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ABSTRACT

Proton radiotherapy offers a dosimetric advantage compared to photon therapy in sparing normal tissue, but the clinical evidence for toxicity reductions in the treatment of head and neck cancer is limited. The Danish Head and Neck Cancer Group (DAHANCA) has initiated the DAHANCA 35 randomised trial to clarify the value of proton therapy (NCT04607694). The DAHANCA 35 trial is performed in an enriched population of patients selected by an anticipated benefit of proton therapy to reduce the risk of late dysphagia or xerostomia based on normal tissue complication probability (NTCP) modelling. We present our considerations on the trial design and a test of the selection procedure conducted before initiating the randomised study.

Background

Radiotherapy alone or in combination with systemic agents is used as part of the initial treatment of approximately 75 % of patients with head and neck cancer (DAHANCA annual report 2021). Current photon-based therapy is effective but inflicts a significant burden of symptoms that can have profound impact on the quality of life (QoL), both as transient acute side effects and as permanent late side effects [1]. In the past decades there has been a clear focus on reducing toxicity with the development of parotid- and swallowing-sparing radiotherapy as a main priority [2]. Due to the specific energy deposition of protons, proton radiotherapy, compared to photon therapy, offers a dosimetric sparing of normal tissue and a potential reduction of toxicity. This advantage is particularly important in the head-neck area, where an abundance of critical organs limits the therapeutic window. The value of proton therapy to reduce doses to organs at risk in head-neck cancer treatment has been shown in in-silica studies and possible toxicity reduction indicated by selected patient series [3–6]. 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 [7,8]. It therefore remains unknown whether the expected benefit can be reproduced in a clinical setting. As proton therapy also comes at an incremental financial cost, the benefit must preferably be established in prospective clinical trials. With the establishment of the Danish Center for Particle Therapy in Aarhus, Denmark, The Danish Head and Neck Cancer Group was given the opportunity to help generate this evidence, and we here present the considerations behind the resultant DAHANCA 35 trial (NCT04607694).

Dosimetric and clinical benefit of proton therapy in head-neck cancer

A vast number of treatment planning studies have verified the benefit

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of protons in reducing the low-to-intermediate dose volumes in head-neck cancer compared to photon treatment (Fig. 1). This low-intermediate dose reduction translates into reduced doses to relevant organs at risk, and reductions in mean doses to the parotids, pharyngeal constrictors and oral cavity in the range of 5–15 Gy have been reported. Based on models for normal tissue complication probability (NTCP), these reductions will often translate into a clinical benefit and up to 35 % of head and neck cancer patients could be selected for proton treatment using these algorithms [9]. The clinical evidence of a gain from protons in head-neck squamous cell carcinoma (HNSCC) is still limited with patient series up to 50 patients [4–6]. Based on these series proton radiotherapy seems safe and with a possible reduction in toxicity compared to historical cohorts of photon-treated patient. While these results are encouraging, the considerable positive selection of proton-treated patients (performance, socio-economic status and HPV-status), makes it difficult to draw firm conclusions on the benefit of proton therapy in HNSCC.

Selection of primary endpoints in a head-neck cancer proton trial

As the dose distribution benefit of proton treatment is determined from the low-intermediate dose volumes, reduction of toxicity is the most obvious endpoint in a trial. However, as not all dose reductions may translate into clinically relevant or observable reductions in toxicity, selecting suitable endpoints is challenging. This is reflected in the heterogeneity of endpoints in current clinical trials of proton therapy in HNSCC (Table 1). The choice of a non-inferiority trial with survival as the primary endpoint has been proposed and will allow post-hoc analysis of toxicity [10]. However, to make a trial feasible a large non-inferiority margin would need to be accepted. For example, if there is truly no difference in survival between the standard and experimental treatment (e.g., 80 % in both groups), then 2,194 patients are required to be 90 % sure that the upper limit of a one-sided 95 % confidence interval (or equivalently a 90 % two-sided confidence interval) will exclude a difference in favour of the standard group of more than 5 %. If a larger non-inferiority margin is accepted in order to conduct a feasible study, the likelihood of detecting differences in toxicity endpoints also decreases. It should also be considered that the benefit of proton therapy needs to be significant, with the increased financial costs and the inconvenience of associated travel to the proton facility kept in mind.

Late dysphagia and xerostomia have repeatedly been shown to impact quality of life in HNSCC patients [11], which can be measured by a range of metrics (patient-reported outcomes, observer-assessed outcomes and functional tests). As dysphagia and xerostomia at six months post-treatment predict long-term disability [12], reductions in the risk of these are desirable and were selected as clinically relevant endpoints in the DAHANCA 35 trial.

