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Acute toxicities in proton therapy for head and neck cancer – A matched analysis of the DAHANCA 35 feasibility study

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ABSTRACT

Background and purpose: As preparation for a national randomized study comparing proton radiotherapy to photon radiotherapy, DAHANCA 35, we performed a non-randomized pilot study to investigate patient selection, logistics, planning, and treatment delivery. With the present study, as a comprehensive safety analysis, we want to compare toxicity during and up to two months after therapy to a historically matched group of patients treated with photon radiotherapy.

Materials and methods: 62 patients treated with protons were matched to 124 patients who received photon treatment outside a protocol. Available data were retrieved from the DAHANCA database. Patients were matched on treatment centre, concurrent chemotherapy, tumour site, stage, p16 status for oropharynx cancers. Selection of patients for proton therapy was based on comparative treatment plans with a NTCP reduction for dysphagia and xerostomia at six months.

Results: Baseline characteristics between groups were well balanced, except for the type of drug used concurrently; more photon patients received Carboplatin (21.2 % vs 5.8 %, $p = 0.01$). Proton therapy was associated with significantly less weight loss at the end of treatment, mean weight loss of 3 % for protons and 5 % for photons ($p < 0.001$). There were more grade 3 skin reactions and grade 3 mucositis after proton treatment compared with photons at the end of treatment, Risk Ratio (RR) 1.9 (95 % CI: 1.01–3.5, $p = 0.04$) and RR 1.5 (95 % CI: 1.3–1.7, $p < 0.001$), respectively. All differences resolved at follow up two months after treatment. There were no significant differences between groups on opioid use, use of feeding tubes, or hospitalization during the observation period.

Conclusion: Proton treatment resulted in excess objective mucositis and dermatitis, which was transient and did not seem to negatively influence weight or treatment compliance and intensity. Selection bias was likely especially since NTCP models were used for selection of proton treatment and photon treated patients were matched manually. We are currently including patients in a randomized controlled trial.

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Introduction

Treatment with intensity-modulated radiotherapy (IMRT) of squamous cell carcinoma (SCC) of the pharynx or larynx provides good locoregional disease control. As expected, the treatment with primary radiation therapy induces significant acute and late side effects and reduced quality of life [1–4]. Acute side effects, including mucositis, dermatitis, dysphagia, pain, xerostomia, and weight loss, increase until approximately two weeks after treatment, after which mucositis and dermatitis resolve. Basic supportive care includes analgesics, feeding tubes, and hospitalization [5–8]. Protons compared to photons can often deliver identical tumor coverage while reducing radiation dose to surrounding healthy tissues due to different dose-deposition, with reduced entrance dose and no exit dose. This could potentially decrease the severity of both acute and late morbidity [9,10]. Early reports on proton therapy for head and neck cancer are promising, showing excellent disease control, overall survival, and acceptable acute and subacute toxicity [11–13].

Multiple-dose planning studies have compared proton therapy to photons in head and neck cancer, showing superior organs at risk (OAR) sparing [14–16]. However, there is a need to confirm whether a dosimetric advantage of proton therapy translates into a clinical benefit. So far, a limited number of retrospective studies directly comparing the toxicity of proton and photon treatments have been published. Results are encouraging, showing reduced feeding tube dependency, hospitalization, dermatitis, need for narcotics and less osteoradionecrosis [17,18]. As proton therapy is more expensive than photon treatment and the availability may be limited, selecting the patients who will likely benefit from protons is necessary. One of the encouraging approaches is to compare proton and photon treatment plans by Normal Tissue Complication Probability (NTCP) models, where the selection of patients is based on a reduction of the estimated risk of side effects, i.e., xerostomia [19] or dysphagia [20] calculated from doses to OARs and clinical parameters [16,21].

DAHANCA 35 is the first national Danish study of proton radiotherapy in squamous cell carcinoma of pharyngeal or laryngeal origin. The study was initiated in April 2019 by the Danish Head and Neck Cancer Group (DAHANCA) and consists of a feasibility study, presented here, and an ongoing randomized part. In the feasibility study, patients were offered proton therapy at the Danish Centre for Particle Therapy (DCPT) if the estimated risk of late dysphagia and/or xerostomia could be reduced [19,20,22,23]. In contrast to other studies [NCT01893307 (US) and Torpedo [24] (UK)] the present study also includes patients with tumors outside the oropharynx, as the study tests if the complications risk can be reduced as expected by the models, and patients with other primaries should not be withheld the opportunity of trial inclusion.

The current study aims to compare toxicity during and up to two months after treatment to a historically matched group of patients treated with photon radiotherapy according to published guidelines [25,26].

Materials and methods

Patients

Between April 2019 and October 2020, 63 patients from all six national head and neck cancer centers with histologically verified squamous cell carcinoma of the pharynx or larynx were selected for proton therapy in the feasibility study of DAHANCA 35. One patient did not receive the planned proton therapy due to complications of gastrostomy tube insertion and prolonged hospitalization before radiotherapy. Instead, the patient received photon therapy at the local center and therefore was excluded from the current study.

