DAHANCA 37
A phase II study of intensity modulated proton therapy (IMPT) for re-irradiation with curative intent for recurrent or new primary head and neck cancer

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Summary

Design
Phase II observational

Inclusion criteria

- Histological verified loco-regional recurrence or new primary
- Available dose plan from primary radiotherapy course
- Comparative dose plan with advantages for proton radiotherapy e.g. integral dose
- Dmax dose (0.03 cm³) on the cumulated photon dose plans ≥ 90 Gy
- Complete Response (CR)* after initial therapy, except in the case where the recurrence is considered a geometric miss (recurrence center of mass (COM) outside the 95% of prescription dose.
- Inoperable or salvage surgery with R1/R2 resection, extranodal extension (ENE) or extensive soft tissue infiltration
- Absence of distant metastasis at both
  - clinical examination AND
  - PET-CT or CT of thorax and upper abdomen
- Life expectancy due to age and co-morbidity of ≥1 year. The general condition must be sufficient to tolerate persistent significant side effects, e.g. tube or cannulae
- PS≤2 (WHO See appendix)

The patients should be able to read Danish in order to participate with quality of life questionnaires, but can participate in the rest of the protocol without being fluent in Danish, if capable of reading the patient information.

Exclusion criteria

- Radical surgery (R0) and absence of adverse prognostic pathological features
- Lymphoma or malignant melanoma
- Inability to attend full course of radiotherapy or follow-up visits in the outpatient clinic
- As of 2019, patients with tracheal cannulas are excluded due to dose uncertainties. This may change if a technical solution becomes available.

Treatment

- 60 Gy/50 fx / 10W⁻¹ at 1.2 Gy/fx
  - i.e. EQD2 tumor=56 Gy, EQD2 late=50.4 Gy at α/β= 10 and 3, respectively
- Proton radiotherapy
- Concomitant cisplatin for eligible patients*

* Complete Response is defined as the situation when a trained clinician, ideally at a multidisciplinary team conference, defines the patient as in complete remission, based on clinical examination and available imaging. This status can of course later be considered wrong as new information becomes available (sub-centimeter nodes grow etc.)
- Nimorazole recommended for SCC*
  *The concurrent medical treatment (weekly cisplatin and nimorazole) are prescribed according to the national treatment guidelines, and are not part of the experimental treatment.

Endpoints
- Primary:
  - Any new late toxicity grade >=3 according to CTC AE 5.0
- Secondary
  - Side effects according to DAHANCA scoring system
  - Quality of life and PROM according to EORTC C30 and HN43
  - Loco-regional control (LRC)
  - Overall survival (OS)

Derived projects
- Morbidity (NTCP) modeling for cumulative doses
- Metrics for uncertainties regarding cumulative doses
# Abbreviations and terminology

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>b.i.d.</td>
<td>Bis in die – twice a day</td>
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<tr>
<td>COM</td>
<td>Center of Mass</td>
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<tr>
<td>Comparative dose plans</td>
<td>A radiotherapy treatment plan for both photons and protons is created in order to compare the two</td>
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<tr>
<td>CR</td>
<td>Complete Response, clinical and imaging</td>
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<td>CTC</td>
<td>Common Toxicity Criteria</td>
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<td>DAHANCA</td>
<td>Danish Head and Neck Cancer Group</td>
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<tr>
<td>DcmCollab</td>
<td>Dicom collaboration. National radiotherapy image bank</td>
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<tr>
<td>DCPT</td>
<td>Danish Center of Particle Therapy</td>
</tr>
<tr>
<td>ENE</td>
<td>Extra Nodal Extension</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for research and treatment of Cancer</td>
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<tr>
<td>EPTN</td>
<td>European Particle Therapy Network</td>
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<tr>
<td>Fx</td>
<td>Fractions</td>
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<tr>
<td>Gy</td>
<td>Gray – always in Co-equivalent doses</td>
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<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy (modern photon treatment)</td>
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<tr>
<td>LRC</td>
<td>Loco-regional control</td>
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<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
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<td>OAR</td>
<td>Organs at risk</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>Initial course of radiotherapy</td>
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<tr>
<td>QA</td>
<td>Quality assurance</td>
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<tr>
<td>Q.d.</td>
<td>Quaque die -once a day</td>
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<tr>
<td>RBE</td>
<td>Relative Biological Effectiveness</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinomas</td>
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<tr>
<td>TCP</td>
<td>Tumor Control Probability</td>
</tr>
<tr>
<td>W</td>
<td>Week</td>
</tr>
<tr>
<td>( \Sigma V_{90\text{Gy}} )</td>
<td>Volume that receives ( \geq 90 \text{ Gy} ) on the summation plan of first and second radiotherapy course</td>
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Background

