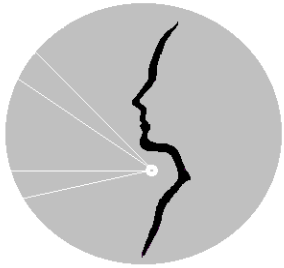
# DAHANCA.dk
## Danish Head and Neck Cancer Group



# Proton treatment for younger patients with head and neck cancer - including cancer of the thyroid and salivary glands - on the indication of risk reduction of radiation-induced cancer

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## Introduction

The risk reduction of radiation-induced cancer (RIC) is often advocated being an indication for radiotherapy with protons. This has previously been an indication for referring Danish patients abroad. In the Netherlands that use a model-based approach for patient selection for proton treatment, a risk reduction of ≥2% for grade 4-5 toxicity is an indication for proton treatment. RIC is life threatening and often an even more severe incident than the index cancer (1).

Hall(2) has estimated that scanning beam proton radiotherapy reduces the risk of RIC to one tenth of that of IMRT. However, the likelihood of generating any data on the risk of using proton versus photon radiotherapy is very slim and only possible after very long observation in large cohorts.

The risk of RIC relates to

- low age: maturing individuals are at higher risk per se
- long expected life time: high age, poor expected prognosis of index cancer or severe comorbidity means the chance of surviving long enough to develop a RIC is low

and to some degree

- dose and irradiated volume(3), and irradiated organs (e.g. considering the dose weighting factor for Sievert(4).

### RIC in head and neck cancer

The risk of a secondary cancer in squamous cell carcinoma of the head and neck (SCCHN) is very high(5), but mainly due to smoking and alcohol. Also non-smoking induced cancers, like thyroid cancer, are increased in head and neck cancer populations irrespective of external beam irradiation(6).

RIC seems to arise due to different mechanisms. Radiation-induced sarcomas often arise in the high dose volume (7),(8). The relative risk of sarcomas after radiation is often high, but the absolute risk is very low due to the low risk of sarcoma in the general population. The decisions about radiotherapy for SCCHN ought not to be affected by the excess risk of developing a sarcoma due to its low incidence and long latency. The excess risk is probably independent of beam quality.

On the other hand, other cancers arise in tissues receiving much lower doses. E.g., some of the highest absolute excess risks seems to be lung cancer after irradiation of prostate(9) and cervical cancer(10), despite lung tissues receive very low doses. In head and neck cancer and lymphoma populations (moderate size studies), actuarial estimates for RIC are about 5% after 10 years, with a

tempero-spatial narrow definition of RIC(1). In an irradiated lymphoma only population, the observed/expected ratio was 12.7, and the absolute excess risk of RIC was 13.3 cases per 10,000 patient years, in general, irrespectively of chemotherapy(11). In a large epidemiological study, proton treatment lead to a significant reduction in second cancer risk compared to IMRT also in head and neck cancer, but with a low absolute risk of 1.5/100 patient year(12).

## Quantification of the absolute risk of RIC in general

There are several models for risk estimation. To be used for patient selection, models should be parametrized using valid published data. However, both model selection, especially the significance of dose >2-5 Gy, and parametrization bring uncertainties (13).
A simple estimate of RIC risk is 0.3%/year for any solid tumour based on data from A-bomb survivors and patients with Hodgkin's disease (14). Therefore, in any patient with a prolonged expected survival, the risk is therefore significant
The data are not likely to be exact in relation to modern radiotherapy. Nevertheless, the estimate has been used for dose planning studies in head and neck(15),(16). These studies result in *higher* estimates of the benefit of protons, and high absolute excess risks.

**Age**

Any applied model for RIC should include age at exposure. Preston(17) concludes that the risk of RIC is proportional with 1/age at the time of exposure.

**Co-morbidity**

No data has been identified for the risk of developing RIC in comorbid patient populations. In an older population, one chronic condition leads to a reduction in expected survival of 2 years(18) meaning that any effect in younger adults will be negligible.

**Conclusion on a model-based selection of patients for proton treatment**

No evidence has been identified that allows for selection of any particular model, and especially for parametrization of any model, to indicate which patients that may benefit from proton treatment for the reduction of RIC.

## Recommendation

- Proton treatment for the reduction of radiation-induced cancer should be discussed with patients below 40 years of age and eligible for curative radiotherapy.
- If uncertainty exists regarding pacemaker, dental implant, target coverage, or radiation doses to specific organs at risk, a comparative dose plan between protons and photons should be made.

**Explanation:**

**Age <30 years**: Many patients may have an indication for protons anyway (sarcomas, children). Patients with a very poor prognosis or serious life threatening co-morbidity may preferably be treated with photons.

**Age 30-39 years**: Based on most reasonable risk estimates, the life time risk reduction from proton vs photon treatment will be ≥2% and thus, patients will qualify with a model based approach. It should be noted that no model for RIC is being used presently in the Netherlands (as per Febr. 2022).

**Age ≥40 years**: As described above, some models may show that this age group may benefit from protons as well, however, the risk reduction will likely be very low in terms of absolute risk.

## Data registration

It is important that the use of photons and protons are recorded in the quality-database of DAHANCA to allow for a register-based analysis of risk reduction of RIC in head and neck cancer patients in the future.

## Appendix: Expected number of patients for protons on RIC indication

The expected number of patients is based on NordCan incidence in patients 20-40 years of age in 2016, expected to receive external beam radiotherapy.

| Site | Patients (male)/year | Patients (female)/year | Patients/year | Expected number of pts. for protons/year |
|---|---|---|---|---|
| **Head and Neck** | 13 | 8 | 21 | 12 |
| **Thyroid** | 12 | 47 | 59 | 3 |
| **Salivary gland** | 4 | 4 | 8 | 8 |
| **Total** | | | | **23** |

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