Protonterapia e tumori testa-collo: gli scenari futuri

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RT Technical progress

Dosimetric gain +++

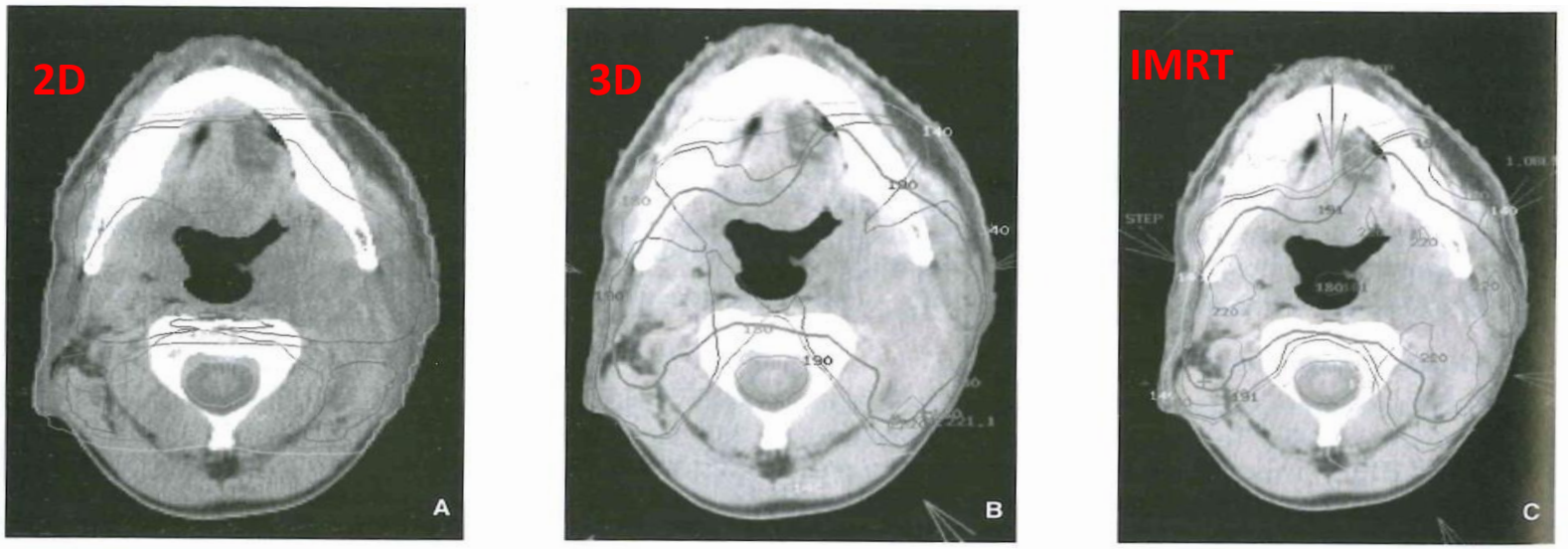

Figure 1 - Example of PTV2 contour and coverage for case 5. A) Conventional plan. B) 5-field conformal plan. C) IMRT plan. Lines shown are PTV2 (red line), 70% isodose (light blue line, 140), 90% isodose (magenta line, 180), 95% isodose (dark blue line, 190) and 110% isodose (green line, 220).

Palazzi M,2006

Five phase III trials comparing 2D/3D vs IMRT

	Site	Stage I/II	Stage III/IV	Overall Npts	RT technique	RT dose, Gy (tumor) 2D/RT	RT dose, Gy (tumor) IMRT	CHT
Pow IJROBP 20106	Naso	45	-	45	2D-RT vs IMRT	68	66-68	no
Kam JCO 2017	Naso	56	-	56	2D-RT vs IMRT	66+/-BT	66+/-BT	no
Nutting LO 2011	Oro-Hypo	23	71	80 14	2D-RT vs IMRT (postop)	65	65	Neo (40%)
Gupta R&O 2014	Oro-Hypo Lar	12	48	32 17 11	3D-RT vs IMRT	70	66	Conc
Peng R&O 2012	Naso	194 422		616	2D-RT vs IMRT	74+/-BT	74+/-BT	Neo/conc/adj

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Intensity-modulated radiation therapy for head and neck cancer: Systematic review and meta-analysis

Gustavo Nader Marta [a,b,*], Valter Silva [c], Heloisa de Andrade Carvalho [a,d], Fernando Freire de Arruda [a], Samir Abdallah Hanna [a], Rafael Gadia [a], João Luis Fernandes da Silva [a], Sebastião Francisco Miranda Correa [a], Carlos Eduardo Cintra Vita Abreu [a], Rachel Riera [c]

- Xerosotomia scores grades 2-4

A siginficant overall benefit in favor of IMRT was found for all studies with an HR of 0.76 (95% CI:0.66,0.67;p< 0.0001)

- Locoregional control (LRC)

Even if not sigificant, there was an increase in locoregional control favoring IMRT:

HR 1.07 (95% CI:0.93,1.23;p< 0.35)

- Overall survival (OS)

Again, any significant increase in OS favoring IMRT was observed:

HR 1.12 (95% CI:0.97,1.29;p< 0.11)

BUT 5-year LRC and OS rates were significantly higher in IMRT group vs 2D-RT group (Peng R&O 2012)

Potential advantages with IMRT:

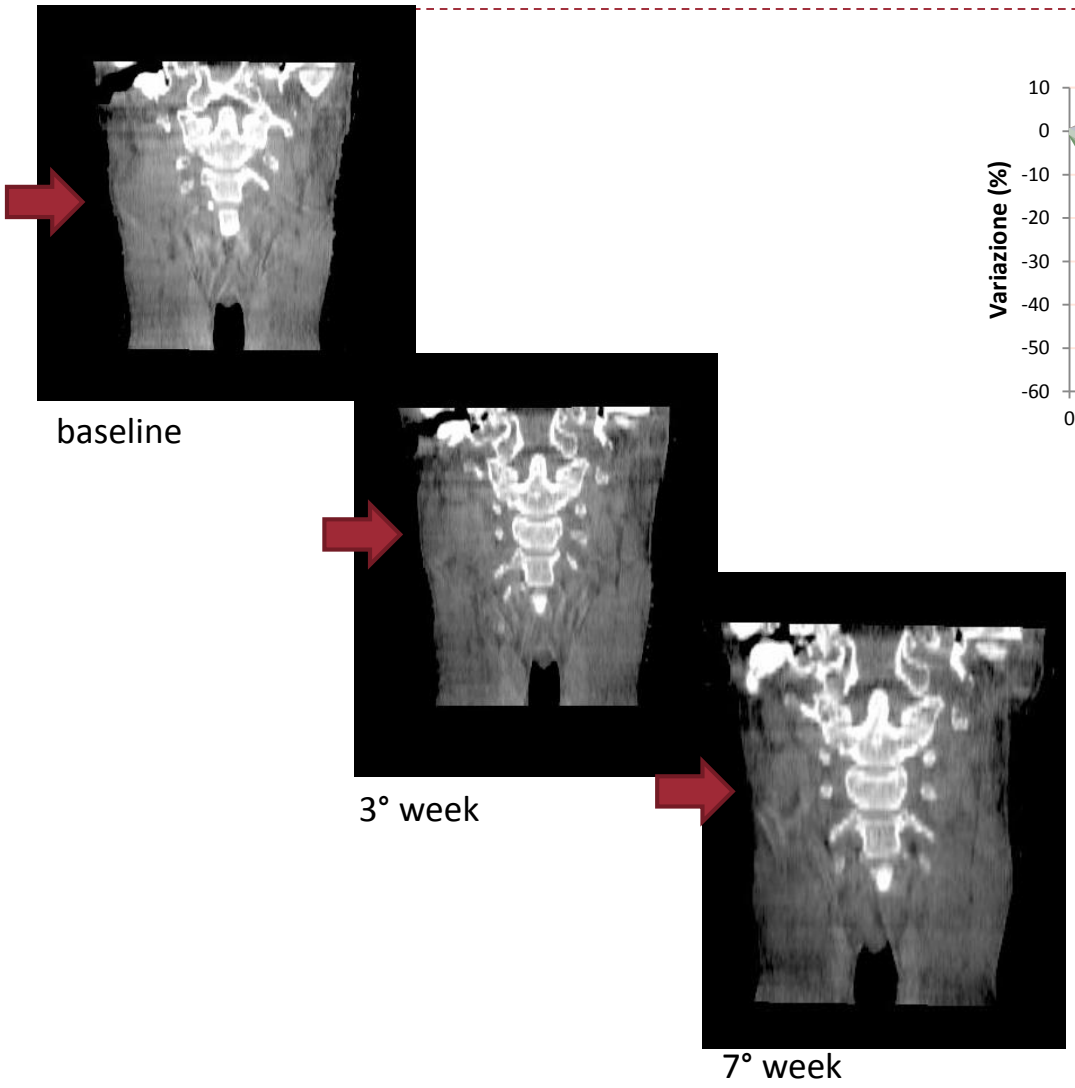
- Sparing of swallowing related structures and minimizing risk of late dysphagia.
- Improvement in Quality of Life (Xerostomia and Dysphagia).
- Reduction of trismus, temporal lobe neuropathy (nasopharyngeal cancers) and hearing loss.