A 2:1 matched cohort of 124 patients who received photon treatment from 2012 to 2020 was selected from the DAHANCA database. The patients were individually matched on the following factors: treatment center, concurrent chemotherapy (yes vs no), tumour site (larynx vs pharynx), TNM stage according to UICC version 8 (stage I-II vs stage III-IV), p16 status (positive vs negative vs unknown) for oropharynx cancers (OPC), and prescribed normal-fractionated radiation dose (66 Gy or 68 Gy). As a result of the detailed matching strategy, an extended photon matching period (2012–2020) was needed but starting with the most recent time period. As all proton treated patients completed RT, controls were only included if they completed radiotherapy to the intended dose and had adequate follow-up data, as this study aimed to examine the toxicity of proton treatment. Information on baseline xerostomia and dysphagia was not available for the photon group and therefore not included in the matching procedure.

Treatment

In both groups, target definition, treatment and quality assurance including adaptation followed local as well as national DAHANCA guidelines [27,28]. Patients in both groups received primary radiotherapy, and no de-escalation regimens were employed. Moreover, the use of surgery was limited to the diagnostic procedures described in the national DAHANCA guidelines. Patients received 66 Gy or 68 Gy to a high-risk area (CTV1), 60 Gy to an intermediate-risk area (CTV2), and 50 Gy to a low-risk area (CTV3), given six fractions weekly for a total of 33 or 34 fractions. All doses are stated in Gy_{RBE} using a constant RBE-factor for protons of 1.1. All patients received treatment with intensity-modulated radiotherapy (IMRT/IMPT) with simultaneous integrated boost. Proton plans were delivered with a pencil beam scanning technique, and a range shifter was used for all patients. The concomitant chemotherapy regimen consisted of weekly cisplatin 40 mg/m^2 IV or carboplatin 1.5 AUC IV if cisplatin was contraindicated. Patients received radiosensitizer nimorazole 1.2 g/m^2 90 min before each fraction.

Patients could be referred for protons if a comparative treatment plan showed a reduced risk of either xerostomia or dysphagia. Both the photon plan and the proton plans were made by the referring departments [29]. Mean doses for upper pharyngeal muscle constrictor, extended oral cavity, contralateral parotid gland, grade of baseline dysphagia and xerostomia (DAHANCA scores, Appendix 1) were used to calculate the estimated possible reduction of dysphagia or xerostomia (ΔNTCP). The model was validated and refitted to match the Danish population at the DAHANCA 35 initiation [22].

Patients were selected for proton therapy if ΔNTCP for dysphagia or xerostomia was estimated to be a minimum of 10 %. However, due to insufficient selection of patients for proton therapy, the cut-off value was changed first to 7 % and later to 5 % for dysphagia or xerostomia. Most patients were selected with a 5 % threshold. Even though 5 % was used as a cut off, a significant dose reduction was observed for the critical OARs in the selected patients [29].

Follow-up during treatment consisted of either weekly or as needed physical examination and recording of acute toxicities according to the DAHANCA score (Appendix 1) [27,28]. A feeding tube, analgesics, and other supportive measures were offered according to institutional guidelines. After treatment, patients were followed at the referring institution at two weeks, eight weeks, six months, and every 6 months year 1–2, and once yearly year 3–5.

Data collection

Data on demographics, smoking history, comorbidities, tumor stage and site, HPV (p16) status, radiation dose, fractionation, use of chemotherapy and nimorazole, opioids use, feeding tube, degree of mucositis, and skin reactions were collected from the DAHANCA database. The electronic medical files added information on hospitalization during or up to 60 days after treatment, and RT laterality (ipsilateral or bilateral treatment). Dosimetric data for normal tissues could not be

included in this study, as it was not available in the database.

Ethics considerations

The regional scientific ethics committee approved the DAHANCA 35 feasibility study in the Central Denmark Region (J. nr. 1-10-72-30-19) and registered on Clinical Trials.com (NCT05423704). All included patients provided written informed consent. The approval from The Danish Clinical Quality Program – National Clinical Registers (RKKP) and The Internal List of Projects in The Central Denmark Region. (J. nr. 1-16-02-49-21) was granted in order to obtain information on the matched photon-treated patients in the DAHANCA database and the additional data from the medical records.

Data analysis

Toxicity data from weekly follow-up during treatment was predominantly missing in the photon group. Therefore, results are presented from the last registered follow-up at the end of the treatment as well as two and eight weeks after completion. Differences in baseline characteristics between the proton and photon groups were assessed by Pearson's Chi-squared test for categorical variables, and *t*-test or Mann-Whitney *U* test for continuous variables. Missing data was analyzed with respect to available patient data and seemed to be missing at random. All statistical calculations, including calculation of relative risks, were therefore performed only on available data and no data imputations were performed.

A p-value less than 0.05 was considered statistically significant. SPSS version 20 (IBM) was used for the analysis.

Results

In total, 186 patients were included. The baseline and clinical characteristics of both groups are presented in Table 1. The mean dose received of nimorazole was 59 g (IQR 52–63) for protons and 44 g (IQR 17–68) for photons patients ($p = 0.002$). Most of the patients treated with concurrent chemotherapy in both groups received four or more cumulative doses of weekly chemotherapy (32 (63 %) proton patients and 61 (61 %) photon patients, $p = 0.3$, Fig. 1).