Management of recurrence or new primary in an irradiated area in the head and neck region is a frequent and difficult clinical scenario. Recurrences from the most frequent histological type, squamous cell carcinomas, are typically localized at the same site as the primary tumor localizations. Surgery is the preferred treatment modality for recurrences or new primaries in a previously irradiated area, but many patients are inoperable. In these situations, a new course of radiotherapy is frequently considered. Very little is, however, known regarding the absolute and relative indications for re-irradiation. A recent Danish study on re-irradiation of 70 head and neck cancer patients, has shown a 5-year overall survival of 27%. The choice of treatment was heterogeneous, half of the patients had postoperative radiotherapy and 41% was treated with concomitant chemotherapy. Half of the patients had hyperfractionated, and often accelerated, radiotherapy\(^1\), reflecting the absence of specific treatment recommendation as well as absence of evidence. Many patients in the mentioned study has been treated with non-IMRT techniques, indicating that more patient has the possibility of receiving re-irradiation today, because there primary RT is given with very conformal technique, hence sparing of normal tissue like the spinal cord.

Surgery

Surgery is the standard treatment for recurrences or second primaries in an irradiated area. Unfortunately, a significant proportion of patients are inoperable and of those who has surgery, a significant proportion has risk factors for recurrence: Non-radical excision, (R1/R2 resection), diffuse soft tissue infiltration or extra nodal extension. A small RCT has shown that re-irradiation have a significant effect on LRC, but not OS\(^2\) in the postoperative setting. The duration of the recurrence free interval from the primary treatment does not seem to carry prognostic information for the result of surgery\(^3\). This is in contrast to the results for radiotherapy. It is known that persistent disease after radiotherapy is probably only curable with surgery.

If salvage surgery has been performed, re-irradiation may be indicated if free margins are not obtained. Postoperative re-irradiation have been reported to be beneficial in several publications\(^4\),\(^5\),\(^6\),\(^7\), but a risk of selection bias is high.

Radiotherapy

Results of re-irradiation on survival are less than impressive, and re-irradiation has probably no positive immediate effect on quality of life. High dose re-irradiation is therefore not a palliative treatment, but is indicated primarily with the purpose of the potential effect on survival and local control\(^7\).

Apart from disease- and patient related criterias, absence of moderate and severe fibrosis and edema, is often used as a selection criteria\(^8\),\(^9\). This excludes 1/3 to 1/2 of the patients. De Crevoisier\(^10\) did not re-irradiate patients who had experienced osteoradionecrosis or extensive mucosal necrosis. Benchalal\(^5\) did not allow persistent grade 3+ toxicity except xerostomia. Ward\(^11\) identified feeding tube or tracheal cannulae dependency, due to toxicity as predictors of a very poor prognosis in re-irradiation.

