study, including rationale, possible treatment in Aarhus and the selection criteria with dose plan comparisons. It will be emphasised that in case of a potential benefit of protons the patient will receive a more thorough information and an offer to participate in the study, and in case of no benefit of proton therapy the patient will continue the photon planning and treatment locally (which is the standard treatment). In case the patient already know that he will not travel to Aarhus or receive proton therapy, the patient will not be informed further.

Following the dose plan comparison (3-4 days later) patients with an expected clinical benefit of proton therapy according to the selection criteria’s, will receive both written and verbal information including the informed consent form. The consultation will take place in a quiet and undisturbed room, and patients are encouraged to bring a companion. Potential participants will be informed that it is voluntary to participate in the trial, and that they, at any time and without justification can withdraw their consent to participate without that affecting their future treatment. The patients are offered 24 hours from the time that oral and written information is given to sign the informed consent form. The form will contain the patient’s dated signature along with the dated signature of an investigator. A copy of the signed and dated consent form will be given to the patient along with the written participant information (if this has not already been handed out) and the booklet "The patients’ rights in a scientific research project” published by the National Research Ethics Committee.

It is the responsibility of the participating physicians to conduct the study according to this protocol, and to ensure that the data recorded are as precise and accurate as possible. It is also the responsibility of the participating physicians complete data forms and data registration relevant for the study and to obtain informed consent from the patients prior to their enrollment in the study.

Informed Consent

All trial patients must sign the consent form to be included in the trial. The signed consent from the patient give the investigators of the trial and relevant authorities direct right to access the patients’ data. Participation in the trial and the date of inclusion will be documented in the database. A member of the investigator team is responsible for ensuring that none of the enrolled patients undergo any study related investigations or activities before the patient has given written informed consent.

Access to patient files and radiation doseplans

Access to patient files is needed to ensure registration of recurrence, death, emigration, unexpected side-effects and physician-scored endpoints in case these have not been registered timely. Access to the radiation doseplans is needed to enable dose-response modelling and to
ensure quality assurance performed by teams of physicists and physicians from other participating institutions in Denmark, as described in the QA paragraph above.

Financial plan
The study protocol was initiated by the Danish Head and Neck Cancer Group (DAHANCA). The trial is supported by a grant of DKK 8.565.384 from the Novo Nordisk Foundation (grant nr. NNF18OC0034612). The grant will support the collection of data (research nurses), the swallowing examinations, establishment of an online QA tool and support the two spin-off studies (health economics and radiogenomics).

There are no financial benefits for the department or the investigators relating to the trial. No health professionals involved in the study have any financial disclosures or conflicts of interests related to the project.

Reimbursements to the patients
No payment or reimbursement will be made to the enrolled patients. However, extra expenses associated with the stay in Aarhus (for patients in the proton therapy arm) will be covered by the patient’s home region. No economical compensation will be provided from the Danish Center for Particle Therapy or DAHANCA.

All trial patients will by law be covered by the general insurance for patients treated in the health care system at the different study locations.
Abbreviations

DAHANCA: Danish Head-Neck Cancer Group
DCPT: The Danish Center for Particle Therapy
DMP: Data Management Plan
EORTC: European Organization for Research and Treatment of Cancer
HNSCC: Head and Neck Squamous Cell Carcinoma
HPV: Human Papilloma Virus
IDMC: Independent Data Monitoring Committee
IMRT: Intensity-Modulated Radiotherapy
MBS: Modified Barium Swallowing
NTCP: Normal Tissue Complication Probability
PCM: Pharynx Constrictor Muscle
QA: Quality Assurance
QoL: Quality of Life
RBE: Relative Biological Effectiveness
VMAT: Volumetric Arc Therapy
Figure 1

- Squamous cell carcinoma of the pharynx or larynx (excl. st. 1/2 glottic larynx)
- Indication for radiotherapy with curative intent
- Absence of severe co-morbidity

**Candidates**

**Photon doseplan >10% risk of either dysphagia or xerostomia**
- DAHANCA score >= grade 2
- Moderate-severe xerostomia (EORTC HN 35)

**Proton doseplan**
- Proton/photon comparison
- ΔNCPT >10% for either dysphagia or xerostomia

**ΔNCPT < 10%**
- Treatment and follow-up according to routine guidelines

**Randomisation**
- Protons vs photons 2:1
- Endpoint based on selection criterium (ΔNTCP)

**Dysphagia (n=242)**
- Assessed at 12 months

**Xerostomia (n=363)**
- Assessed at 12 months

Secondary endpoints analysed for both groups combined
References


47. Armoogum, K.S. and N. Thorp, Dosimetric Comparison and Potential for Improved Clinical Outcomes of Paediatric CNS Patients Treated with Protons or IMRT. Cancers (Basel), 2015. 7(2): p. 706-22.


Appendices

a. Protokolresume/lægmandsbeskrivelse (bilag A)
b. Patientinformation pilot studie (bilag B)
c. Patientinformation randomiseret studie (bilag C)
d. Samtykke erklæring pilot studie (bilag D)
e. Samtykke erklæring randomiseret studie (bilag E)
f. Procedure spytopsamling (bilag F)
g. Patient-reported outcome EORTC QLQ-C30 (bilag G)
h. Patient-reported outcome EORTC HN35 (bilag H)
i. Patient-reported outcome EQ-5D (bilag I)
j. DAHANCA registration (On-study, under behandling, follow-up, bilag J)
k. Forsøgspersoners rettigheder i et sundhedsvidenskabeligt Forskningsprojekt