Proton therapy was associated with significantly less weight loss at the end of RT, with mean weight loss for protons 2.6 ± 4.3 kg (SD) and 4.5 ± 4.7 kg for photons ($p = 0.01$) corresponding to a mean of 3 % weight loss at the end of RT for protons and 5 % for photons ($p < 0.001$) (Fig. 2). Median and range of weight loss at the end of treatment was 1.8 kg (range; −5.0, 18.8) and 4.1 kg (range; −14.4, 15.5)) for protons and photons respectively. At the end of treatment, the risk of ≥ 5 % weight loss was also significantly lower for protons (Relative Risk (RR) 0.5; 95 % CI: 0.3–0.8, $p = 0.004$). At first follow up after therapy, the difference between the groups were no longer significant for any endpoint.

Equal proportions of the proton (34 %) and photon patients (37 %) required hospitalization during and up to 60 days after treatment completion (RR 0.9; 95 % CI: 0.6–1.4, $p = 0.7$). The median number of days spent in hospital was 8 days (IQR 2–18.5) and 6 days (IQR 3–14), respectively ($p = 0.5$). Four patients (6.5 %) in the proton group and 14 (11.3 %, RR 0.5, 95 % CI:0.2–1.66, $p = 0.3$) in the photon group were hospitalized more than once during the treatment and up to 60 days after. The reasons for the first hospitalization are presented in Table 2.

There was no significant difference between groups for opioid use in the observation period (Fig. 3). Grade 3 mucositis at the end of treatment was registered in 61 (100 %) protons and 65 (65 %) photons patients (RR 1.5 95 % CI: 1.3–1.7, $p < 0.001$, Fig. 2). Information on the grade of mucositis at the end of RT was missing in 19 % (24) of photon patients (Table 3). At 8-weeks post-treatment, 5 (8 %) patients in the proton group and 7 (6 %) patients in the photon group still had persisting grade 3 mucositis (RR 1.3, 95 % CI; 0.45–4.1, $p = 0.6$).

Proton therapy was associated with more grade 3 skin reactions at

Table 1
Baseline characteristics of groups. Abbreviations: RT=radiotherapy, OPC=oropharyngeal cancer, RBE=relative biological effectiveness.

	Protons N=62 (%)	Photons N=124 (%)	Chi-square or *t*-test p-values (missing values were excluded)
Sex			0.9
Male	48(77.4)	95(76.6)	
Female	14(22.6)	29(23.4)	
Age			0.5
Median(years)	61	62	
Mean	61	62	
Range	41–80	40–85	
Interquartile range (IQR)	55–67	56–68	
WHO Performance status			0.5
0	50(80.7)	73(58.9)	
1	11(17.7)	25(20.2)	
2	1(1.6)	1(0.7)	
Smoking status			0.3
Never	25(40.3)	38(30.6)	
Former	21(34)	57(46)	
Current	16(25.7)	29(23.4)	
Charlson Comorbidity Index score			0.5
0	51(82.3)	92(74.2)	
1	7(11.3)	24(19.4)	
2	3(4.8)	5(4.0)	
3	1(1.6)	3(2.4)	
Disease site			0.4
Oropharynx	54(87.2)	106(85.5)	
Nasopharynx	2(3.2)	9(7.3)	
Hypopharynx	3(4.8)	2(1.6)	
Larynx	3(4.8)	7(5.6)	
P16 status OPC			0.9
Positive	48(88.9)	95(89.6)	
Negative	5(9.3)	9(8.5)	
Unknown	1(1.8)	2(1.9)	
Clinical stage (UICC version 8)			0.8
Stage I-II	46(74.2)	94(75.8)	
Stage III-IV	16(25.8)	30(24.2)	
Tumour stage (UICC version 8)			0.7
T1	16(25.8)	36(29)	
T2	32(51.6)	59(47.6)	
T3	9(14.5)	22(17.7)	
T4	5(8.1)	6(4.8)	
N stage (UICC version 8)			0.1
N0	2(3.2)	10(8.1)	
N1	32(51.6)	76(61.3)	
N2	26(42)	34(27.4)	
N3	2(3.2)	4(3.2)	
Chemotherapy			1.0
Concurrent	52(83.9)	104(83.3)	
None	10(16.1)	20(16.7)	

(*continued on next page*)

Table 1 (*continued*)

	Protons N=62 (%)	Photons N=124 (%)	Chi-square or *t*-test p-values (missing values were excluded)
Type of drug used			0.02*
Cisplatin	49(94.2)	82(78.8)	
Carboplatin	3(5.8)	22(21.2)	
RT dose			0.5
66 Gy (RBE)	28(45.2)	62(50)	
68 Gy (RBE)	34(54.8)	62(50)	
RT laterality			0.4
Bilateral	44(71)	95(76.6)	
Unilateral	18(29)	29(23.4)	
Baseline weight (kg)			0.5
Mean	86.5	84.5	
Range	48–152	49.5–169	
Interquartile range (IQR)	74.5–95.5	74–106	

the end of RT (RR 1.9; 95 % CI: 1.01–3.5, p = 0.04, Fig. 3). Two patients in the proton group experienced skin ulceration at the end of the treatment. At 8 weeks post-RT, no grade 3 or 4 skin reactions were registered in protons compared to 1 patient in the photon group. At the end of the treatment, 14 (23 %) protons and 37 (30 %) photons patients had a feeding tube (RR 2.6; 95 % CI: 0.68–10.4, p = 0.3). At 8-weeks post-RT, feeding tube was used for 6 (10 %) of proton-treated patient's vs 8 (6 %) for photons (p = 0.5).