The applied doses in re-irradiation are often lower than those used for initial radical therapy, due to the risk of severe side effects. There are, however, no known clinical or preclinical findings to
suggest that recurrences should be more radiosensitive than primary tumors. Higher doses are often associated with higher LRC in retrospective studies. Takia found doses >70 Gy advantageous for LRC and, using protons, MacDonald found higher doses significant for LRC in a multivariate analysis. Hyperfractionation and acceleration is used in the primary radiotherapy setting to increase local control without increasing the risk of late toxicity. These findings are often extrapolated to re-irradiation. A single RCT has compared hyperfractionated radiotherapy (plus cetuximab) 60Gy/50fx b.i.d. to conventional fractionated radiotherapy in a split-course regimen (60Gy /30fx /5 q.d. every other week) plus intensive chemotherapy, and found comparable OS and PFS. A larger retrospective analysis found that hyperfractionated accelerated radiotherapy using 60 Gy/40 fx b.i.d. i.e 1,5 Gy per fx, resulted in an increased risk of carotid blow out.

Often, a GTV-CTV margin of 0,5-2 cm has been applied. Elective nodal irradiation has seldom been reported, does not seem to increase LRC, and carries a risk of increased risk of side effects. As, in the primary radiotherapy setting, a propensity for in-fields recurrences has been observed, but in postoperative radiotherapy, more marginal recurrences have been seen in spite of larger GTV-CTV margins.

There are no clinical data to suggest more acute side effects during the second course of radiotherapy, compared to the first. Severe acute side effects are relatively rare (<7%). The reported mortality have been associated to a deteriorated general condition and correlated with high age.

The risk of late effects is significant. The actuarial risk of grade 3-5 side effects may be as high as 80%. Margalit reported a risk of persistent need of a feeding tube at 50%, 18% risk of tracheal cannulae due to side effects and 19% risk of severe soft tissue necrosis.

Myelopathy is a serious life-threatening side effect. The accepted risk of myelopathy in the primary treatment is therefore 0% using the conventional doses of 45 Gy in 30-56 fx. In the QUANTEC report the risk is estimated to be <1% at 54 Gy and <10% at 60 Gy using 1,8-2 Gy/fx. Available clinical and animal studies suggest that a significant recovery takes places. It is very difficult to quantitate this recovery, since it is dependent on dose and time since primary therapy. Woolley and Jones modeled recovery, based on the data by Ang and found a recovered dose of 25% of primary dose after 1 year. Modern primary IMRT have potentially spared the spinal cord more efficiently, allowing for re-irradiation without exceeding the dose tolerances.

Carotid blowout is a severe and dreaded side effect. The syndrome is evidently correlated to tumor growth into the artery and is often observed in the cases of persistent disease. The absolute risk is small (2,6% in a meta-analysis), but seems to be increased after hyperfractionated accelerated radiotherapy (1,5 Gy BID) and is very much dependent on carotid wall invasion, overlying ulcerations and irradiated volume. A reasonable dose-response correlation is not available.

Concomitant chemotherapy is probably most efficient in chemo-naïve patients. Radiochemotherapy probably increases locoregional control but also acute toxicity, treatment related acute mortality and possibly late side effects. A common approach to re-irradiation was expressed by Hehr. Because recurrences after radiotherapy within the irradiated area are
likely to be less radiation sensitive than previously untreated tumors, most investigators designed schedules to give as much chemotherapy as possible concurrently with radiotherapy, using potentially radiation sensitizing drugs.” In extreme cases this demands that the treatment course is prolonged as in "Vokes regimen" using alternating chemo-and radiotherapy. This regimen has recently been compared to bio-radiotherapy\textsuperscript{15}. In the primary setting, cisplatin is most commonly used reflecting available evidence. No evidence is available to suggest superior drugs or guidelines regarding drug-resistance.

**Proton therapy**

Proton therapy offers a reduction of volumes that receive moderate or low doses. These dose levels may contribute significantly to the overall risk of side effects, since the dose is added to the dose of the primary therapy\textsuperscript{36}. In some patients there may be advantages of photon radiotherapy due to a sharper lateral penumbra, and a comparative dose plan is therefore indicated before considering proton therapy\textsuperscript{37}.