Trial design considerations

A randomised trial (RCT) is the gold standard used to assess the outcome (value/effect) of new treatments and also represents the most generally accepted way of comparison. An unbiased control group minimises selection due to social, geographical or insurance factors and enables the study of unanticipated effects. However, RCTs are time-consuming and recruitment may suffer from the randomisation. Also, as the dose reduction with protons may not translate into clinically measurable effects in all patients, an RCT without selecting patients with a likely benefit may end up negative and thereby conceal the benefit in others.

An alternative to RCT is the non-randomised NTCP-model based selection promoted in the Netherlands [13]. NTCP models are generated from multivariate analysis of large datasets containing information on radiation dose to organs, toxicity observations and clinical parameters, and can be used to predict the risk of a side effect or complication. Comparing proton and photon treatment plans for individual patients, NTCP models can be used to select patients for protons based on a predefined reduction in the probability of clinically relevant toxicity, such as dysphagia and xerostomia. Subsequent clinical measures of the selected endpoint are then used to validate the selection model and hence determine the benefit of proton therapy in selected patients. A benefit with this strategy is clearly defined criteria for selection, closely associated the observed endpoints, cost-efficiency and that all potential candidates receive protons. However, the design puts a lot of confidence in mainly photon-developed NTCP models, which may be population-specific, with limited external validity. The lack of an unbiased comparative group also limits the possibility of identifying unknown differences.

In the DAHANCA, we discussed the applicability of any future trial results; the NTCP model-based selection has an advantage since it offers clinicians a tool to select patients for proton therapy, a tool which theoretically could be used in local centres, and which could be refined with the development of improved NTCP models. Therefore, trying to combine the advantages of the RCT and NTCP model-based selection, we proposed a randomised trial in an enriched population selected on an assumed benefit of proton therapy based on NTCP models. In this trial setting new patients with pharynx or larynx cancer planned for primary radiotherapy are screened in local treatment centres with proton–photon plan comparisons and may enter the trial if the risk of late dysphagia or xerostomia is above a predefined clinical threshold. The

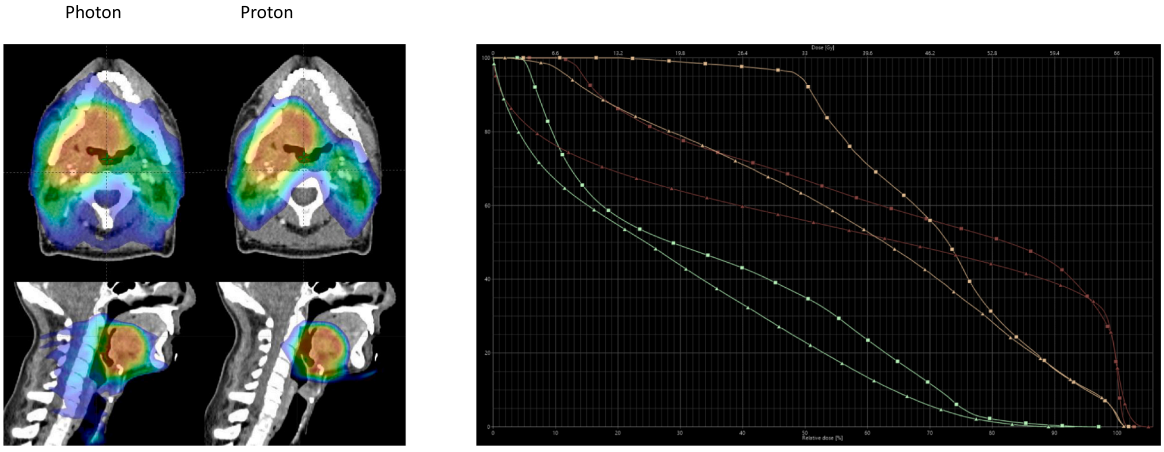

Fig. 1. a) 30 Gy dose colorwash from photons and protons in a patient with squamous cell carcinoma of the tonsil b) Dose-volume histogram of comparative photon (squares) and proton (triangles) treatment plans from the same patient. Pharyngeal constrictor muscles combined (light brown), modified oral cavity (dark brown) and parotid glands combined (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Selected clinical trials in primary radiotherapy for HNSCC and the National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer in the Netherlands.