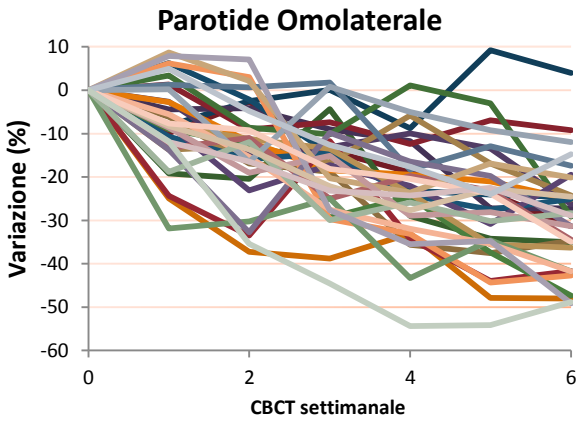
- Dose gradient are steep ,especially near organs at risk

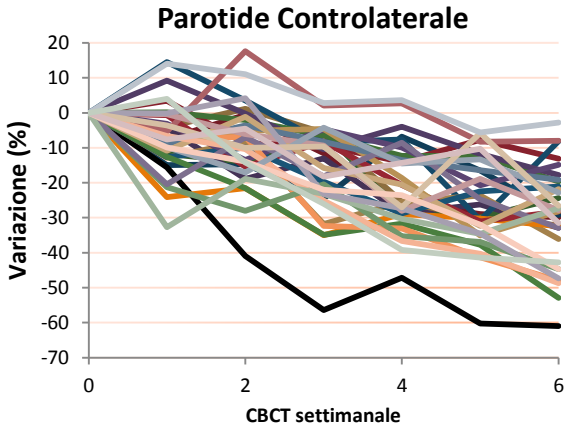
- Inacurrancies in repositioning and anatomical changes during RT may influence target volume coverage and sparing of OARs

Careful imaging protocols (image guided radiotherapy, IGRT)

Monitoring setup, 3D technique: CBCT-CT simulation







Adaptive radiotherapy (ART)

ELSEVIER

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2016

Systematic review

Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help?

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Johannes A. Langendijk, Nanna M. Sijtsema *

University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, The Netherlands

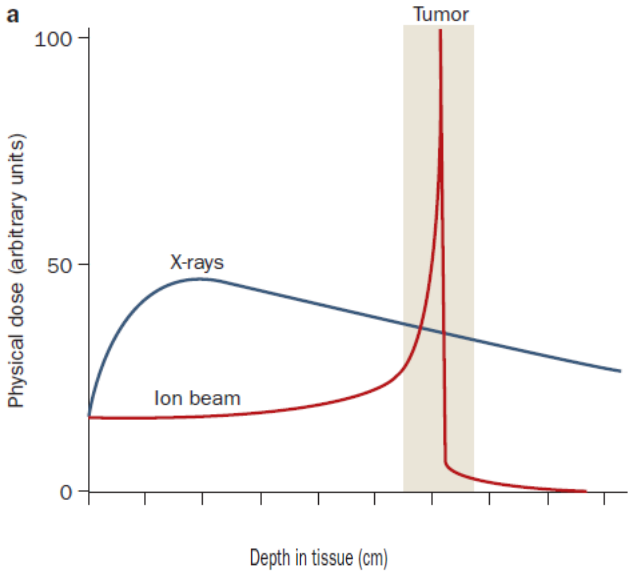
Photon therapy: limitations

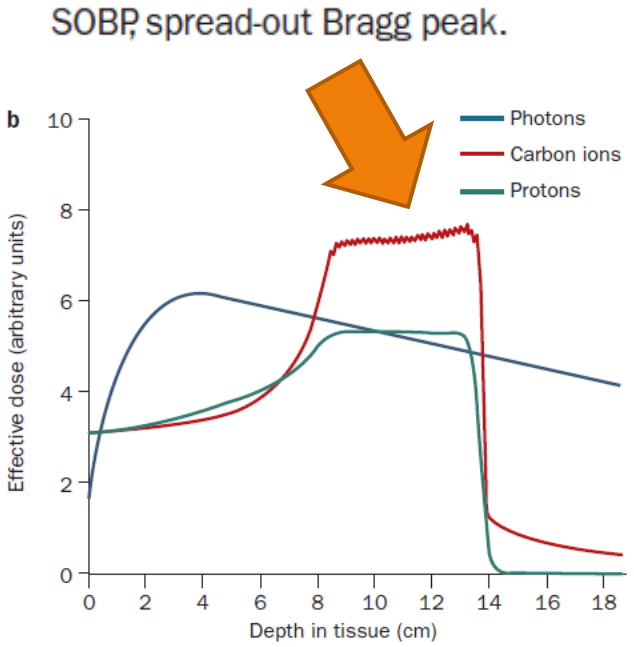
- From a ballistic and dosimetric point of view, Photon therapy is likely to have reached a plateau

- Unavoidable irradiation of normal tissues from low to moderate doses even at substantial distances from the tumor
  - extensive toxicities
  - nausea, vomiting , acute fatigue, occipital alopecia
    anterior oral mucositis
  -

- No more RT dose escalation for radioresistant tumors

CHARGED PARTICLE THERAPY

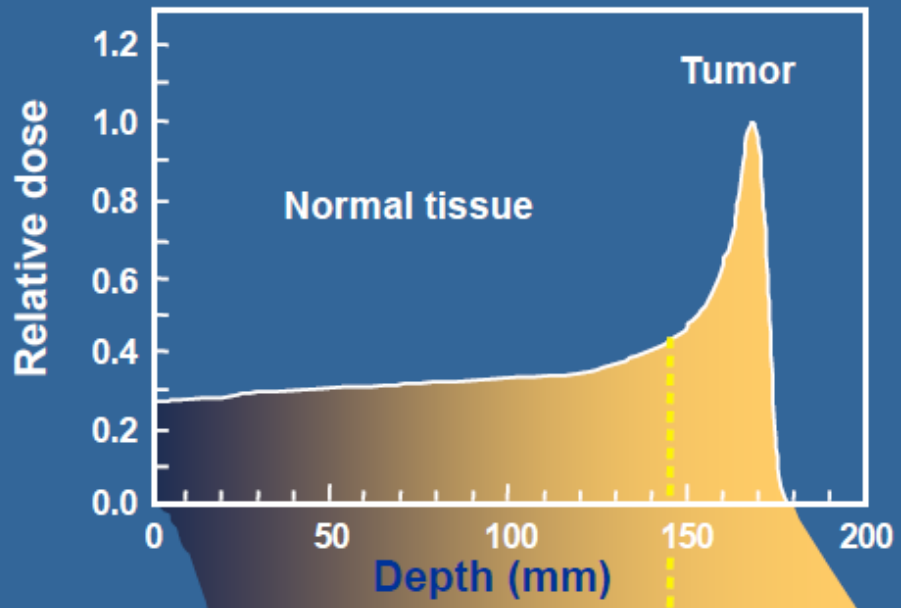




Durante M, 2010

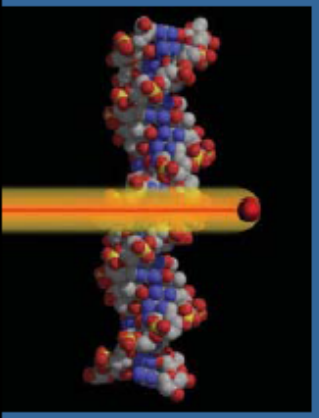
Durante & Loeffler,

Nature Rev Clin Oncol 2010



Potential advantages

HEAVY ION THERAPY



Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Cell migration	Increased	Decreased