Discussion

Patients receiving proton radiotherapy all completed the planned radiotherapy, and patients seemed to lose less weight than the control group. Nevertheless, more acute objective toxicity was observed at the end of radiotherapy, in the proton treated group compared to the historical control group of photon treated patients. Similar rates of use of opioids, feeding tubes, and hospitalization rates were registered in both groups. These results are, to some degree, consistent with previously reported studies. Blanchard et al. performed a matched analysis of 50 IMPT and 100 IMRT OPC patients. They found no statistical differences in acute grade 3 or higher mucositis or dermatitis between groups, as opposed to the present study. The composite endpoint of grade 3 or higher weight loss or gastrostomy tube (PEG) placement rates were significantly lower for IMPT patients at 3 months and 1 year after treatment in that study. No differences in frequency of hospitalization were noticed in both groups [30]. The present results confirm statistically significant less weight loss at the end of RT for proton treated patients and similar rates of hospitalization in both groups. Still, there was no difference in feeding tube use at 8-weeks post-RT follow-up. Another difference is the shorter observation period in the present study and inclusion of all tumors sites (26 non-OPC patients across both groups).

In a more recent study comparing IMPT and IMRT treatment for OPC, IMPT was linked to lower rates of PEG placement (19.6 % IMPT vs 46.3 % IMRT; p = 0.001) and less hospitalization (8.7 % vs 31.3 %, p < 0.001 [31]), which was not confirmed in this report. In addition, significantly more mucosa infections and non-significant more dermatitis were reported with IMPT. Unlike in the current cohort, there was a relative risk reduction of 22 % for the use of narcotics at the end of treatment with IMPT [31]. Another retrospective study of 41 patients (18 received proton therapy and 23 IMRT) treated unilaterally for major

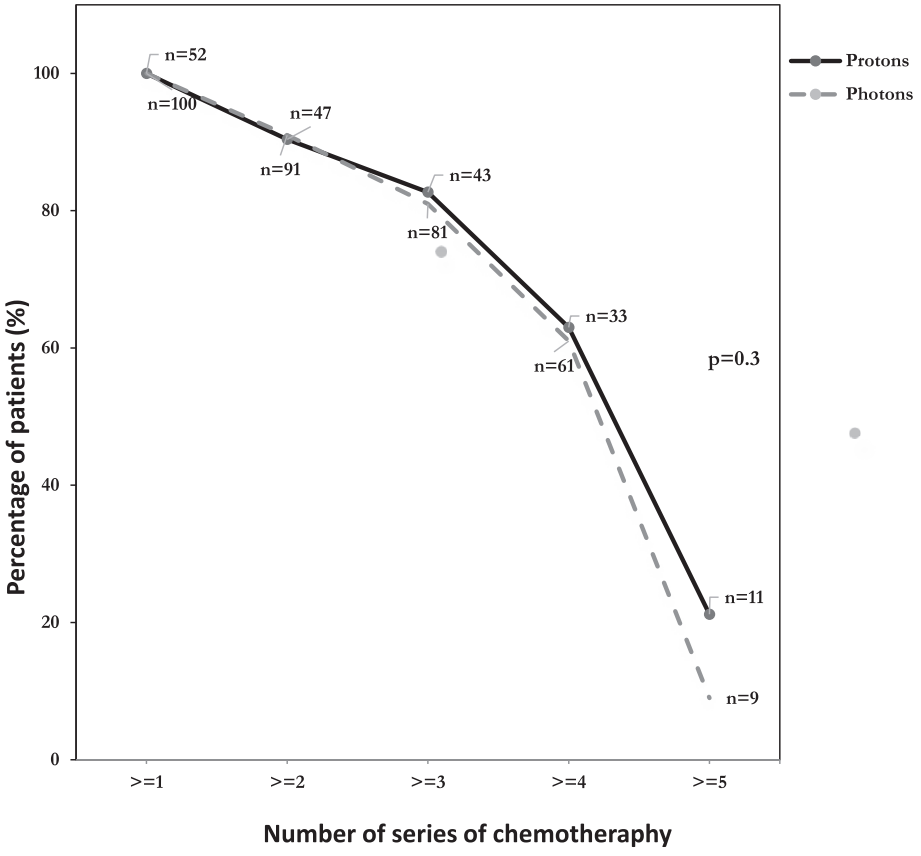

Fig. 1. The percentage (%) and number (n) of patients receiving ≥ 1, 2, 3, 4, and 5 series of concurrent chemotherapy.