Trial number	Type	Institution	Trial name	Inclusion	Treatment	Primary endpoints
NCT01893307	RCT	MD Anderson (USA)	Intensity-Modulated Proton Beam Therapy or Intensity-Modulated Photon Therapy in Treating Patients With Stage III-IVB Oropharyngeal Cancer	St. III-IVb (AJCC 7th) HNSCC	IMPT: IMRT (1:1)	Overall survival/Progression-free survival (phase III)
NCT03829033	RCT	Lund (Sweden)	Photon Therapy Versus Proton Therapy in Early Tonsil Cancer. (ARTSCAN V)	Tonsil carcinoma (T1-2 N0-2b M0) – unilateral RT (non-chemotherapy)	IMPT: IMRT (1:1)	Locoregional side effects (acute and late)
ISRCTN: 16424014	RCT	Christie (UK)	Phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer (TORPEDO)	Locally advanced OPSCC, chemo-RT and bilateral neck treatment	IMPT: IMRT (2:1)	Co-primary endpoint 1) University of Washington physical toxicity composite score and 2) feeding tube dependence or severe weight loss 12-months post-RT.
NCT04607694	RCT	DAHANCA (Denmark)	Proton Versus Photon Therapy for Head-Neck Cancer (DAHANCA 35)	HNSCC, T1-4, N0-N3, M0 (excl. larynx T1-2N0M0)	IMPT: IMRT (2:1)	1) Observer-reported dysphagia (DAHANCA late toxicity score) 2) Patient-reported xerostomia (EORTC HN 35) at six-month post-RT
National protocol	NTCP-based	Netherlands	National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer in the Netherlands	Head-Neck Cancer	IMPT	Reduction in the risk of: 1) moderate-severe xerostomia, 2) dysphagia ≥ grade 2,3) tube feeding dependence

patients are then randomised (2:1) to proton or photon RT where the primary endpoint is dysphagia or xerostomia at six months post-RT, corresponding to the selection criteria (Fig. 2).

The trial is run as two separate studies DAHANCA 35D for patients selected based on a reduction in the risk of dysphagia and DAHANCA 35X for patients selected based on a reduction in the risk of xerostomia. Patients in both categories are analysed together for secondary endpoints. We believe this 1) provides an unbiased assessment of the potential benefit of protons 2) decreases the likelihood of type 2 error, and 3) optimises local involvement in the identification of patients for proton therapy, and thereby recruitment for the trial and improving the ability of selecting relevant patients for proton therapy after the trial.

The cut-off value, the specific choice of reduction in the NTCP-model estimated risk (ΔNTCP) with protons that allows the patient to