Protons have not been compared to photons for re-irradiation of head and neck cancer in randomized trials. In silico studies\textsuperscript{36} have shown the expected dosimetric advantages for several organs at risk and integral dose. Whether this translates into a clinical advantage is unknown since there are limited clinical data on very high cumulated doses. Three recent clinical reports are available: Mcdonald\textsuperscript{38} reported on the treatment of a mixed head and neck cancer population (N=61) with skull base involvement not considered candidates for photon re-irradiation. Concomitant chemotherapy was especially used for SCC. Two-year OS was 33%. The patients were heavily pretreated with radiotherapy. Grade 3-5 late toxicity was seen in 26%. Dose significant dose response correlations were identified. Phan\textsuperscript{17} reported on 60 patients with primarily SCC. Two-year OS was 69%. A 26% actuarial risk of grade 3 late toxicity was observed at 2 year. No significant dosimetric or clinical factors predicted OS or LRC, but irradiated volume was correlated with both acute and late side effects. Romesser\textsuperscript{39} reported on 92 patients with primarily SCC of the oropharynx, intensively pretreated, i.e. 16 patients had previous re-irradiation. Two-year OS was 42% (reading]). Of 69 patients at risk at 3 months 25% developed grade\textgreater=3 toxicity. The results for especially acute toxicity had been evaluated as superior compared to published photon data. No excess risk of carotid blowout has been reported despite considerations regarding RBE\textsuperscript{40}

To conclude, current results of photon-based re-irradiation in inoperable head and neck cancer are unsatisfactory. The hitherto applied doses, primarily around 60 Gy, result in relatively high incidence of morbidity and a modest chance of tumor control.

**Aim**

The purpose of the present protocol is to test the efficacy of proton therapy for re-irradiation with curative intention in patients with head and neck tumors in a previously irradiated area. The investigational treatment aims to lower the risk of severe side effects. The results of the study can be used as evidence for patient selection and treatment for future protocols. An important secondary effect will be a national standardization of treatment guidelines and follow up.
Protocol

Design
Phase II observational

Inclusion criteria
- Histological verified loco-regional recurrence or new primary
- Available dose plan from primary radiotherapy course
- Comparative dose plan with advantages for proton radiotherapy e.g. integral dose
- Dmax dose (0.03 cm³) on the cumulated photon dose plans ≥ 90 Gy
- Complete Response (CR)* after initial therapy, except in the case where the recurrence is considered a geometric miss (recurrence center of mass (COM) outside the 95% of prescription dose.
- Inoperable or salvage surgery with R1/R2 resection, extranodal extension (ENE) or extensive soft tissue infiltration
- Absence of distant metastasis at both
  - clinical examination AND
  - PET-CT or CT of thorax and upper abdomen
- Life expectancy due to age and co-morbidity of >=1 year. The general condition must be sufficient to tolerate persistent significant side effects, e.g. tube or cannulae
- PS<=2 (WHO See appendix)
- Age ≥ 18 years
- The patients should be able to read Danish in order to participate with quality of life questionnaires, but can participate in the rest of the protocol without being fluent in Danish, if capable of reading the patient information.

* Complete Response is defined as the situation when a trained clinician, ideally at a multidisciplinary team conference, defines the patient as in complete remission, based on clinical examination and available imaging. This status can of course later be considered wrong as new information becomes available (sub-centimeter nodes grow etc.)

Exclusion criteria
- Radical surgery (R0) and absence of adverse prognostic pathological features
- Lymphoma or malignant melanoma
- Inability to attend full course of radiotherapy or follow-up visits in the outpatient clinic
- As of 2019, patients with tracheal cannulas and pacemakers are excluded due to uncertainties. This may change if a technical solution becomes available.

