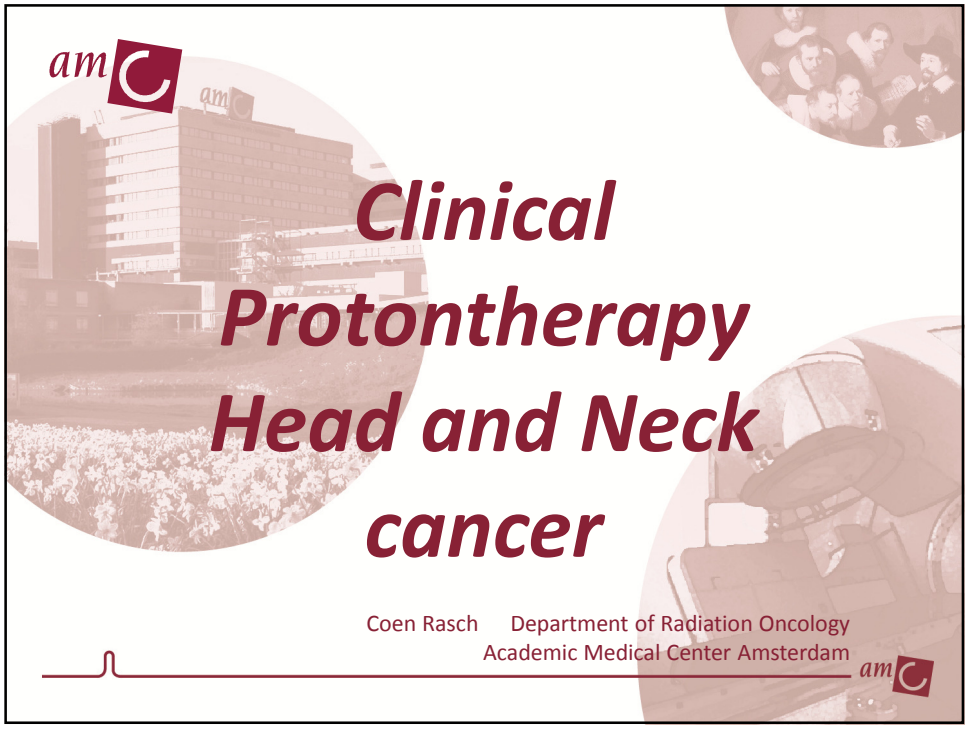

Clinical
Protontherapy
Head and Neck
cancer
Coen Rasch Department of Radiation Oncology
Academic Medical Center Amsterdam


• No disclosures

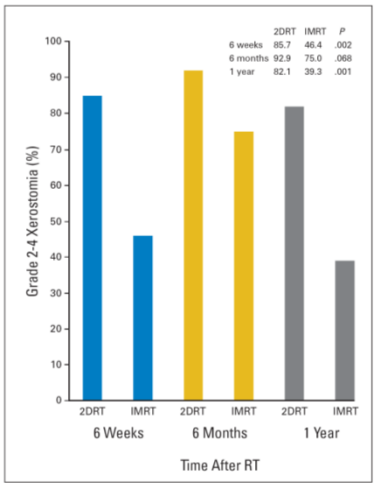
# Introduction

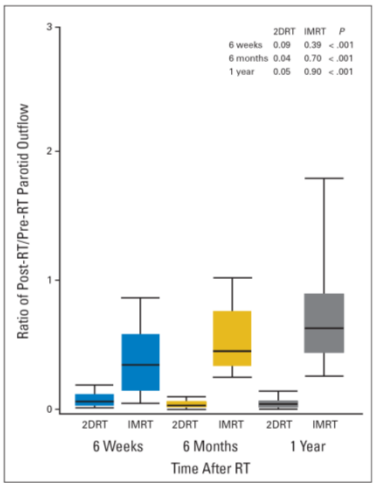
- Proton vs Photon in the literature
- Model based indication protocol in The Netherlands
- Conclusions

# IMRT vs 3D-CRT

- IMRT was introduced in the 90's
- Publication, including the few randomised trials used tumor prognostic factors (eg.TNM) as entry criteria where others like Medical Oncologists used treatment predictors as entry criterion for a long time already.