High tumor dose, normal tissue sparing

Effective for radioresistant tumors

Effective against hypoxic tumor cells

Increased lethality in the target because cells in radioresistant (S) phase are sensitized

Fractionation spares normal tissue more than tumor

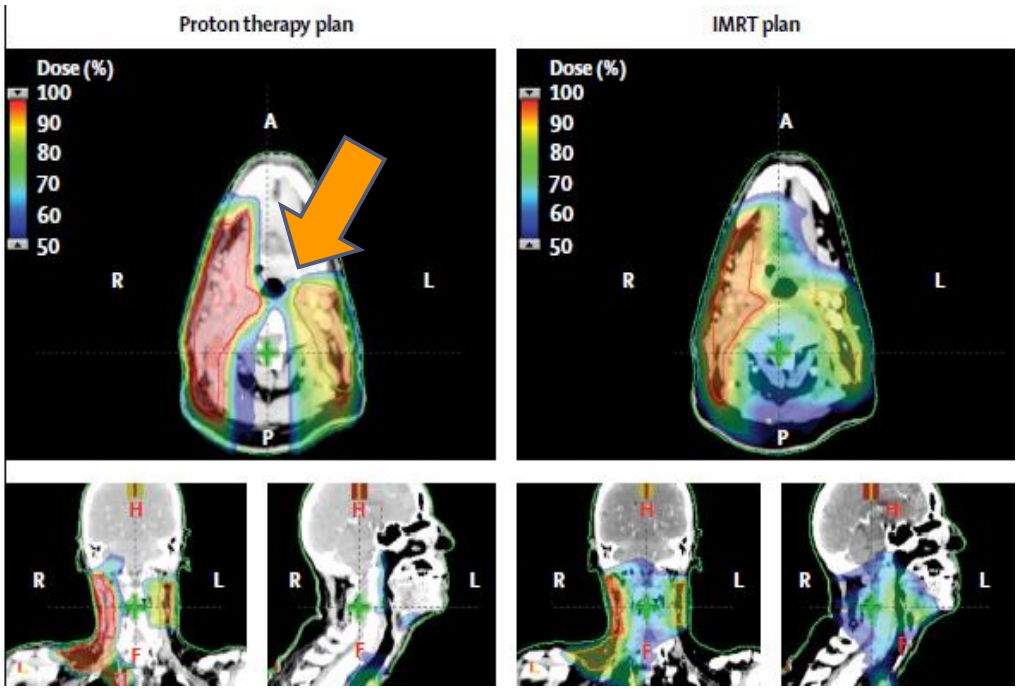
Reduced angiogenesis and metastatization

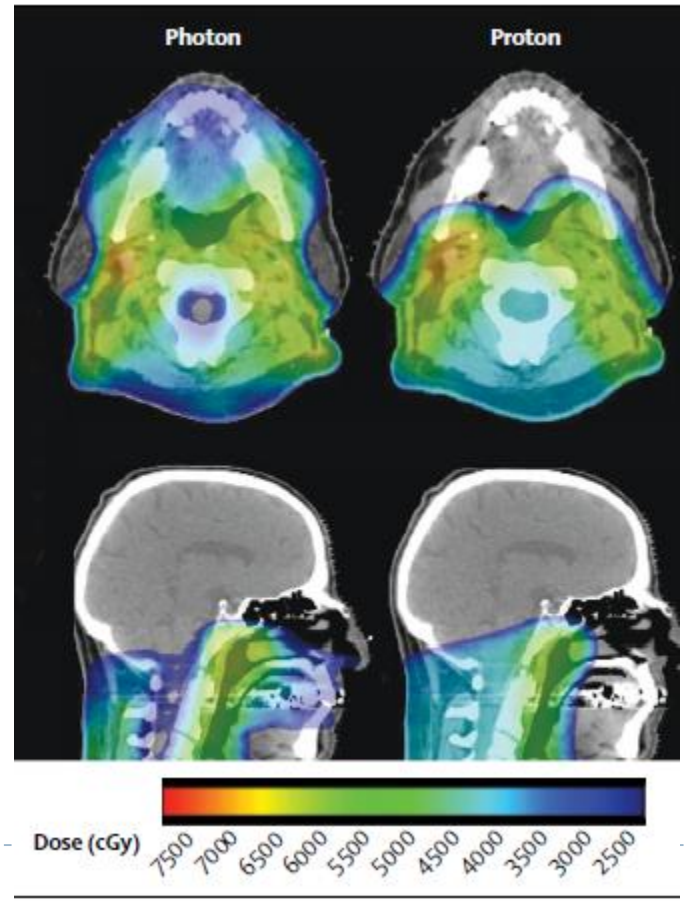
Courtesy by Durante

Physical (dosimetric) advantages of PT (Proton Thrapy) over IMRT:

- to significantly reduce the normal tissue irradiation while delivering a similar dose to the tumor
- and/or
- to escalate the dose to the tumor without exceeding the radiation dose delivered to the surrounding normal tissues

- OPC: sparing of multiple critical organs including the oral cavity (in particular the anterior mucosa) , major salivary glands (van de Water TA , 2011, 2012; Cozzi L 2001, Holliday EB 2016) and mandible (Zhang W, 2017) ; reduction or elimination of the dose to uninvolved controlateral oropharyngeal and nasopharyngeal mucosa (Perkins SM 2012)





- Unilateral head and neck irradiation: reduction of 10 times of higher to critical medline (oropharyngeal mucosa) and contralateral OARS (Kandula S 2013, Stromberger C 2016)

- NPC: lower doses to multiple OARs, including major salivary glands, spinal cord, brainstem and optic chiasm; reduction of the averaged mean dose to OARs by a factor of 2–3(Widesott L, 2008);reduction of low-to medium dose volumes (Liu SW, 2010; Lewis GD 2016)

- PNSC: lower doses to pituitary gland, optical pathway structures, brain, non target tissue by up to 65% (Lomax AJ 2003;Mock U 2004, Chera BS 2009, Cavallo A 2014)

Can we increase the dose with particle therapy versus IMRT? A dosimetric study for sinonasal cancer

PURPOSE: **Dosimetric comparison among treatment plans from different RT techniques aiming at the evaluation of the impact of combined treatment modalities on target coverage and OARs sparing for sinonasal tumors.**

MATERIALS and METHODS:

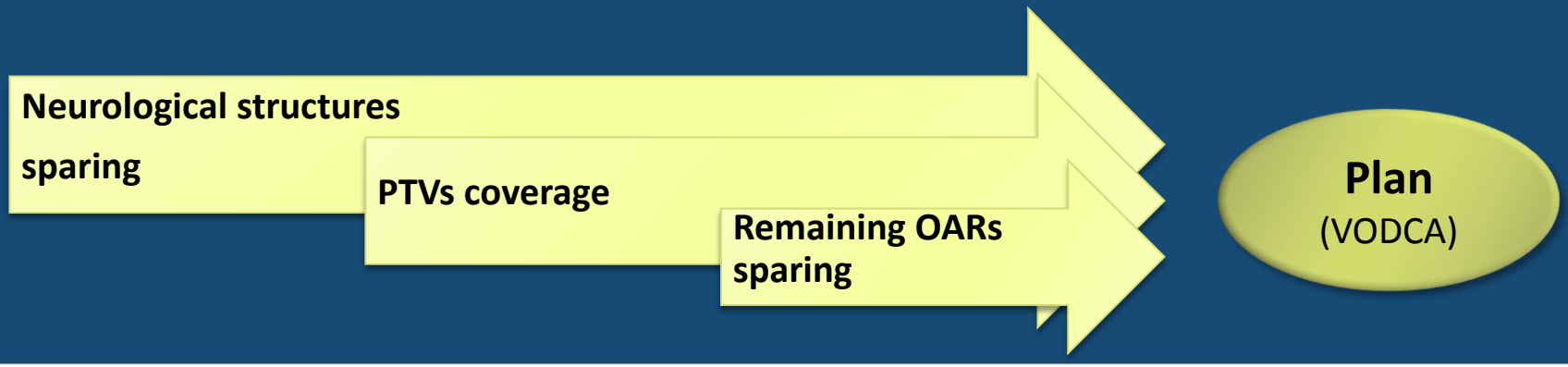
Patients	• 5 (SINTART 2) • with ENI (upper neck)
Plans	• SIB photons (ph) • Sequential photons + Carbon-ions (ph+C) • Sequential protons + Carbon-ions (p+C)
Technique	• VMAT (Varian Eclipse) for ph plans – 2/4 coplanar and non-coplanar arcs [Orlandi, RO, 2014] • IMPT (Siemens Syngo) for p/C plans

Prescription doses (PD)

*C boost of 21 Gy(RBE) at 3 Gy(RBE)/fr

	ph	ph+C	p+C
HR-PTV	70 Gy 2 Gy/fr	54 Gy + 21 Gy(RBE) *	(54 + 21) Gy(RBE) *
LR-PTV	56 Gy 1.6 Gy/fr	54 Gy 2 Gy/fr	54 Gy(RBE) 2 Gy(RBE)/fr

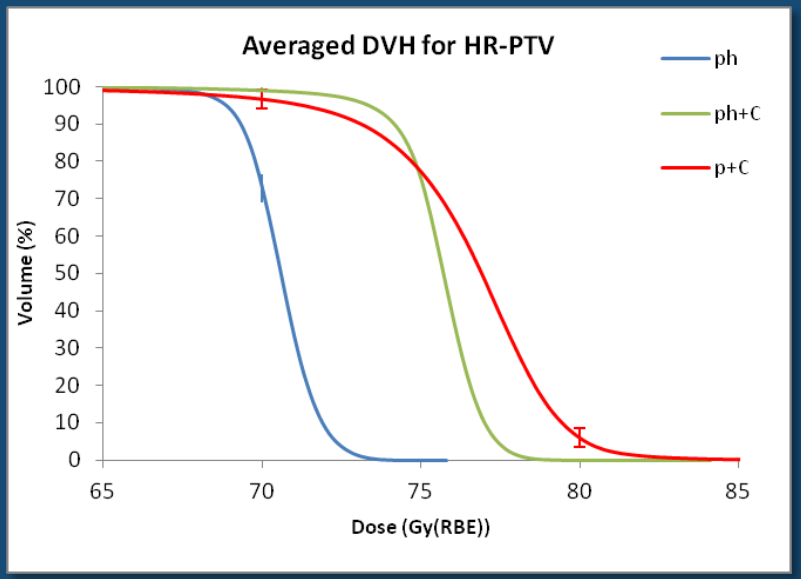
Optimization process



RESULTS

HR-PTV coverage

- CI and HI: better for **ph** plan
- Dmin ↑ for **ph** plan
- V70Gy ↑ for **+C** plan



	Dmin (%)	V70Gy (%)	CI	HI
ph	96.5	72.86	1.135°	0.063ª
ph+C	93.5	99.00*	1.259	0.077ª
p+C	88.0	96.64*	1.333	0.161

* is statistically significant for **p+C** and **ph+C** vs SIB ($p<0.001$)

° and ª are statistically relevant for **ph** vs p+C ($p=0.003$ and $p<0.02$)

All plans could be considered clinically acceptable and deliverable.

RESULTS

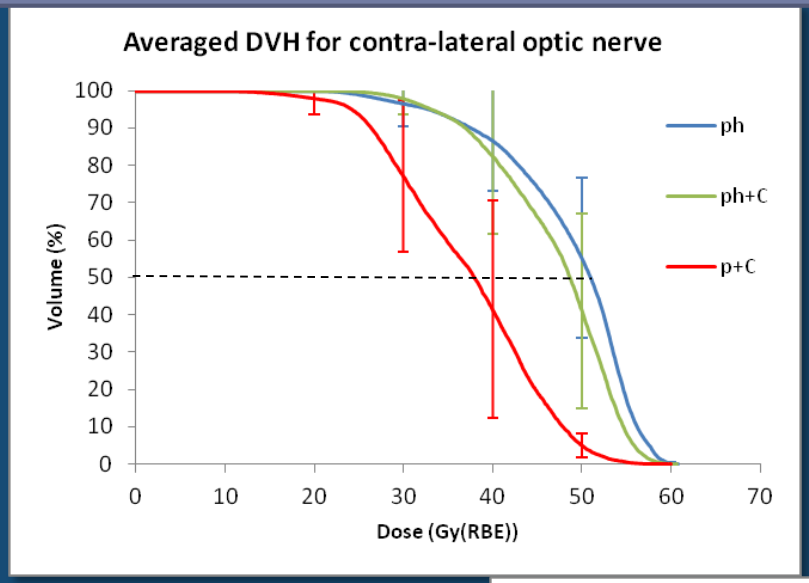
OARs sparing

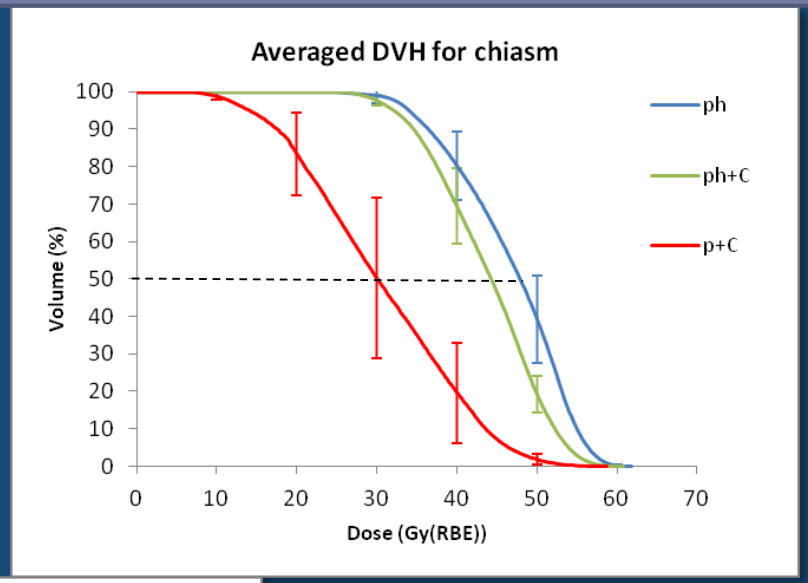
- Dmean ↓ in **p+C** plans for contra-lateral optic nerve, chiasm and cochleae ($p<0.03$)
- V10Gy ↓ in **p+C** plans for temporal lobes and brain ($p<0.05$)