Relative contraindications
The fulfillment of the inclusion criteria is not sufficient to define re-irradiation as the optimal treatment solution for the patient. Many patient-, clinical- and dosimetric factors should be considered, when deciding to re-irradiate with curative intent. And the decision should rely on the
sum of these factors. Therefore, the in- and exclusion criteria has been as unrestricted as possible. Nevertheless,

- Presence of severe side effects before re-irradiation, is not an absolute exclusion criterion, but should be considered at inclusion.
- Time since primary therapy is a very important prognostic factor and should be considered. The longer the better.
- Carotid invasion and especially overlying ulceration are predictive of carotid blow out and should be considered at inclusion.

**Patient recruitment, inclusion and work-flow**

The patients are identified at the departments of oncology in Denmark. If external radiotherapy with curative intent is indicated, and the patient fulfills the clinical criteria in the protocol, the patients will be informed of the possibility of proton therapy. However, final eligibility requires a planning CT in treatment position and delineation of the target and normal tissues. If the target seems reasonable, a comparative dose plan is made, and the patient is referred for video-conference with DCPT (National Proton Conference) and presented there by the referring physician according to standard DCPT guidelines. If the proton plan shows benefits for proton therapy the patient is informed by the referring physician and written informed consent is obtained after necessary time for consideration. The patient is thereafter referred to DCPT for treatment.

Inclusion form, patient consent and base line scoring of symptoms are performed at the referring center and the Onstudy Form is send to the DAHANCA Secretariat. All available relevant diagnostic and treatment scans and dose plans are sent to the DCPT and the DcmCollab database. After radiotherapy the patient is referred back to the regional department of oncology for follow up.

**Endpoints**

- Primary:
  - Any new late toxicity grade >=3 according to CTC AE 5.0
- Secondary
  - Side effects according to DAHANCA scoring system
  - Quality of life and PROM according to EORTC C30 and HN43
  - Loco-regional control (LRC)
  - Overall survival (OS)
  - Results of the National Proton Conference

**Dose and fractionation**

The meanCTV is prescribed 60Gy/50fx/1.2 Gy per fraction. This fractionation equals an EQD$_2$ = 56 Gy for tumor and EQD$_2$ = 50.4 Gy for late reactions. Ten fractions per week should be delivered, with at least 6 hours between all fractions, i.e. overall treatment time will be 5 weeks. Target coverage and critical normal tissue sparing are secured through robust optimization and evaluation with the margins and procedures defined by the guidelines of DCPT.
**Target**

There is no elective area, and only one dose level. In case of a well-defined GTV, no further margin is added for microscopic disease or delineation uncertainties. In case of ill-defined tumors up to 10 mm margin can be applied. This is especially recommended in postoperative radiotherapy, where the volume harboring tumor cells evaluated on preoperative scans, per-operative findings and pathological results can be added a further 10 mm margin.

**Organs at risk**

The cumulative doses of the combined initial radiotherapy and re-irradiation must be considered for all late effects. The spinal cord and brain stem are spared according to DAHANCA constraints if possible. The effects of fractionation, according to the LQ model assuming an $\alpha/\beta=3$ and a recovery of 25% of primary dose after 1 year can be used.

The carotid arteries are defined from the top of the sternum to the base of skull. The arteries should be spared, especially contra-laterally. Invasive tumor growth, especially in case of overlying ulcerations, is a relative contraindication for re-irradiation.

**Hypoxic radiosentiziser**

No evidence is available for nimorazole in the re-irradiation setting. Nevertheless, hypoxic tumors are more prone to recurrence and nimorazole is therefore recommended according to DAHANCA 9 guidelines for SCC (standard therapy according to the national guidelines for re-irradiation. See DAHANCA.dk). I.e. nimorazol, 1200 mg/m$^2$ 1½ time before the first daily fraction and 1000 mg weight independent before the second daily fraction.

**Chemotherapy**

All patients who fulfill the criteria below are offered concomitant chemotherapy, irrespective of histological type, stage or surgery. Cisplatin 40mg/m$^2$ once weekly is used according to normal DAHANCA guidelines

- WHO performance status $\leq 2$
- Biological age <70 years
- Absence of insufficient kidney function (GFR <50 ml/min)
- Absence of moderate or severe neuropathy
- Sufficient bone marrow function

The concurrent medical treatment (weekly cisplatin and nimorazole) are prescribed according to the national treatment guidelines and are not part of the experimental treatment.