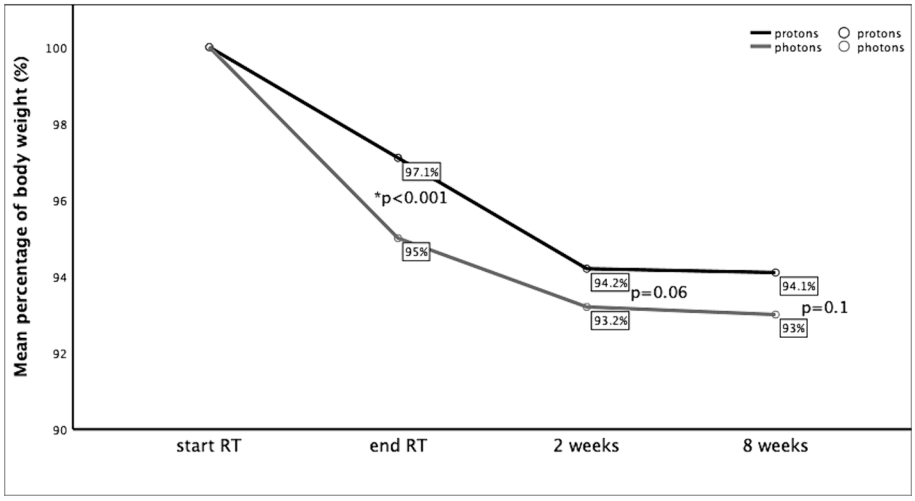

Fig. 2. Changes of mean percentage of body weight (%) for protons and photons patients at the end of RT, 2 weeks and 8 weeks post-RT.

Table 2
Reasons for the first hospitalisation for up to 60 days of the treatment. Patients may have more than one indication for admission.

	Protons (N=62)	%	Photons (N=124)	%
Any	21	34	46	37
Nutritional problems, dehydration and nausea	14	23	22	18
Non-neutropenic infection	3	5	6	5
Neutropenic fever	1	2	4	3
Diagnostic procedures	1	2	5	4
Thromboembolic disease	1	2	2	2
Worsening of comorbidity	0	0	4	3
Pain, morphine side-effects	1	2	5	4
Other	4	6	6	5

salivary gland cancer or cutaneous SCC showed improved acute toxicity and lower doses to the organ at risk with proton therapy. As the mucous membranes were not always in the target, this translated into significantly less grade 2 or higher of mucositis (16.7 % vs 52.2 %, $p = 0.019$), nausea (11.1 % vs 56.5 %, $p = 0.003$), and dysgeusia (5.6 % vs 65.2 %, $p < 0.001$). However, grade ≥ 2 dermatitis was more frequent in proton-treated patients than in IMRT (100 % vs 73.9 %, $p = 0.019$), also noticed in the current study. According to the authors, one reason for that was the delivery of protons with uniform scanning, which resulted in an increased entrance dose [32]. The limitations of the studies mentioned above are the retrospective, non-randomized single-center design, treatment selection based on health insurance coverage and heterogeneity of registration and follow-up practices. Access to proton therapy differs worldwide due to the high costs of building and maintaining the facility. In the United States, only 0.2 % of head and neck cancer patients received proton therapy from 2005 to 2014. Patients treated at the academic centers with higher median income and distance of fewer than 13 miles were most likely to receive protons [33]. In the present study, the Danish Healthcare System covered the costs of treatment, including accommodation and transport. Patients had access to proton treatment from every photon clinic, as all centers participated in DAHANCA 35. In other words, the economic issues and the facility type were not obstacles to receiving proton therapy in Denmark. However, the geographic distance and other psychosocial factors might have played a role in the recruiting process for DAHANCA 35. Those were not explored in the present study and need further examination [34].

In our study, protons were delivered with pencil beam scanning and were associated with higher grade 3 mucositis and dermatitis rates at the end of the treatment, but the differences were transient and not present after 8-weeks.

The shortcomings of the present study may be differences in follow-up practice between the DCPT and the photon clinics: Not all centers performed endoscopy routinely during the follow-up leading to the incompleteness of mucositis registration or possible registration of only oral mucositis (Appendix 1). Nevertheless, the difference is intriguing. An effect of RBE being > 1.1 cannot be ruled out [35,36], but as the effect was not present at 8 weeks and did not lead to an increase in grade 4 mucositis, no alterations were made in the protocol. Another intriguing result is that even though more grade 3 mucositis was observed in proton treated patients, that did not translate into increased use of narcotics nor hospitalization in this group, in contrast reduced weight loss was registered by the end of treatment. One explanation could be that using DAHANCA scoring does not provide information on the extension of mucositis but only the highest intensity of mucosal reaction, and with protons, the area of mucositis is probably decreased, as dose to the oral cavity is significantly decreased [8,28].