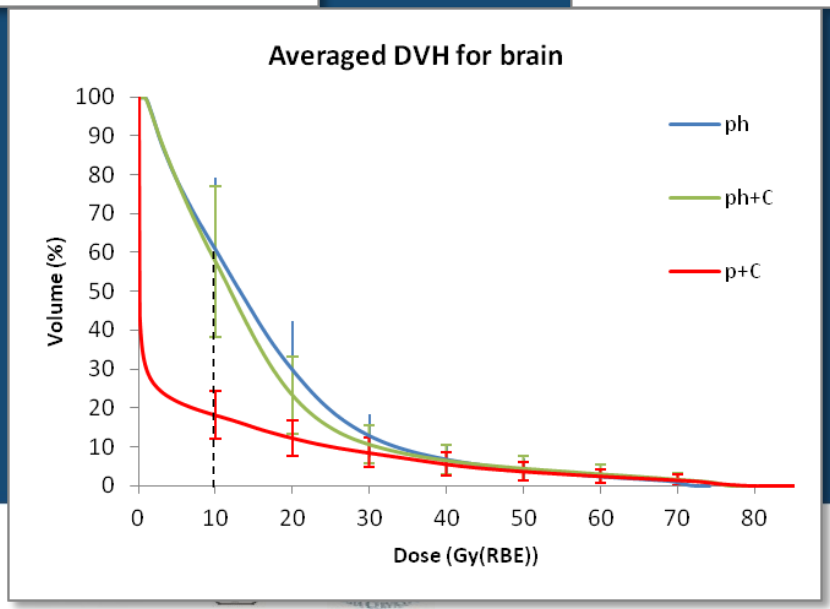
Healthy tissue

- Integral dose to HT ↓ in **p+C** plans vs the others, but also in ph+C vs ph ($p<0.01$)

p+C: better sparing of OARs far from and not involved in PTVs


Averaged DVH for contra-lateral optic nerve
Volume (%)
Dose (Gy(RBE))
ph
ph+C
p+C


Averaged DVH for chiasm
Volume (%)
Dose (Gy(RBE))
ph
ph+C
p+C


Averaged DVH for brain
Volume (%)
Dose (Gy(RBE))
ph
ph+C
p+C

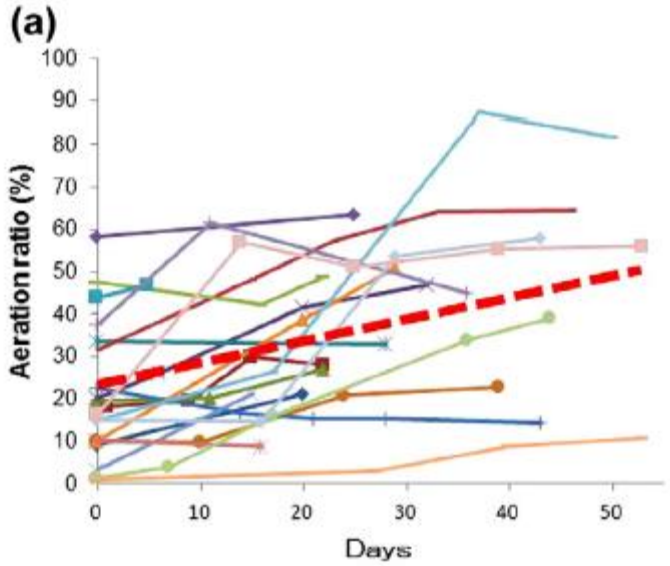
Potential Concerns (1)

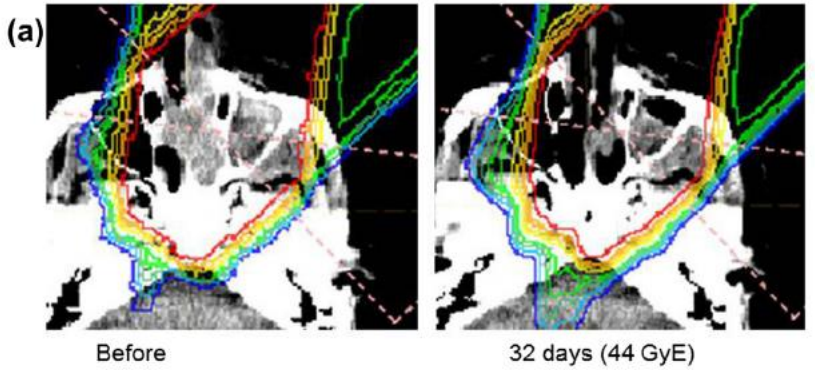
- High sensitivity of proton dosimetry to tissue heterogeneity and changes in target depth.

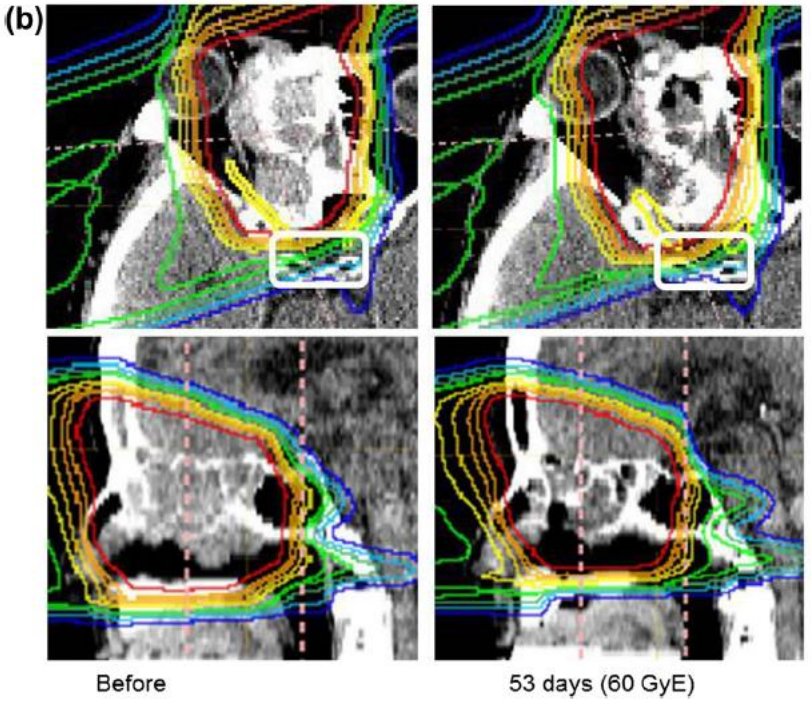
- Protons are more sensitive to geometric variations (due to setup inaccuracies, tumor shrinkage, weight loss, and organ motion) during treatment than photons