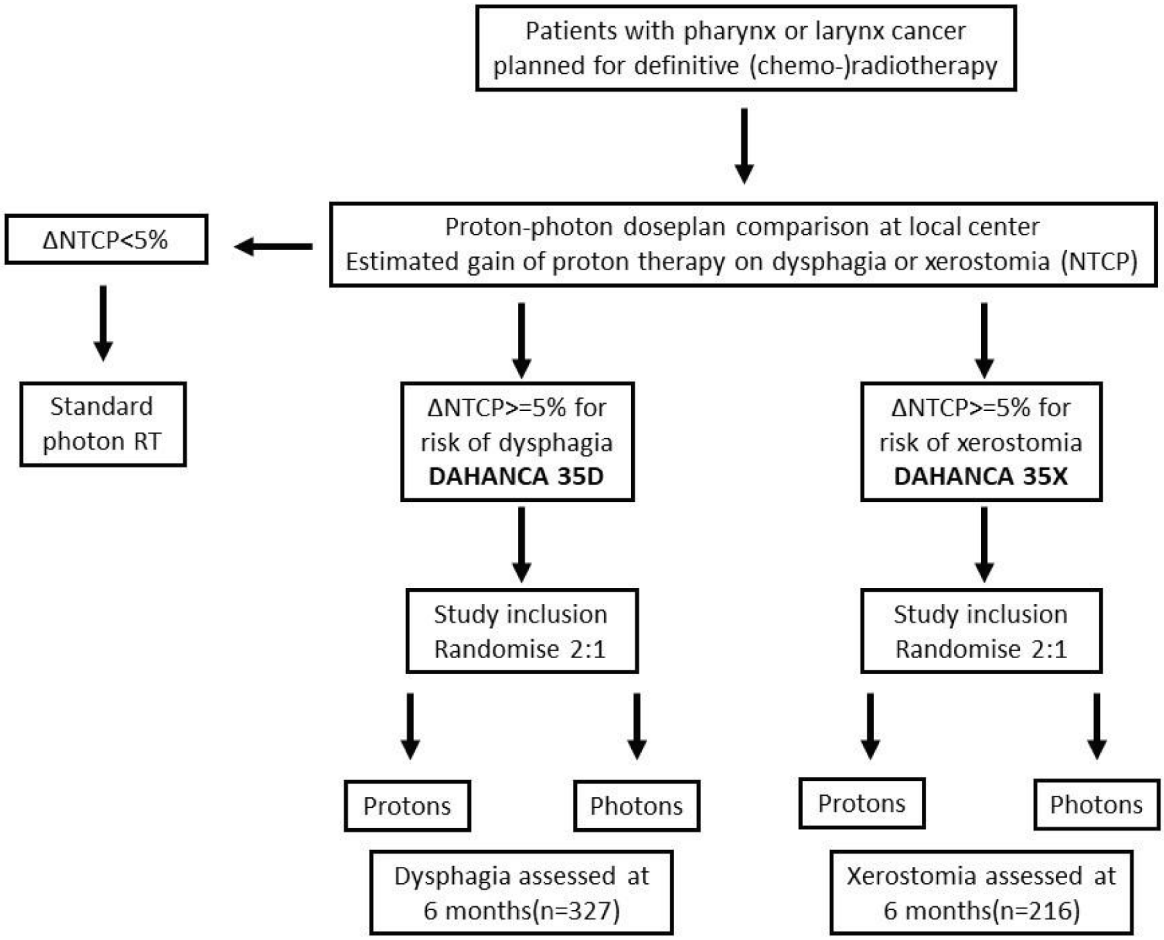

Fig. 2. DAHANCA 35 flowchart.

participate in the trial is arbitrary. The proposed design will test whether selecting patients for proton therapy using NTCP-models is possible and accurate. Using these results and the secondary outcomes the clinically relevant cut-off value after the study can be discussed by health authorities, doctors, and patients.

Specific endpoints

An NTCP-model has been developed for grade 2–4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria [14]. The grading used in the model is comparable to the observer-assessed DAHANCA score, which has been used routinely in Denmark for the past 25 years, and was therefore selected as a primary endpoint in the DAHANCA 35D trial. The DAHANCA scoring is a Danish observed-based scoring system of acute and late toxicity in head and neck cancer radiotherapy. A translation of the scoring used during the acute phase (weekly during treatment, two weeks and eight weeks post-treatment) and the late phase (from six months post-treatment) is provided in supplementary. The study group discussed alternative dysphagia endpoints, including the M.D.Anderson Dysphagia Inventory (MDADI), used as the primary endpoint in the DAHANCA 34 trial on Trans-Oral Robotic Surgery (TORS) versus primary radiotherapy in early oropharynx cancer (NCT04124198). However, no validated NTCP model based on MDADI exists and there was concern regarding the significant clinical difference in MDADI scores. A model for patient-reported xerostomia at six months have also been developed, using the EORTC QLQ-HN35 questionnaire [15], and constitute the primary endpoint in the DAHANCA 35X study. Both the dysphagia and xerostomia NTCP-models have been developed in photon-treated patients and have later been validated in a cohort of proton-treated patients [16].

NTCP models for dysphagia and xerostomia is a dynamic research field and more precise models are likely to appear during the course of the study. The study is not aimed at testing a specific NTCP model, which is solely used to select appropriate candidates for proton therapy, but models may change and improved models may be derived during the trial period. The two current models selected for the randomised trial are a) a dysphagia model including mean dose to extended oral cavity, mean doses to the three pharyngeal constrictors, baseline dysphagia and tumor site b) a xerostomia model including mean dose to extended oral cavity and squared mean doses for the four large salivary glands and baseline xerostomia (see supplementary for exacts formulas) [17]. New NTCP models should be validated in a Danish cohort, which specifically may be achieved by the DAHANCA 19 cohort as described previously [18], and be significantly superior to the present NTCP model in use. The group of investigators shall agree to a change of the applied NTCP model while also considering the patient population and treatments that form the basis of the new model.

Secondary endpoints will be collected and include loco-regional tumour control, disease-specific survival and overall survival. Additional QoL measures include EORTC QLQ-C30 (specifically items related to fatigue, nausea and vomiting), EORTC QLQ-HN35 (specifically items related to swallowing and social-eating), the MD Anderson Dysphagia Index (MDADI) and Euro QoL EQ-5D. Acute and late toxicity will also be registered using the DAHANCA toxicity scoring. Stimulated whole mouth salivary flow will be measured at baseline and post-treatment. For additional information on primary and secondary endpoint see the statistical analysis plan in supplementary materials.