The control group includes patients treated in before the proton treated patients. Practice may have changed but the treatment guidelines have remained unaltered. Incomplete data, mainly in photons-treated patients, could have played a role in overestimating the differences in toxicity between groups as the missing values were excluded from analyses (Appendix 1). Data on dysphagia and xerostomia during therapy was not available to an extend that allowed a meaning full comparison.

Another limitation of the study is its non-randomized character and the matching strategy, which was conducted manually and is subjected to bias. Only patients who have completed radiotherapy and had data on follow-up were selected, leading to the underrepresentation of the real-life photon cohort. Another issue is that patients had to travel to DCPT to receive proton therapy, possibly introducing a selection for patients who could overcome geographic and psychosocial barriers for participation in DAHANCA 35, exemplified by the slightly higher non-significant proportion of patients in PS 0 in the proton group. This could especially be important for the frequency of hospital admissions. As the selection of patients for proton therapy was based on reducing the absolute risk, patients with a small estimated risk (e.g., NTCP %) of the photon plan would not enter the proton cohort, as a reduction of the absolute risk was not possible. This would possibly lead to the underrepresentation of patients with a low risk of dysphagia treated with protons. Patients were treated with moderately accelerated radiotherapy and nimorazole, which may restrict the generalizability of the results.

Therefore, prospective randomized studies are needed to validate the clinical benefits of protons regarding both acute and late morbidity. The ongoing randomized study will solve the biases of the present study.

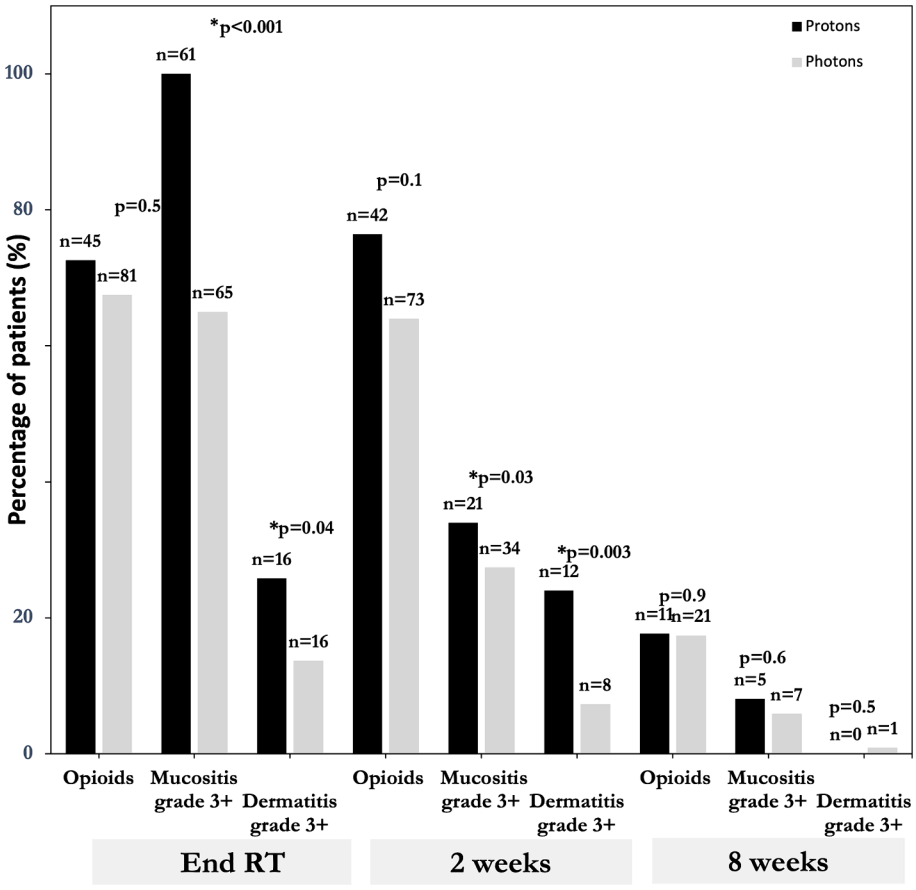

Fig. 3. The number (n) and percentage of patients using opioids, experiencing at least grade 3 mucositis and dermatitis at the end of the treatment, 2 weeks and 8 weeks post-RT.

Table 3
The number and the percentage of patients in both groups with available data.

	Protons			Photons		
	Patients N=62		%	Patients N=124		%
	Yes	No		Yes	No	
Opioid use at the end of RT	45	17	73	81	39	68
Opioid use-2 weeks post-RT	42	13	76	73	41	64
Opioid use-8 weeks post-RT	11	51	18	21	100	17
Mucositis grade 3+- end of RT	61	0	100	65	35	65
Mucositis grade 3+-2 weeks post-RT	21	20	51	34	70	33
Mucositis grade 3+-8 weeks post-RT	5	57	8	7	111	6
Dermatitis grade 3+-end of RT	16	46	26	16	101	14
Dermatitis grade 3+-2 weeks post-RT	12	38	24	8	101	7
Dermatitis grade 3+-8 weeks post-RT	0	60	0	1	112	1
5 % weight loss at the end of RT	18	43	30	61	51	54

In conclusion, our study showed an increase in skin toxicity and mucositis but reduced weight loss with proton therapy, but differences were transient. Selection bias was likely especially since NTCP models were used for selection of proton treatment and photon treated patients were manually matched. However, we found no indications of severe toxicity compared to photons and we have therefore proceeded with the randomized study, which is including at time of writing.