# Phase III trial IMRT vs 3D-CRT



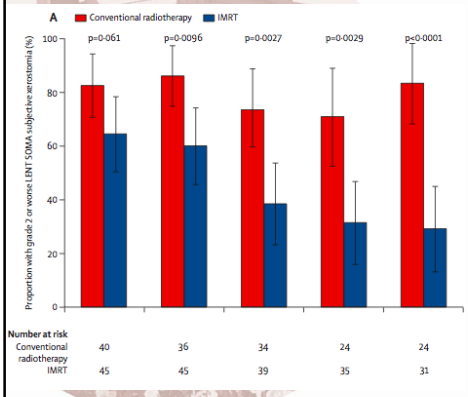



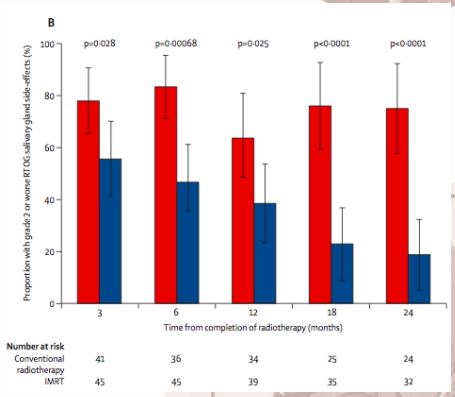

•Kam et al JCO 2007

**Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial**

*Lancet Oncol* 2011; 12: 127–36

94 patients randomized to standard vs IMRT RT




Proportion of patients with Grade 2 or higher toxicity

# So, IMRT works in sparing OAR

- The randomised trials based upon tumor prognostic factors demonstrate less side effects.
- Use preceded proof of superiority by about ten years
- But what is actually happening to the dose with IMRT/VMAT?

# IMRT does not remove dose to the patient, it just moves it around...

I. J. Radiation Oncology ● Biology ● Physics Volume 72, Number 3, 2008

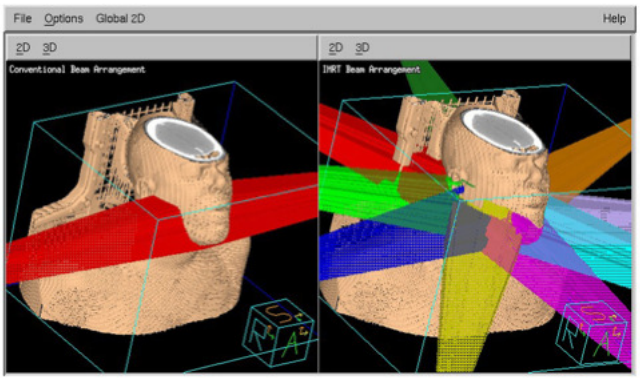
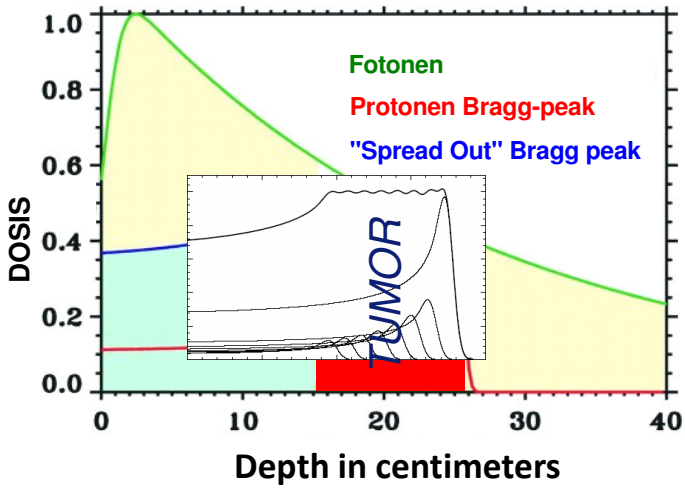


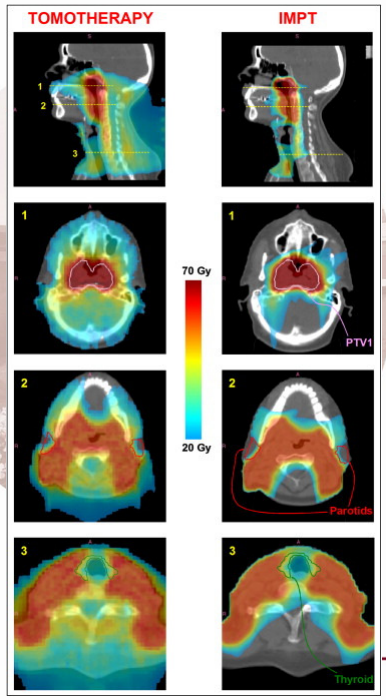

Fig. 1. Comparison of nontarget beam paths in intensity-modulated radiotherapy (top) vs. conventional three-dimensional technique (bottom).