Blanchard 2017, Gregoire 2015, Leeman 2017

The aeration ratio



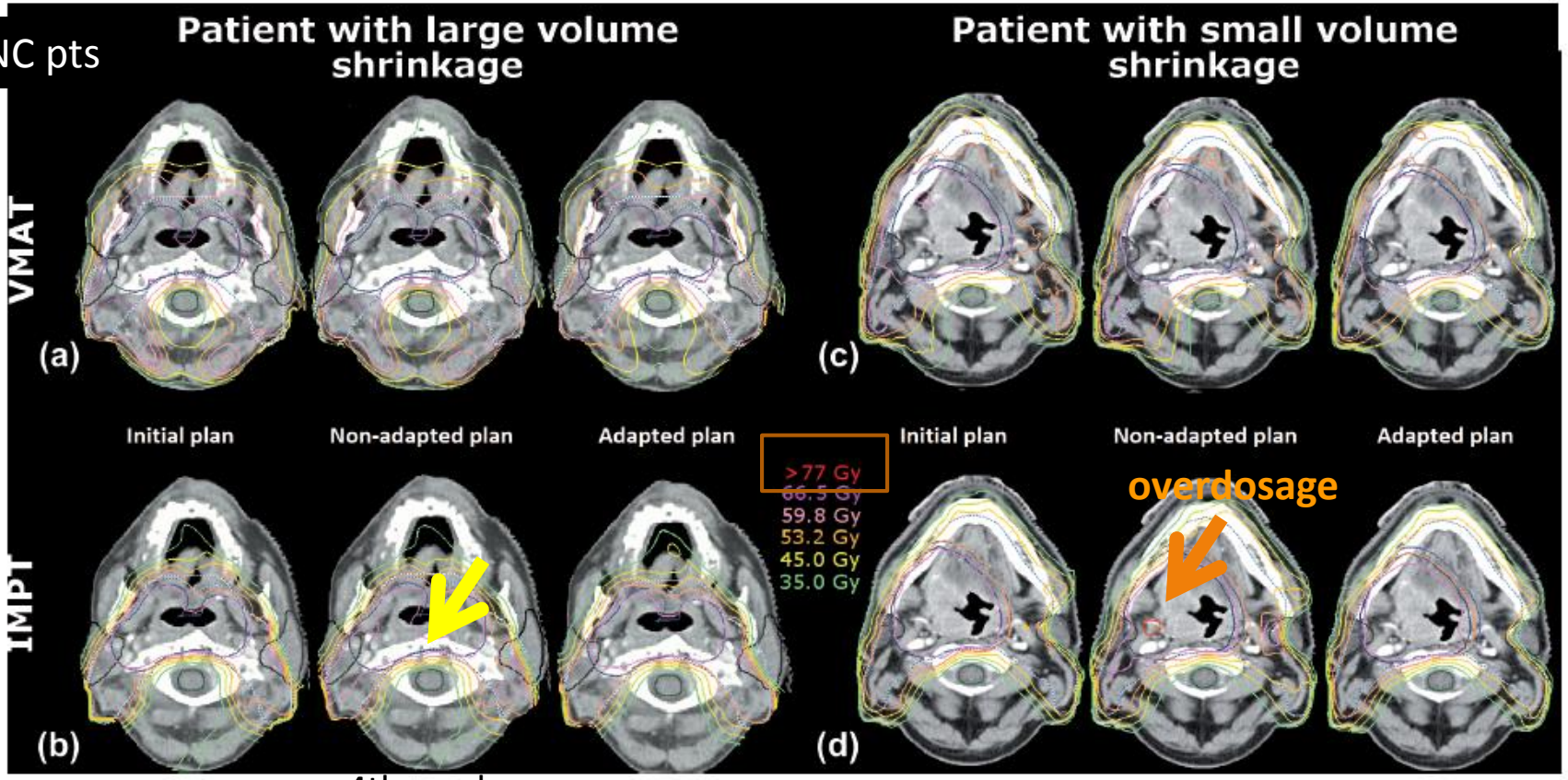




Results: The aeration ratio was increased in 18 patients. The largest increase was from 15% to 82%. Three patients had a simulated maximum cumulative dose in the brainstem of beyond 60 GyE, while 10 patients had a simulated maximum cumulative dose in the optic chiasm of beyond 50 GyE. The shortest simulated time period to reach the dose limitation was 21 days.

Fukumitzu, 2014

8 HNC pts

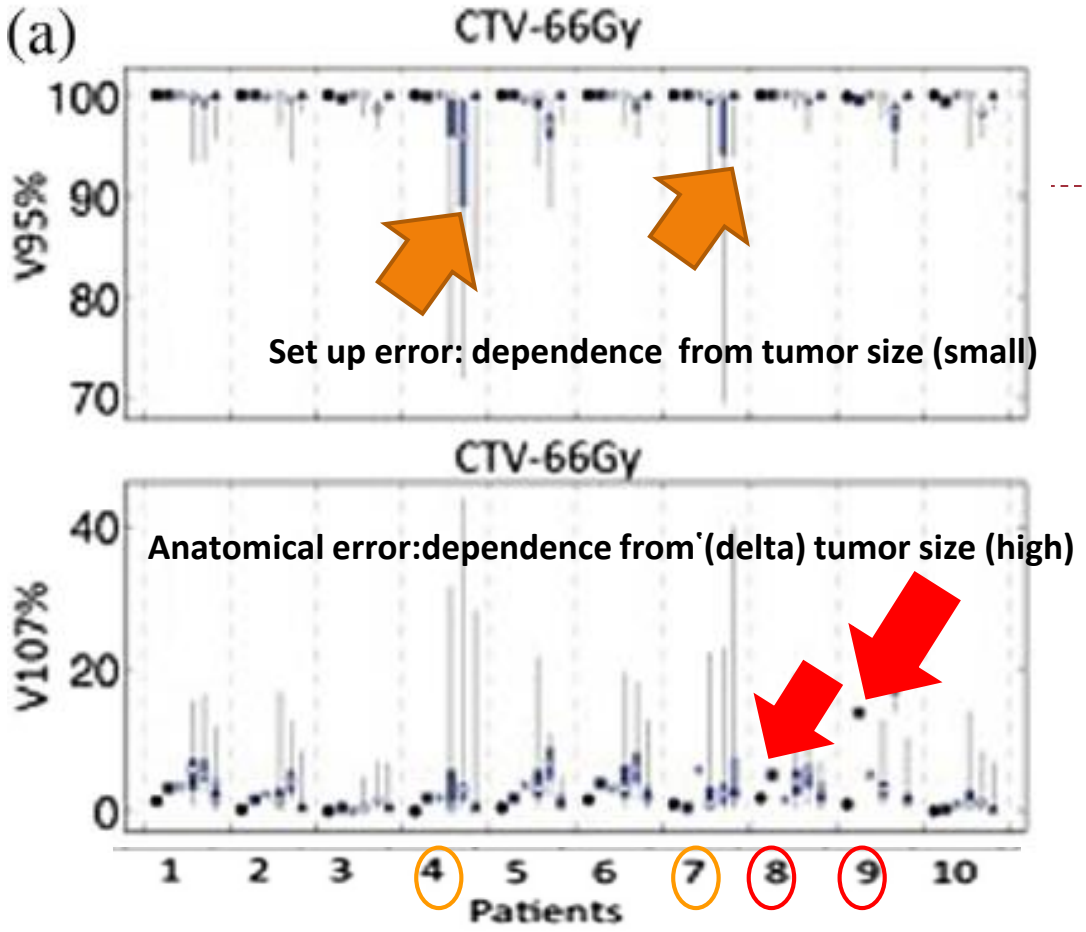


4th week

4th week

half of the patients, treatment plan parameters were still acceptable with VMAT ($V_{95\%} > 95\%$, OARs within limits) after recalculating the initial plan on the updated CTs. Treatment plan adaptation, performed for those patients, optimized OARs sparing even further. For IMPT none of the recalculated plans was found to be acceptable in terms of target coverage, since even small anatomic variations had a large impact on the resulting dose distributions.

Gora, 2015



10 OPC pts

Without action against treatment uncertainties, the treatment intent (D98% ≥95% for at least 90% of the patient population) was not fulfilled. Given the mixed causes for major deviations observed, we advise acquisition of repeat CT scans and dose recalculation to properly assess

Kraan 2013

Potential Concerns (1)