Statistical considerations

As patients are selected based on a reduction in ΔNTCP of dysphagia or xerostomia, a low risk-reduction cut-off (e.g., 5 %) would facilitate recruitment, but increase numbers needed to show a difference, while the opposite is the case for a high cut-off in risk reduction (e.g., 15 %). As up to 50 % of possible participants are expected to refuse participation because of geographical concerns, and because a high treatment plan comparison volume is necessary to maintain proton planning expertise, a low cut-off was preferred. However, in the sample size calculations a larger NTCP benefit was used. The reasons for this are; a) the ΔNTCP distribution will have an average value greater than the ΔNTCP threshold cut-off; b) as the NTCP models used are developed from photon treated patients, we anticipate the reduced low-moderate dose volume in proton therapy to further reduce the late toxicity. Based on the above the expected toxicity reduction in the sample size calculation was chosen to ensure a feasible study. Despite selecting patients with an anticipated benefit of proton therapy for the trial, there is a risk of a negative trial. However, as patients are selected based on an individual NTCP value, an explorative analysis may identify patients with a high anticipated benefit (high NTCP) that have a clinical benefit. Moreover, the secondary endpoints, which includes other QoL measures and salivary flow measurements, will also provide valuable information.

DAHANCA-35D: The grade 2 + dysphagia prevalence at six months for the DAHANCA19 trial was 28 %, which is expected to be reduced to 16 %. The two-sample one-sided superiority comparison of proportions with a significance level of 5 % and power of 80 % require 218 patients in the proton treatment arm and 109 patients in the photons.

DAHANCA-35X: Patient-reported xerostomia outcomes have not been systematically collected in DAHANCA, and for the power calculation observer-assessed xerostomia was used. The grading is none (0), limited (1), moderate (2) and severe (3). The prevalence of the highest grade of xerostomia by the DAHANCA scale (3) at six months in the DAHANCA19 trial was 10 %, which is expected to be reduced to 2 %. The two-sample one-sided comparison of proportions with a significance level of 5 % and power of 80 % requires 144 patients in the proton treatment arm and 72 patients in the photons.

Patients will be censured at the time of disease recurrence, new cancer or death. Before the primary endpoint 6 months' time point, 10 % of the patients are expected to be censured, but as some patients will be selected on both endpoints, the total number of participants are expected to be around 550. The randomisation will be stratified according to the following strata: treatment centre, topography (P16-pos OPSCC/P16-neg OPSCC/other pharynx-larynx),concurrent chemotherapy (yes/no) and ΔNTCP (5–8 %,8–12 %,>12 %). If the patient is a candidate for both DAHANCA 35D and 35X the stratification will follow the dysphagia study (35D).

Radiotherapy dose (66-68gy), fractionation (6 fx/week), target volumes (GTV/CTV) and indications for concurrent weekly cisplatin will be the same for photons and protons and follow DAHANCA guidelines. All patients will also be offered the hypoxic modification with nimorazole unless there are contra indications.

Data will also be collected to 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.

Waiting time

Treatment of cancer needs to be initiated as soon as possible. This is especially relevant in HNSCC, where studies have documented the negative impact of waiting for treatment [19]. For the 25 % of HNSCC patients with fast-growing tumours, 20 % loss of tumour control was estimated within four weeks. These observations were fundamental for defining waiting-times for Danish cancer patients, with a maximum of 11 calendar days from treatment decision to start of radiotherapy for head-neck cancer [20]. Selecting patients for proton therapy based on NTCP-based treatment plan comparison before referral will increase this interval and an additional maximum of seven days has therefore been added to the fast-track clinical pathways by DAHANCA and the Danish health authorities. While these seven days theoretically may have a negative impact on tumour control probability, the total interval of 18 days is well below the four weeks studied earlier [19]. However, with a large variation in tumour volume doubling time, identifying patients

with the highest negative impact of waiting is challenging and continued focus on reducing the extra time needed for the model-based selection of patients into the trial is necessary. In DAHANCA 35, interim analyses of recurrence rates have been planned after 100 and 200 patients, and the significance of waiting time in proton therapy should be included in future pooled analyses of studies.

The DAHANCA proton feasibility study (2019–2021)