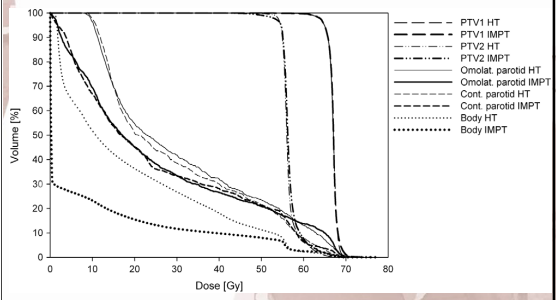
# Protons versus photons

## 80% of Photon energy is in the wrong place




# Equivalent Coverage but Reduced Dose Bath



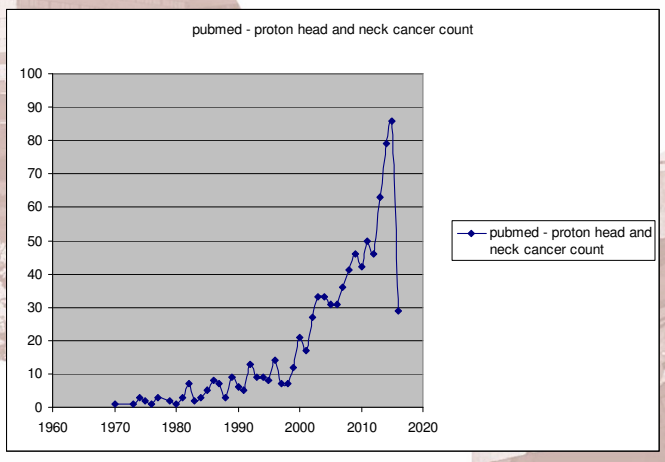

WIDESOTT et al.
IMPT vs. tomotherapy in nasopharynx cancer *IJROBP* 2008

# IMPT vs IMRT

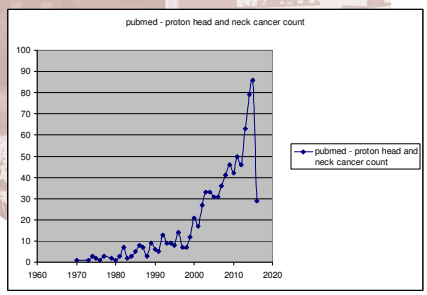
- So, theoretically it should be better.
- What is the published evidence?

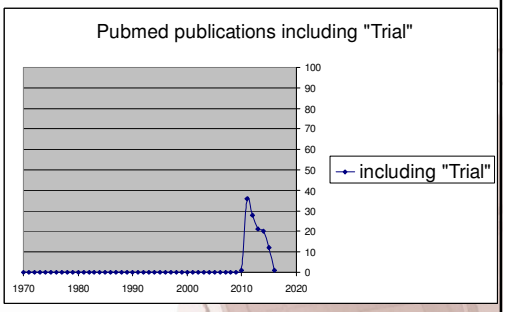
# Pubmed search:

## # of publications “proton” AND “Radiotherapy” AND “Head and Neck Cancer”



# Pubmed search: # of pubs “proton” AND “Radiotherapy” AND “Head and Neck Cancer” AND “Trial” OR “Clinical”




# IMRT vs PBRT for ipsilateral RT

- Cohort comparison when introducing proton beam RT for ipsilateral radiation
- 23 vs 18 patients selected upon availability of proton beam
- Reduction in clinical observed acute toxicity

- Romesser et al R&O 2015

# IMRT vs IMPT for ipsilateral RT

- Grade II or more:
  - Dermatitis 74 vs 100%
  - Mucositis 52 vs 17
  - Nausea 56 vs 11
  - Dysgeusia 65 vs 6
  - Dysphagia 0 vs 0
  - Fatigue 9 vs 6