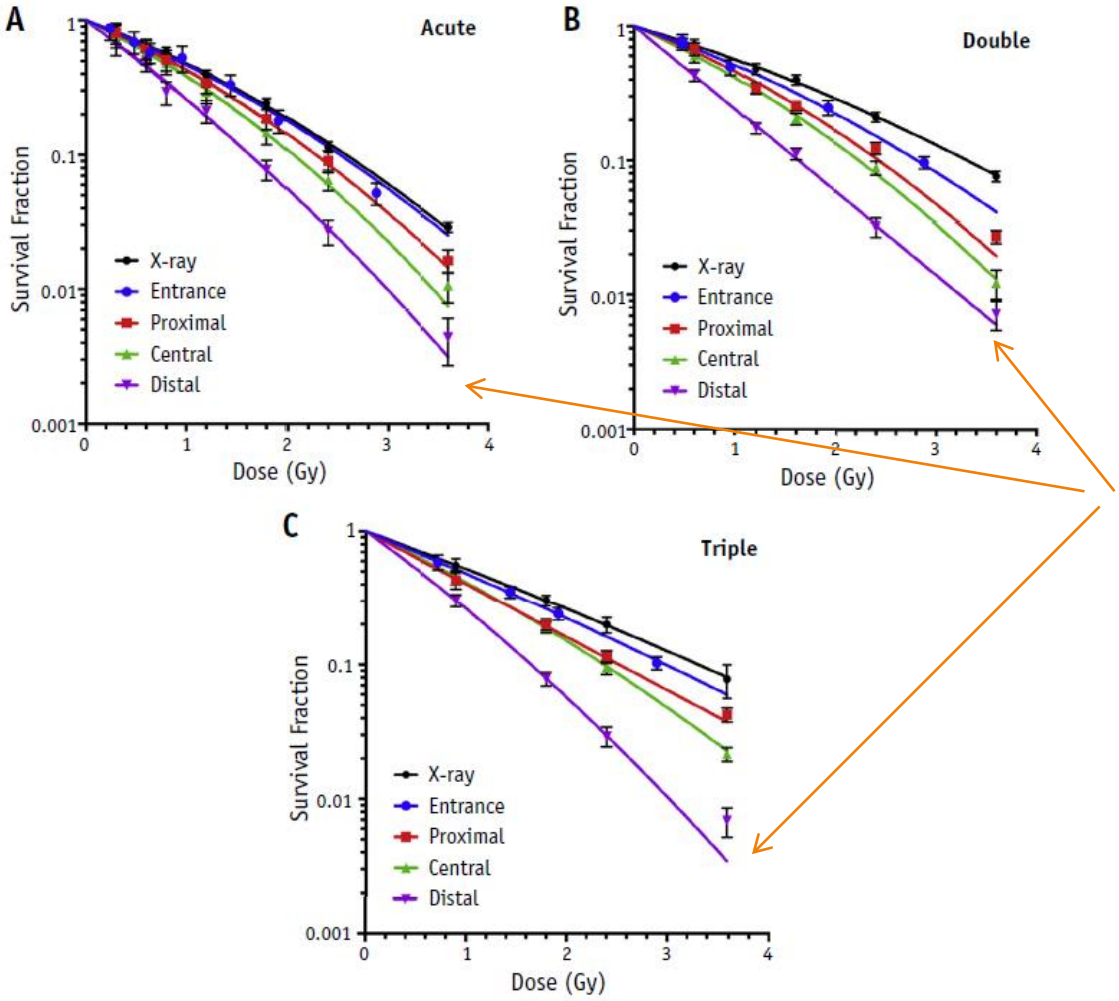
- A uniform RBE (radiobiological effective dose), or measurement of proton efficacy compared with photon, of 1·1 is assumed almost universally for the purposes of proton beam therapy treatment planning, despite evidence that the RBE might fluctuate depending:

- proton's depth in tissue (SOBP size and position)

- Fraction size and fractionation

- types of cells

SOBP position and fractionation



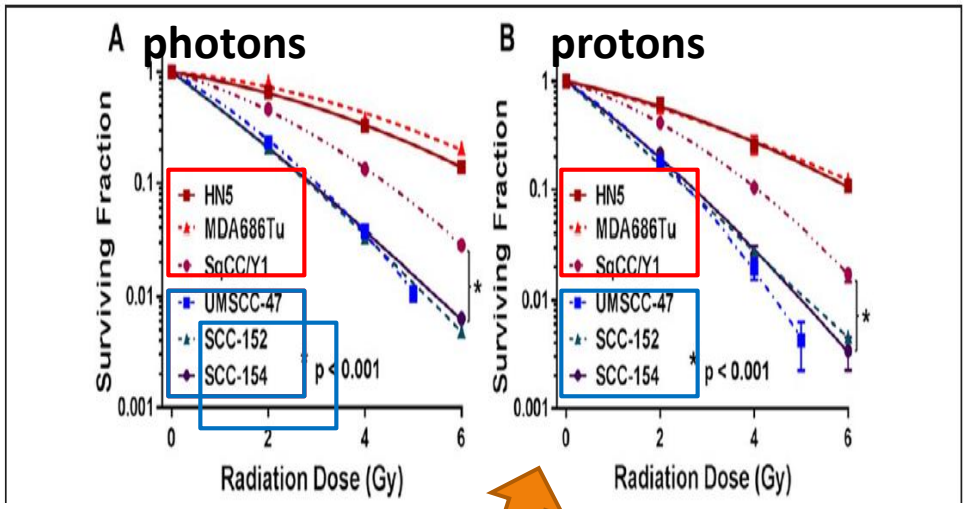
Increased LET and increased RBE

critical neurological structures!!!

Marshall, 2016

HPV pos

HPV neg



HPV-positive HNSCC cells were more sensitive to protons than were HPV-negative cells (all $p < .001$;

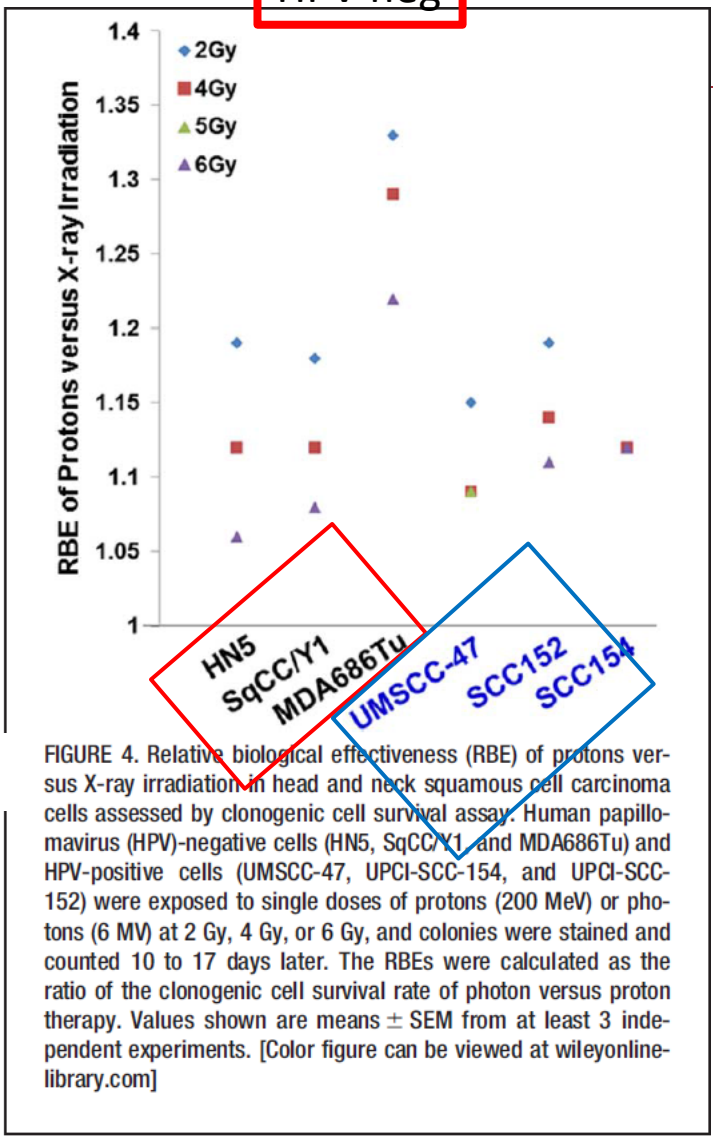
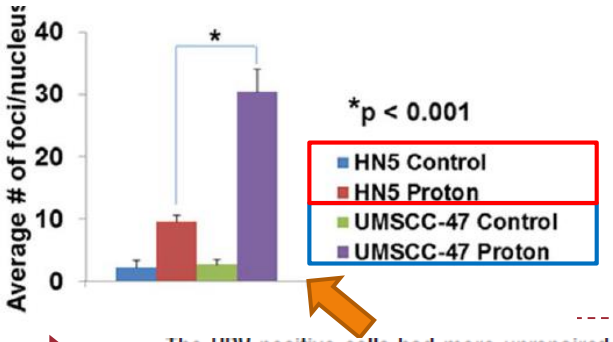