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CRediT authorship contribution statement

K. Nowicka-Matus: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Writing – review & editing, Project administration, Validation. **J. Friborg:** Conceptualization, Methodology, Funding acquisition, Investigation, Writing – review & editing, Validation. **C.R. Hansen:** Conceptualization, Methodology, Writing – review & editing, Validation. **M. Bernsdorf:** Investigation. **U.V. Elstrøm:** Writing – review & editing. **M. Farhadi:** Investigation. **C. Grau:** Writing – review & editing, Funding acquisition. **J.G. Eriksen:** Investigation, Writing – review & editing. **J. Johansen:** Investigation, Writing – review & editing. **M.S. Nielsen:** Writing – review & editing. **A. Holm:** . **E. Samsøe Hinsby:** Writing – review & editing. **P. Sibolt:** Writing – review & editing. **B. Smulders:** Writing – review & editing. **K. Jensen:** Supervision, Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Validation.

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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Data sharing

This study was based on the DAHANCA database and Danish National Clinical Registers. Authors do not own these data and hence are not permitted to share them. Research data are not available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100835.

References

[1] Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of Radiation-Induced Xerostomia on Quality of Life After Primary Radiotherapy Among Patients With Head and Neck Cancer. Int J Radiat Oncol Biol Phys 2007;69 (3):751–60. https://doi.org/10.1016/j.ijrobp.2007.04.021.

[2] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008; 26(22):3770–6. https://doi.org/10.1200/JCO.2007.14.6647.

[3] Toledano I, Graff P, Serre A, et al. Intensity-modulated radiotherapy in head and neck cancer: Results of the prospective study GORTEC 2004–03. Radiother Oncol 2012;103(1). https://doi.org/10.1016/j.radonc.2011.12.010.

[4] Vergeer MR, Doornaert PAH, Rietveld DHF, Leemans CR, Slotman BJ, Langendijk JA. Intensity-Modulated Radiotherapy Reduces Radiation-Induced Morbidity and Improves Health-Related Quality of Life: Results of a Nonrandomized Prospective Study Using a Standardized Follow-Up Program. Int J Radiat Oncol Biol Phys 2009;74(1):1–8. https://doi.org/10.1016/j.ijrobp.2008.07.059.

[5] Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66 (3):253–62. https://doi.org/10.1016/S0167-8140(02)00404-8.

[6] Mortensen HR, Overgaard J, Jensen K, et al. Factors associated with acute and late dysphagia in the DAHANCA 6 & 7 randomized trial with accelerated radiotherapy for head and neck cancer. Acta Oncol (madr) 2013;52(7). https://doi.org/10.3109/0284186X.2013.824609.

[7] Givens DJ, Lucy B, Karnell H, et al. Adverse Events Associated With Concurrent Chemoradiation Therapy in Patients With Head and Neck. Cancer 2009;135. https://jamanetwork.com/.

[8] Hansen CR, Bertelsen A, Zukauskaite R, et al. Prediction of radiation-induced mucositis of H&N cancer patients based on a large patient cohort. Radiother Oncol 2020;147:15–21. https://doi.org/10.1016/j.radonc.2020.03.013.

[9] Meijer TWH, Scandurra D, Langendijk JA. Reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. Br J Radiol 2020; 93(1107):20190955. https://doi.org/10.1259/bjr.20190955.

[10] Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The Potential Benefit of Radiotherapy with Protons in Head and Neck Cancer with Respect to Normal Tissue Sparing: A Systematic Review of Literature. Oncologist 2011;16(3): 366–77. https://doi.org/10.1634/theoncologist.2010-0171.

[11] Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: Early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys 2005;62(2):494–500. https://doi.org/10.1016/j.ijrobp.2004.09.064.

[12] Gunn GB, Blanchard P, Garden 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;95(1). https://doi.org/10.1016/j.ijrobp.2016.02.021.

[13] Aljabab S, Liu A, Wong T, Liao JJ, Laramore GE, Parvathaneni U. Proton Therapy for Locally Advanced Oropharyngeal Cancer: Initial Clinical Experience at the University of Washington. Int J Part Ther 2019;6(3). https://doi.org/10.14338/IJPT-19-00053.1.

[14] Van Dijk LV, Steenbakkers RJHM, Ten Haken B, et al. Robust Intensity Modulated Proton Therapy (IMPT) increases estimated clinical benefit in head and neck cancer patients. PLoS One 2016;11(3). https://doi.org/10.1371/journal.pone.0152477.

[15] Holliday EB, Kocak-Uzel E, Feng L, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: A case-matched control analysis. Med Dosim 2016;41(3): 189–94. https://doi.org/10.1016/j.meddos.2016.01.002.