Romesser et al R&O 2015

**Table 3**
Acute toxicity.

| Toxicity | IMRT ($N = 23$) | PBRT ($N = 18$) | $P$ value |
|---|---|---|---|
| *Dermatitis* | | | |
| Grade 0 | 0 (0.0%) | 0 (0.0%) | 0.032 |
| Grade 1 | 6 (26.1%) | 0 (0.0%) | |
| Grade 2 | 9 (39.1%) | 13 (72.2%) | |
| Grade 3 | 8 (34.8%) | 5 (27.8%) | |
| Grade 4 | 0 (0.0%) | 0 (0.0%) | |
| *Mucositis* | | | |
| Grade 0 | 3 (13.0%) | 12 (66.7%) | 0.005 |
| Grade 1 | 8 (34.8%) | 3 (16.7%) | |
| Grade 2 | 10 (43.5%) | 3 (16.7%) | |
| Grade 3 | 2 (8.7%) | 0 (0.0%) | |
| Grade 4 | 0 (0.0%) | 0 (0.0%) | |
| *Nausea* | | | |
| Grade 0 | 7 (30.4%) | 15 (83.3%) | 0.003 |
| Grade 1 | 3 (13.0%) | 1 (5.6%) | |
| Grade 2 | 13 (56.5%) | 2 (11.1%) | |
| Grade 3 | 0 (0.0%) | 0 (0.0%) | |
| *Dysgeusia* | | | |
| Grade 0 | 4 (17.4%) | 14 (77.8%) | <0.001 |
| Grade 1 | 4 (17.4%) | 3 (16.7%) | |
| Grade 2 | 15 (65.2%) | 1 (5.6%) | |
| *Dysphagia* | | | |
| Grade 0 | 12 (52.2%) | 15 (83.3%) | 0.101 |
| Grade 1 | 9 (39.1%) | 2 (11.1%) | |
| Grade 2 | 2 (8.7%) | 1 (5.6%) | |
| Grade 3 | 0 (0.0%) | 0 (0.0%) | |
| Grade 4 | 0 (0.0%) | 0 (0.0%) | |
| *Fatigue* | | | |
| Grade 0 | 2 (8.7%) | 11 (61.1%) | 0.002 |
| Grade 1 | 19 (82.6%) | 6 (33.3%) | |
| Grade 2 | 2 (8.7%) | 1 (5.6%) | |
| Grade 3 | 0 (0.0%) | 0 (0.0%) | |

**Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy**

Emma B. Holliday, MD[1]; Adam S. Garden, MD[1]; David I. Rosenthal, MD[1]; C. David Fuller, MD, PhD[1]; William H. Morrison, MD[1]; G. Brandon Gunn, MD, PhD[1]; Jack Phan, MD, PhD[1]; Beth M. Beadle, MD, PhD[1]; Xiarong R. Zhu, PhD[2]; Xiaodong Zhang, PhD[2]; Ehab Hanna, MD[3]; Bonnie S. Glisson, MD[4]; Katherine A. Hutcheson, PhD[3]; Adel K. El-Naggar MD[5]; Ji-Hong Hong, MD, PhD[6]; Tsung-Min Hung, MD[6]; Esengul K. Uzel, MD[7]; Gary Lewis, MD[8]; and Steven J. Frank, MD[1]

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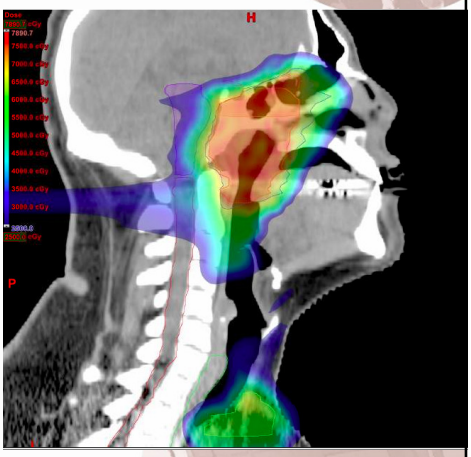
Published 20 Jul 2015