For a multicentre trial using local selection of patients with proton–photon treatment plan comparison to succeed, several factors need to be addressed prior to initiation: Prerequisites for such a trial include 1) consistency in contouring between participating institutions 2) experience in both photon and proton treatment planning [21] 3) smooth referral process 4) patient's willingness to travel for treatment and well organized travel and accommodation 5) concordance between the selection plan and the clinical plan and 6) quality assurance of all these steps. To test the overall feasibility of selecting head-neck cancer patients for proton therapy locally based on NTCP-based risk assessment, the DAHANCA group performed a non-randomised proton feasibility study 2019–2021 at all six Danish head-neck cancer centres (NCT05423704). The aim of the study was to test the above-mentioned steps before initiation of a randomised study. Thus, newly diagnosed patients with head-neck cancer underwent comparable photon-proton treatment planning and if a clinically relevant benefit in reduction of the risk of long-term dysphagia or xerostomia was evident, the patient was offered inclusion into the trial and proton therapy at the Danish Center for Particle Therapy. Regarding the prerequisites, 1): A national contouring guideline for target and OARs in head and neck cancer incorporating international consensus recommendations is produced and updated by the DAHANCA group and followed by all Danish treatment centres [22–25]. 2) The national proton centre has developed a proton planning template for head-neck cancer (see supplementary for details) and has offered an educational program for dose planners and physicians in patient selection and proton planning 3) A national proton video conference accessible for all Danish treatment centres has been introduced, and a review of the comparative photon and proton treatment plan at this conference is mandatory prior to patient trial inclusion. Besides the treatment plans, considerations on target delineation, radiation dose and adjuvant systemic treatment is presented and discussed. The conference serves as quality control and facilitate sharing of knowledge between the treatment centres.

To assess the risk of dysphagia and xerostomia in the feasibility study published NTCP models for dysphagia (6 months) ≥ grade II (DAHANCA toxicity score) or xerostomia (6 months) ≥ grade II (EORTC HN35), were used [18].

From June 2019 to December 2020, selected patients with squamous cell carcinoma of the pharynx or larynx at all six Danish head-neck cancer centres were offered proton–photon plan comparison. In case of an NTCP reduction of at least 7 %-point (until Nov 2019) or 5 %-point (after Nov 2019) in favour of proton treatment for dysphagia or xerostomia, the patient was offered proton treatment at the national proton therapy centre. Two centres continued the feasibility phase until March 2021. In the initial experience with model-based selection for proton therapy in Groningen, 30–40 % of patients were selected based on cut-offs of >= 10 % in dysphagia and xerostomia or >= 15 % combined [9]. In our feasibility study we would select 12 % of patients if the same cut-offs were applied. The feasibility study was conducted as a non-randomised study, thus all patients with an anticipated benefit above the cut-off were offered proton therapy. With the introduction of randomisation, we anticipated a drop in recruitment, and we therefore chose a lower NTCP cut-off in order to sustain a reliable workflow at each center.

Results of the feasibility trial

Proton-photon plan comparisons were performed in 141 patients from June 2019 to December 2020, constituting 113 oropharynx, 12 hypopharynx, 12 larynx and 4 nasopharynx carcinomas. A total of 71 (50 %) patients achieved an NTCP reduction above the clinical goal (reduction in the risk of dysphagia and/or xerostomia). These 71 patients constituted 55 % (62/113) of all oropharynx cancers, 17 % (2/12) of all hypopharynx, 33 % (4/12) of all larynx, and 3/4 of all nasopharynx cancers. In general, more patients were selected based on a reduction in the risk of dysphagia (Table 2). A larger proportion of patients receiving unilateral than bilateral neck treatment was selected based on the risk of dysphagia (58 % and 42 %, respectively) with equal portions for xerostomia (27 % and 29 %). However, lymph node negative patients were selected less frequently than lymph node positive patients for both dysphagia (20 % and 47 %) and xerostomia (10 % and 31 %). Of the 71 patients, 55 (77 %) accepted referral to proton treatment. In these 55 patients, the median time from radiotherapy decision to the first proton treatment was 19 calendar days (interquartile range 18–23) and 9 days (interquartile range 8–11) from referral to the national proton therapy centre to first proton fraction. Patients were informed about the extra time needed for renewed treatment planning prior to referral and all referred patients accepted this delay. The six Danish head-neck cancer centres each selected at least five patients, but there was significant variation in numbers from each centre. Surprisingly there was no association between number of the patients recruited and the distance to the DCPT.

This pilot trial proved that local selection of patients for proton therapy based NTCP models was feasible, and that the majority of patients accepted the referral. We concluded that the logistic framework for a randomised trial was satisfactory and that patients could be treated with proton therapy within a reasonable timeframe. The feasibility study also enabled the local centres to establish a clinical experience in proton planning, and as a learning curve in proton planning is likely, treatment plan quality is expected to increase. To ensure continued improvement in plan quality, all local selection plans are still reviewed at national conferences with direct feed-back and the overall quality discussed at bi-annual meetings in the DAHANCA QA group. Other important results from the feasibility trial such as the concordance between the selection proton treatment plan and the clinical proton treatment plan, and the safety of proton therapy will be addressed in the two recent papers [21,26].

Keeping track of the population

Reports from the US suggest that the use of proton therapy may be associated with disparities and that insurance denial is an additional factor to consider when interpretating studies [27–29]. Healthcare in Denmark, including proton therapy, is universally covered and

Table 2
The distribution of patients undergoing comparative photon-proton doseplanning, according to NTCP-based expected risk reduction of dysphagia and xerostomia in the DAHANCA proton feasibility study (NCT05423704).