[16] Rwigema JCM, Langendijk JA, Paul van der Laan H, Lukens JN, Swisher-McClure SD, Lin A. A Model-Based Approach to Predict Short-Term Toxicity Benefits With Proton Therapy for Oropharyngeal Cancer. Int J Radiat Oncol Biol Phys 2019;104(3):553–62. https://doi.org/10.1016/j.ijrobp.2018.12.055.

[17] Zhang W, Zhang X, Yang P, et al. Intensity-modulated proton therapy and osteoradionecrosis in oropharyngeal cancer. Radiother Oncol 2017;123(3):401–5. https://doi.org/10.1016/j.radonc.2017.05.006.

[18] Meijer TH, Langendijk SD, Meijer TWH, Scandurra D, Langendijk JA. Proton TheraPy SPecial Feature: Review Article Reduced Radiation-Induced Toxicity by Using Proton Therapy for the Treatment of Oropharyngeal Cancer.; 2020.

[19] Beetz I, Schilstra C, Van Der Schaaf A, 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;105(1):101–6. https://doi.org/10.1016/j.radonc.2012.03.004.

[20] Christianen MEMC, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: Results of a prospective observational study. Radiother Oncol 2012;105(1):107–14. https://doi.org/10.1016/j.radonc.2011.08.009.

[21] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. Radiother Oncol 2013;107(3):267–73. https://doi.org/10.1016/j.radonc.2013.05.007.

[22] Hansen CR, Friborg J, Jensen K, et al. NTCP model validation method for DAHANCA patient selection of protons versus photons in head and neck cancer radiotherapy. Acta Oncol (madr) 2019;58(10). https://doi.org/10.1080/0284186X.2019.1654129.

[23] Friborg J, Jensen K, Eriksen JG, et al. Considerations for study design in the DAHANCA 35 trial of protons versus photons for head and neck cancer. Radiother Oncol November 2022;2023. https://doi.org/10.1016/j.radonc.2023.109958.

[24] Thomson DJ, Cruickshank C, Baines H, 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;38:147–54. https://doi.org/10.1016/j.ctro.2022.11.010.

[25] Hansen CR, Johansen J, Samsøe E, et al. Consequences of introducing geometric GTV to CTV margin expansion in DAHANCA contouring guidelines for head and neck radiotherapy. Radiother Oncol 2018;126(1). https://doi.org/10.1016/j.radonc.2017.09.019.

[26] Jensen K, Friborg J, Hansen CR, et al. The Danish Head and Neck Cancer Group (DAHANCA) 2020 radiotherapy guidelines. Radiother Oncol 2020:151. https://doi.org/10.1016/j.radonc.2020.07.037.

[27] Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. Lancet 2003;362(9388):933–40. https://doi.org/10.1016/S0140-6736(03)14361-9.

[28] Jensen K, Bonde Jensen A, Grau C. The relationship between observer-based toxicity scoring and patient assessed symptom severity after treatment for head and neck cancer. A correlative cross sectional study of the DAHANCA toxicity scoring system and the EORTC quality of life questionnaires. Radiother Oncol 2006;78(3). https://doi.org/10.1016/j.radonc.2006.02.005.

[29] Hansen CR, Jensen K, Smulders B, et al. Evaluation of decentralised model-based selection of head and neck cancer patients for a proton treatment study. DAHANCA 35. Radiother Oncol 2023;xxxx):109812. https://doi.org/10.1016/j.radonc.2023.109812.

[30] Blanchard P, Garden AS, Gunn GB, 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;120(1): 48–55. https://doi.org/10.1016/j.radonc.2016.05.022.

[31] Manzar GS, Lester SC, Routman DM, et al. Comparative analysis of acute toxicities and patient reported outcomes between intensity-modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) for the treatment of oropharyngeal cancer. Radiother Oncol 2020;147:64–74. https://doi.org/10.1016/j.radonc.2020.03.010.

[32] Romesser PB, Cahlon O, Scher E, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. In: *Radiotherapy and Oncology*. Vol 118. Elsevier Ireland Ltd; 2016:286-292. doi: 10.1016/j.radonc.2015.12.008.

[33] Lee A, Kang J, Yu Y, 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 2020;5(4). https://doi.org/10.14338/IJPT-19-00051.1.

[34] Wilhøft Kristensen A, Lunde Jensen A, Jensen K, Oksbjerre Dalton S, Friborg J, Grau C. Exploring patient-reported barriers to participating in proton therapy clinical trials. *Tech Innov Patient Support*. Radiat Oncol 2024;29(November 2023). https://doi.org/10.1016/j.tipsro.2023.100230.

[35] Wagenaar D, Schuit E, van der Schaaf A, Langendijk JA, Both S. Can the mean linear energy transfer of organs be directly related to patient toxicities for current head and neck cancer intensity-modulated proton therapy practice? Radiother Oncol 2021;165:159–65. https://doi.org/10.1016/j.radonc.2021.09.003.

[36] Singh A, Kitpanit S, Neal B, et al. Osteoradionecrosis of the Jaw Following Proton Radiation Therapy for Patients With Head and Neck Cancer. JAMA Otolaryngol Head Neck Surgery 2023;149(2):151. https://doi.org/10.1001/jamaoto.2022.4165.