**Recording of side effects and treatment results**

At base line, weekly during therapy and at all follow up visits, the side effects are registered according to DAHANCA and CTC AE 5.0. At baseline, at end of treatment and at all follow up visits, the patient fills out EORTC QLQ C30 og HN43. Follow up will follow the normal DAHANCA guidelines after radiotherapy (14 days, 2, 3, 6, 12, 24, 36, 48 and 60 months). Treatment response will be assessed following local guidelines. Any recurrences/ persistent tumor/ first distant metastasis should be histological verified. Any locoregional recurrence should be scanned (CT,
PET/CT or MR) and the scanning transferred to DcmCollab for a detailed analysis with respect to any geographical miss.

**Questionnaires**
The validated questionnaires of the EORTC will be used (QLQ C30 and HN43). If the patient is not physically or mentally capable of filling out the questionnaire, support should be offered by a health professional. Patients not being able to fill out questionnaires are allowed in the protocol. A research nurse will contact the patient in case of missing returned questionnaire.

**Translational studies**
No translational studies are planned, ie, no biological material will be collected

**National Proton Conference**
A screening log will be made for any patient with a planning CT. The data will be entered in the clinical DAHANCA database for later analysis, by the DAHANCA group. The screening log will contain the same data as the minute mentioned below;
For each patient presented at the National Proton Conference a structured minute will be made by the referral centre. This minute will contain data on compromises in dose planning regarding target coverage, accepted dose to critical normal tissues, assumed fractionation effects and normal tissue repair, as well as a conclusion regarding inclusion in the protocol. These data will be entered as a clinical parameter quality assurance in the DAHANCA database on all patients irrespective of inclusion in the protocol. It will be necessary to conclude anything regarding referral praxis and future inclusion criteria.

**Power calculation**
The previous Danish nationwide study (Engelmann) identified 70 evaluable patients during 7 years, i.e. approximately 10 patients per year as possible candidates. A target number of 20 patients will be included. Such a sample size will make it possible to analyze a parameter for dose response analysis with the primary endpoint (any grade≥3 toxicity) using actuarial analysis. The pre-specified parameter will be $\Sigma V_{90 Gy}$.
An estimate of the frequency of grade ≥3 toxicity comes from Tao et al$^{15}$ where 5 of 25 patients in the hyperfractionation arm (60 Gy in 50 fractions b.i.d.) experienced grade 3-4 toxicity at 6 months. With 20 patients in the present study we have a power of 80% and an alpha of 5% to detect a tripling of the frequency of severe toxicity. Each case of severe morbidity (as well as recurrences) will therefore be scrutinized for causes.

**Radiation safety**
Patients referred for proton radiotherapy will receive less overall dose than those treated with photons outside the protocol.

**Data management**
The DAHANCA database will serve as the central database in the study. The database has been refined for research purposes the past 40 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 CRFs, protocol parameters, questionnaires, morbidity and outcome registrations. Data will be collected regarding the patient (comorbidity, gender, age, smoking, preexisting symptoms), oncologic treatment (previous treatment and protocol specific treatment), side effects during and after radiotherapy, outcome (recurrence, death). All these data are important for assessing the efficacy and efficiency of the treatment. Patient reported data will be collected using well validated questionnaires. The questionnaires contain sensitive data regarding sexuality, mental problems and physical symptoms.

For most patients data on initial disease and treatment will be available from the clinical quality database of DAHANCA, for the remaining the data will be collected from medical records on study specific CRF’s and entered into the database.

As the treatment is potentially lethal, it is necessary to acquire detailed information about any mortality regarding cause. The local/referring investigator, must therefore access electronic medical records in case of mortality or contact the general physician of the patient, to acquire knowledge of the cause of death.