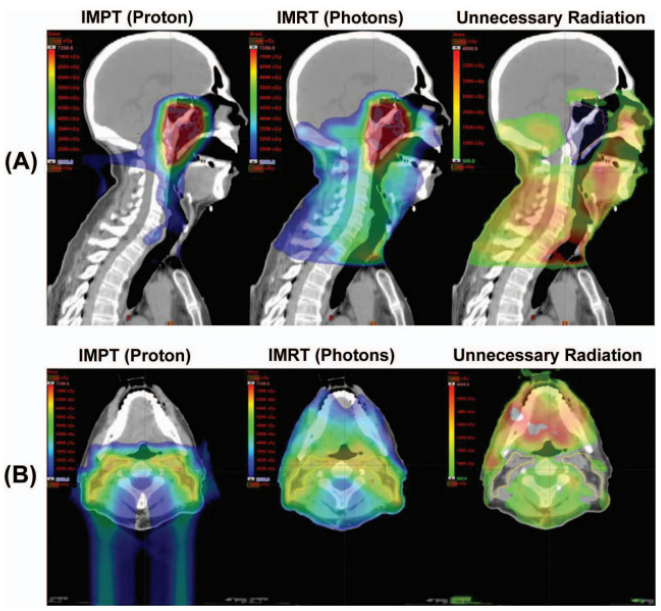

Courtesy Dave Fuller

**Table 1.** Comparison of patient characteristics between those treated with IMPT for NPC and matched patients treated with IMRT.

| | IMPT (N = 10) | IMRT (N = 20) | *P* value[a] |
|---|---|---|---|
| Age at RT, median (IQR), y | 45 (18-55) | 51 (39-59) | .194 |
| Sex, N (%) | | | 1 |
| Male | 7 (70) | 14 (70) | |
| Female | 3 (30) | 6 (30) | |
| T-stage, N (%) | | | .930 |
| T1 | 4 (40) | 8 (40) | |
| T2 | 2 (20) | 3 (15) | |
| T3 | 2 (20) | 3 (15) | |
| T4 | 2 (20) | 6 (30) | |
| N-stage, N (%) | | | .468 |
| N0 | 1 (10) | 4 (20) | |
| N1 | 3 (30) | 3 (15) | |
| N2 | 6 (60) | 10 (50) | |
| N3 | 0 (0) | 3 (15) | |
| WHO grade, N (%) | | | .519 |
| I | 0 (0) | 2 (10) | |
| II/III | 9 (90) | 15 (75) | |
| Unknown | 1 (10) | 3 (15) | |
| RT dose, median (IQR) | 70 (70-70) Gy (RBE) | 70 (70-70) Gy | .480 |
| Induction chemotherapy, N (%) | | | .526 |
| Platinum/taxane | 8 (80) | 13 (65) | |
| Platinum/taxane/cetuximab | 0 (0) | 2 (10) | |
| None | 2 (20) | 5 (25) | |
| Concurrent chemotherapy, N (%) | | | .255 |
| Platinum | 10 (100) | 17 (85) | |
| Cetuximab | 0 (0) | 1 (5) | |
| None | 0 (0) | 2 (10) | |
| Adjuvant chemotherapy, N (%) | | | .32 |
| Platinum/taxane | 1 (10) | 0 (0) | |
| None | 9 (90) | 20 (100) | |

**Abbreviations:** IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; IQR, interquartile range; WHO, World Health Organization.

**Figure.** Representative sagittal (A) and axial (B) IMPT and IMRT plans for the same patient with nasopharyngeal carcinoma. (A) The dose distribution of the IMPT plan; the center panels show the dose distribution of the comparative IMRT plan. (B) The result of a dose subtraction in order to show unnecessary radiation that is spared when using IMPT as compared to IMRT. Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy.




Courtesy Dave Fuller

# Dose reduction to OARs

IMPT for nasopharyngeal carcinoma

**Table 2.** Comparison of mean dose to nearby critical structures between those treated with IMPT for NPC and matched patients treated with IMRT.

| | IMPT (IQR) | IMRT (IQR) | *P* value[a] |
|---|---|---|---|
| Mean oral cavity dose, median (IQR) | 17.3 Gy (RBE) (12.2-24.2) | 40.6 Gy (33.7-42.5) | <.001 |
| Mean brainstem dose, median (IQR) | 26.7 Gy (RBE) (23.2-28.7) | 34.2 Gy (29.9-38.5) | .002 |
| Mean whole brain dose, median (IQR) | 6.53 Gy (RBE) (4.89-8.34) | 10.94 Gy (9.2-12.93) | <.001 |
| Mean mandible, median (IQR) | 32.62 Gy (RBE) (20.38-42.09) | 42.65 Gy (38.05-47.28) | .020 |

**Abbreviations:** IMPT, intensity-modulated proton therapy; NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; IQR, interquartile range.
[a]The Kruskal-Wallis test was used for between-group comparisons of continuous numeric variables. $P < .05$ was considered significant, and all tests were 2-sided.