Delta NTCP in favor of protons	**Tumorsite**			
	Oropharynx	Hypopharynx	Nasopharynx	Larynx
Dysphagia ≥ grade II				
< 5%	57	10	3	9
5–7 %	32	2	1	2
7–10 %	19	0	0	1
> 10 %	5	0	0	0
Xerostomia>=grade II				
< 5%	81	11	2	9
5–7 %	11	0	2	1
7–10 %	11	1	0	2
> 10 %	10	0	0	0

insurance denial is therefore not an issue. Still, as patients need to travel and stay in Aarhus for the duration of the treatment, a social imbalance in patients receiving proton therapy may still be present. Although transportation, food and accommodation are covered, well-functioning patients may be more likely to accept proton therapy. To quantify and investigate this possible imbalance, a screening log of all candidates in Denmark that fulfil the trial inclusion criteria will be kept for the duration of the randomised study. Reasons for non-participation will be noted (e.g., concern over distance to treatment centre, concern over the extra delay). This screening log will make it possible to account for the total number of potential study candidates, along with reasons for not offering comparable treatment planning upfront or for not entering the study after comparable treatment planning. We believe this population-based overview will be a powerful tool for identifying reasons and possible solutions to imbalances in proton trial participation and more generally to secure equal opportunities for proton therapy in the future. The understanding of barriers to enrolment in proton studies is also an exploratory focus of the randomised TORPEDO study in the UK [30].

In conclusion, the DAHANCA 35 randomised trial represents the Danish contribution to provide evidence for proton radiotherapy in the treatment of head-neck cancer. The trial is performed in an enriched population of patients selected for an anticipated benefit of proton therapy to reduce the risk of late dysphagia or xerostomia using NTCP models. The randomised study has now been initiated following a successful feasibility trial testing logistics and safety.

CRediT authorship contribution statement

J. Friborg: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **K. Jensen:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **J.G. Eriksen:** Conceptualization, Methodology, Investigation, Writing – original draft. **E. Samsøe:** Conceptualization, Methodology, Investigation, Writing – original draft. **C. Maare:** Conceptualization, Methodology, Investigation, Writing – original draft. **M. Farhadi:** Conceptualization, Methodology, Investigation, Writing – original draft. **P. Sibolt:** Conceptualization, Methodology, Investigation, Writing – original draft. **M. Nielsen:** Conceptualization, Methodology, Investigation, Writing – original draft. **M. Andersen:** Conceptualization, Methodology, Investigation, Writing – original draft. **A.I.S. Holm:** Conceptualization, Methodology, Investigation, Writing – original draft. **P. Skyt:** Conceptualization, Methodology, Investigation, Writing – original draft. **B. Smulders:** Conceptualization, Methodology, Investigation, Writing – original draft. **J. Johansen:** Conceptualization, Methodology, Investigation, Writing – original draft. **J. Overgaard:** Conceptualization, Methodology, Writing – original draft, Funding acquisition. **C. Grau:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **C.R. Hansen:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109958.