The digital radiotherapy treatment plans incl. diagnostic imaging will be collected in the DcmCollab database 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 analyzed. The DMP will be based on the obligations and requirements from the Danish Data Protection Agency, The Act on Processing of Personal Data (Databeskyttelsesloven and databeskyttelses-forordningen) and the National Research Ethics Committee. All authorities who need to access data by law will be permitted data access from the database. The trial will be registered at ClinicalTrials.gov.

**Radiotherapy Quality Assurance (QA)**

If nothing else is stated, the radiotherapy follows the DAHANCA radiotherapy guidelines (DAHANCA.dk). The online QA will consist of the national proton therapy conferences, were plans are reviewed by the participating investigators. All data will be reviewed off line, according to the specified QA measures by DAHANCA and DCPT. DcmCollab will be used as a QA platform. The review experience will be evaluated and shared in at regular DAHANCA QA meetings.

The generation of $\sum V_{90 Gy}$ will initially be generated by deformable registration of the 30 Gy isodose, converted to a structure, of the initial plan to the re-treatment plan and calculating the $\sum V_{90 Gy}$ to that structure. As the physics studies progress, this might change to a more sophisticated procedure.

**Physics studies**

The original dose plans will be transferred and deformed to the proton planning-CT to perform the dose accumulation calculations. A project regarding the robustness/ uncertainty of this procedure will be initiated and methods and terminology will be developed for future studies of re-irradiation. These results will be used for the modeling study of normal tissue complication probability (NTCP).

**Timetable**

Inclusion will start as soon as the protocol has been approved by the necessary authorities. Earliest patient will be treated Q3 2019, when treatment capacity is available at DCPT. The expected inclusion period will be 2 years, but this may be prolonged. An analysis will be made 6 months after the last fraction of last patients.

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 analyzed 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.

Ethical considerations
The prognosis of these patients is very grave irrespective of treatment. The dose is comparable to the one offered to some Danish patients before the initiation of the trial, but hyperfractionation and the use of protons are expected to secure that the toxicity level of the study treatment is acceptable. No randomized trials are available. For most Danish patients, proton treatment will require extra time spend traveling or staying at a hotel for weekdays for 5 weeks. Time to start of treatment from diagnosis may also increase with a few days, as the treatment preparation at DCPT can only begin after a comparative dose plan and inclusion. Apart from questionnaires there are no study specific procedures for the patient. The recommended systemic treatment is in accordance with published national guidelines. The study will be conducted according to current legislation and the Helsinki declaration. All data is treated confidentially, and each recruiting center is responsible of managing the data safe and in compliance with the Danish Data Protection Agency.

Participant information and written informed consent
Newly diagnosed eligible patients will be informed of the study trial aims at the first consultation by a clinical oncologist, e.g. at the multidisciplinary team conference. The information will in broad terms cover the study, including rationale, possible treatment in Aarhus. A target delineation and possible a comparative dose plan will be made, to determine if the patient could benefit from re-irradiation in general within or outside of the protocol. In case the patient already know that he will not travel to Aarhus nor receive proton therapy, the patient will not be informed further of this possibility. Following the dose plan comparison, patients 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 and they will then be offered photon radiotherapy. 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 to 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 gives 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 procedures before the patient has given written informed consent. A comparative dose plan is not considered a study related procedure as this possibility is defined in the DAHANCA Radiotherapy Guidelines as a standard procedure to ensure referral of suitable patients for proton therapy.

Financial plan
The study protocol was initiated by the Danish Head and Neck Cancer Group (DAHANCA). The trial is not supported by any grants. 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 will be covered by the patient’s home region.

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

References


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Appendix

WHO performance status classification

0: able to carry out all normal activity without restriction
1: restricted in strenuous activity but ambulatory and able to carry out light work
2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3: symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden
4: completely disabled; cannot carry out any self-care; totally confined to bed or chair.