# IMRT vs IMPT

- 10 patients retrospectively planned
- Comparison of:
  - VMAT
  - MFO-protons
    - (Multi-field optimization i.e. the combination of fields with a good coverage)
  - SFO-protons
    - (Single-Field optimization i.e. every field with a good coverage)

Barten et al 2015

# IMRT vs IMPT

- Dose to Salivary glands and swallowing muscles:

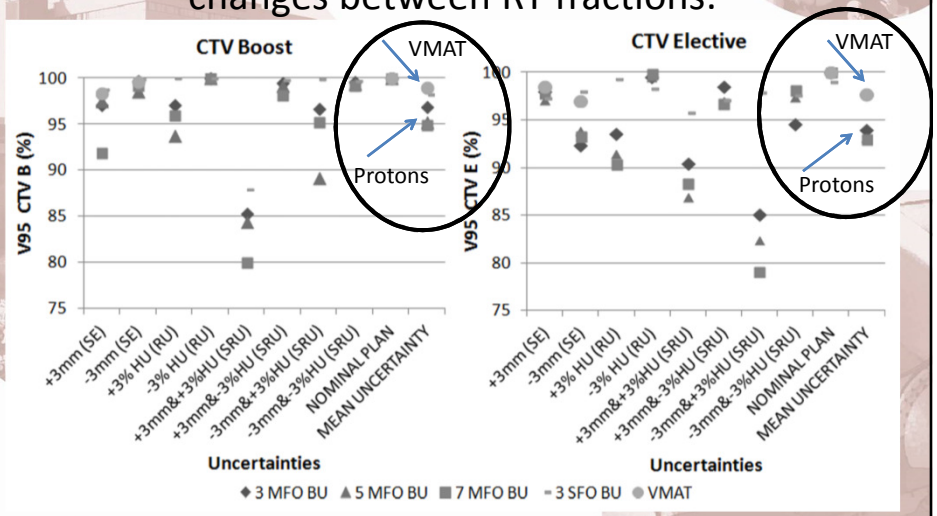
| Technique | Salivary gland combined (Gy) | Swallowing structures combined (Gy) |
|---|---|---|
| VMAT | 23 | 23.5 |
| MFO | 14 | 16 |
| SFO | 20 | 23.7 |

  - Conclusion: Proton plans deliver less dose to OAR
  - BUT:

Barten et al 2015

# IMRT vs IMPT

Proton plans are slightly less robust to changes between RT fractions:




Barten et al 2015

## So where do we stand?

- Proton treatment plans are in general NTCP superior to IMRT plans but:
  - not for all patients and
  - historical controls are currently the closest we get

## So where do we stand?

- Proton treatment plans are in general NTCP superior to IMRT plans but:
  - not for all patients and
  - historical controls are currently the closest we get

- With this uncertainties:
- Which patient to select for proton treatment?

# Selection the Dutch way

- If the ball play is on side effects:
- Then the selection criterion should be made on side effects as well, not on TNM-staging

- National consensus on general indications for proton therapy
- Consensus on NTCP models

Nederlandse Vereniging voor Radiotherapie en Oncologie

# NTCP-based selection criteria

(Normal Tissue Complication Probability)

| | |
|---|---|
| CTCAE: Grade 1 | Not used in comparison |
| Grade 2 | At least 20% occurence in IMRT plan,<br>Delta between IMRT and IMPT should be 10% or more<br>(15% in case of combined toxicity) |
| Grade 3 | At least 10% in IMRT plan,<br>Delta between IMRT and IMPT should be 5% or more,<br>(7.5% in case of combined toxicity) |
| Grade 4 | Delta 2% between IMRT and IMPT |
| Grade 5 | |

## NTCP-based selection criteria

(Normal Tissue Complication Probability)

- Current status:
  - Model based criterium is developed within the NVRO.
  - Per tumor site consensus on NTCP formula to be used.
  - Head and Neck is currently the first but others are soon to follow.
  - Government bodies follow the NVRO guidelines
  - First treatment is scheduled end 2017 (?)

## Better selection means more power

- We all use DVH for selection of our plan, why not use it for selection of our treatment?
- If in a group of patients the toxicity drops from 30 to 25% with IMPT you need for 90% predictive power **2x337 patients**.
- If with the same group you select the ones with 10% or more difference you need **2x85 patients** for the same power of your trial.

# Conclusion

- Proton therapy provides theoretical advances beyond photon therapies
- Radiation therapeutic community should enter the 20th (sic!) century and should go where other oncological professions have paved the way.

# 9F IMRT vs. Proton Dose Bath