References

[1] van der Laan HP, Van den Bosch L, Schuit E, Steenbakkers R, van der Schaaf A, Langendijk JA. Impact of radiation-induced toxicities on quality of life of patients treated for head and neck cancer. Radiother Oncol 2021 Jul;160:47–53.
[2] Gregoire V, Langendijk JA, Nuyts S. Advances in radiotherapy for head and neck cancer. J Clin Oncol 2015 Oct 10;33:3277–84.
[3] Holliday EB, Frank SJ. Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. Int J Radiat Oncol Biol Phys 2014 Jun 01;89:292–302.
[4] Sio TT, Lin HK, Shi Q, Gunn GB, Cleeland CS, Lee JJ, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: First comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys 2016 Jul 15;95:1107–14.
[5] Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. Radiother Oncol 2016 Jul;120:48–55.
[6] Gunn GB, Blanchard P, Garden AS, Zhu XR, Fuller CD, Mohamed AS, et al. Clinical outcomes and patterns of disease recurrence after intensity modulated proton therapy for oropharyngeal squamous carcinoma. Int J Radiat Oncol Biol Phys 2016 May 01;95:360–7.
[7] Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. Physics in medicine and biology. 2014 Nov 21;59:R419-72.
[8] Kraan AC, van de Water S, Teguh DN, Al-Mamgani A, Madden T, Kooy HM, et al. Dose uncertainties in IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. Int J Radiat Oncol Biol Phys. 2013 Dec 01;87:888-96.
[9] Tambas M, Steenbakkers R, van der Laan HP, Wolters AM, Kierkels RGJ, Scandurra D, et al. First experience with model-based selection of head and neck cancer patients for proton therapy. Radiother Oncol 2020 Oct;151:206–13.
[10] Frank SJ, Blanchard P, Lee JJ, Sturgis EM, Kies MS, Machtay M, et al. Comparing intensity-modulated proton therapy with intensity-modulated photon therapy for oropharyngeal cancer: The journey from clinical trial concept to activation. Semin Radiat Oncol 2018 Apr;28:108–13.
[11] Høxbroe Michaelsen S, Grønhøj C, Høxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer 2017 Jun;78:91–102.
[12] Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol 2009 Feb;90:189–95.
[13] Langendijk JA, Hoebers FJP, de Jong MA, Doornaert P, Terhaard CHJ, Steenbakkers R, et al. National Protocol for Model-Based Selection for Proton Therapy in Head and Neck Cancer. Int J Part Ther. 2021 Summer;8:354-65.
[14] Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol 2012 Oct;105:107–14.
[15] Beetz I, Schilstra C, van der Schaaf A, van den Heuvel ER, Doornaert P, van Luijk P, et al. NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: the role of dosimetric and clinical factors. Radiother Oncol 2012 Oct;105:101–6.
[16] Blanchard P, Wong AJ, Gunn GB, Garden AS, Mohamed ASR, Rosenthal DI, et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. Radiother Oncol 2016 Dec;121:381–6.
[17] Van den Bosch L, van der Schaaf A, van der Laan HP, Hoebers FJP, Wijers OB, van den Hoek JGM, et al. Comprehensive toxicity risk profiling in radiation therapy for head and neck cancer: A new concept for individually optimised treatment. Radiother Oncol 2021 Apr;157:147–54.
[18] Hansen CR, Friborg J, Jensen K, Samsoe E, Johnsen L, Zukauskaite R, et al. NTCP model validation method for DAHANCA patient selection of protons versus photons in head and neck cancer radiotherapy. Acta Oncol 2019 Oct;58:1410–5.
[19] Jensen AR, Nellemann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 2007 Jul;84:5–10.
[20] Lyhne NM, Christensen A, Alanin MC, Bruun MT, Jung TH, Bruhn MA, et al. Waiting times for diagnosis and treatment of head and neck cancer in Denmark in 2010 compared to 1992 and 2002. European journal of cancer (Oxford, England : 1990). 2013 May;49:1627-33.
[21] Hansen CR, Jensen K, Smulders B, Holm AIS, Samsoe E, Nielsen MS, et al. Evaluation of decentralised model-based selection of head and neck cancer patients for a proton treatment study. DAHANCA 35. Radiother Oncol. 2023 Jul 20:109812.
[22] Jensen K, Friborg J, Hansen CR, Samsøe E, Johansen J, Andersen M, et al. The danish head and neck cancer group (DAHANCA) 2020 radiotherapy guidelines. Radiother Oncol 2020 Aug 8.
[23] Brouwer CL, Steenbakkers RJ, Bourhis J, Budach W, Grau C, Gregoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol 2015 Oct;117:83–90.
[24] Gregoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG,

NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol 2018 Jan;126:3–24.
[25] Gregoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014 Jan;110:172-81.
[26] Nowicka-Matus K. Acute toxicities in proton therapy for head and neck cancer – a matched analysis of the DAHANCA 35 pilot study. Submitted. 2022.
[27] Lee A, Kang J, Yu Y, McBride S, Riaz N, Cohen M, et al. Trends and Disparities of Proton Therapy Use among Patients with Head and Neck Cancer: Analysis from the National Cancer Database (2005-14). Int J Part Ther. 2019 Spring;5:1-10.
[28] Nogueira LM, Sineshaw HM, Jemal A, Pollack CE, Efstathiou JA, Yabroff KR. Association of race with receipt of proton beam therapy for patients with newly diagnosed cancer in the US, 2004–2018. JAMA Netw Open 2022 Apr 1;5:e228970.
[29] Hernandez M, Lee JJ, Yeap BY, Ye R, Foote RL, Busse P, et al. The Reality of Randomized Controlled Trials for Assessing the Benefit of Proton Therapy: Critically Examining the Intent-to-Treat Principle in the Presence of Insurance Denial. Adv Radiat Oncol. 2021 Mar-Apr;6:100635.
[30] Thomson DJ, Cruickshank C, Baines H, Banner R, Beasley M, Betts G, et al. TORPEdO: A phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer. Clin Transl Radiat Oncol 2023 Jan;38:147–54.