FIGURE 4. Relative biological effectiveness (RBE) of protons versus X-ray irradiation in head and neck squamous cell carcinoma cells assessed by clonogenic cell survival assay. Human papillomavirus (HPV)-negative cells (HN5, SqCC/Y1, and MDA686Tu) and HPV-positive cells (UMSCC-47, UPCI-SCC-154, and UPCI-SCC-152) were exposed to single doses of protons (200 MeV) or photons (6 MV) at 2 Gy, 4 Gy, or 6 Gy, and colonies were stained and counted 10 to 17 days later. The RBEs were calculated as the ratio of the clonogenic cell survival rate of photon versus proton therapy. Values shown are means ± SEM from at least 3 independent experiments. [Color figure can be viewed at wileyonlinelibrary.com]

The RBE for protons depends more on cell type and fraction size than on HPV status.



The HPV-positive cells had more unrepaired DNA double-strand breaks after treatment than did the HPV-negative cells (*$p < .001$).

Wang L2016

Direct comparisons of photon versus proton toxicity in head and neck cancer

	Number of patients	Disease sub-site	Methodology	Toxicity evaluated	Outcomes		
					Photon	Proton/charged particle	p value
Romesser et al (2016)[3]	18 proton beam therapy, 23 intensity modulated radiotherapy	Unilateral head and neck cancer (major salivary gland or cutaneous primary)	Retrospective cohort comparison	Mucositis, grade 2 or worse; nausea, grade 1 or worse; dysgeusia, grade 1 or worse; fatigue, grade 1 or worse; dermatitis, grade 2 or worse	52%; 70%; 83%; 91%; 74%	17%; 17%; 22%; 39%; 100%	0·005; 0·003; <0·001; 0·002; 0·032
McDonald et al (2016)[7]	14 proton beam therapy, 12 intensity modulated radiotherapy, 14 proton beam therapy to primary site and intensity modulated radiotherapy to neck	Nasopharyngeal, nasal cavity or paranasal sinus cancer	Retrospective cohort comparison	Gastrostomy tube dependent at completion of radiotherapy; gastrostomy tube dependent 1 month after radiotherapy; equivalent morphine dose greater than baseline at end of radiotherapy	0·03 (<0·01–0·15)*; 0·11 (<0·01–0·61)*; 0·09 (0·01–0·57)*	·· ·· ··	<0·001; 0·028; 0·006
Sio et al (2016)[5]	35 intensity modulated proton therapy, 46 intensity modulated radiotherapy	Oropharyngeal cancer	Retrospective cohort comparison	Subacute food taste symptoms†; subacute appetite symptoms†; chronic appetite symptoms†; subacute mucous symptoms (% with moderate–severe symptoms)	7·70; 6·37; 4·14; 84%	5·76; 4·68; 2·12; 62%	0·01; 0·048; 0·036; 0·038
Blanchard et al (2016)[6]	50 intensity modulated proton therapy, 100 intensity modulated radiotherapy	Oropharyngeal cancer	Retrospective case-matched control comparison	Patient-rated xerostomia, grade 2–3, 3 months after radiotherapy; gastrostomy tube presence or weight loss >20%, 1 year after radiotherapy	61%; 25%	42%; 8%	0·009; 0·010
Holliday et al (2015)[4]	10 intensity modulated proton therapy, 20 intensity modulated radiotherapy	Nasopharyngeal cancer	Retrospective case-matched control comparison	Gastrostomy tube needed during or after treatment	65%	20%	0·02
Patel et al (2014)[8]	286 charged particle (proton, carbon ion, helium ion, or other), 1186 photon (41 studies included)	Nasal cavity and paranasal sinus cancer	Systematic review and meta-analysis	Neurological toxicity (95% CI)	0·04 (0·02–0·08)	0·20 (0·13–0·31)	<0·001

MDASI-HN=MD Anderson Symptom Inventory-Head and Neck. *Proton *vs* photon odds ratio (95% CI). †mean MDASI-HN score.

Table 1: **Direct comparisons of photon versus proton toxicity in head and neck cancer**

Leeman JE 2017

Nasopharyngeal carcinoma

➢Chan A, Adams JA, Weyman E, et al. A phase II trial of proton radiation therapy with chemotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys 2012;* ***84: S151–52.***

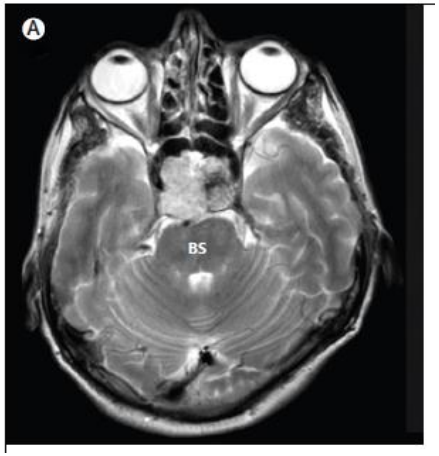
23 patients treated with a combined photon and proton technique : LC 100%;OS : 100 (2y). Toxiciy: grade 3 or worse hearing loss: 29% ; grade 3 or worse weight loss: 38% and no grade 3 xerostomia

➢Chan A, Liebsch L, Deschler D, et al. Proton radiotherapy for T4 nasopharyngeal carcinoma. ASCO Annual Meeting Proceedings. *J Clin Oncol 2004;* ***22: 557***

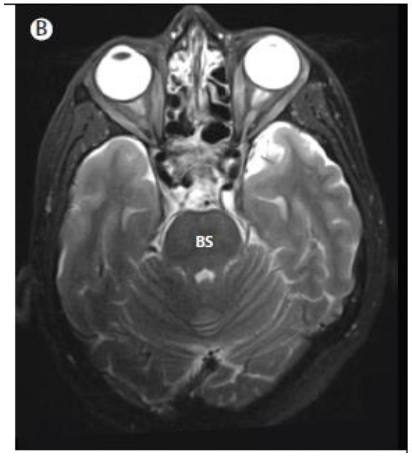
17 patients, only one local failure median fu 43 m. Late toxicities: radiographic temporal lobe changes (29%), one case of endocrine dysfunction, and one case of mandibular osteoradionecrosis

Skull base cordoma and condrosarcoma

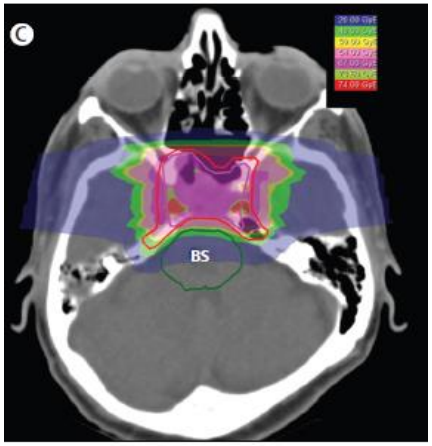
✓Radioresistent tumors



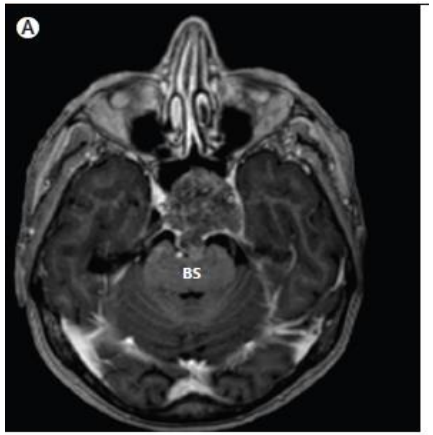
Diagnosis



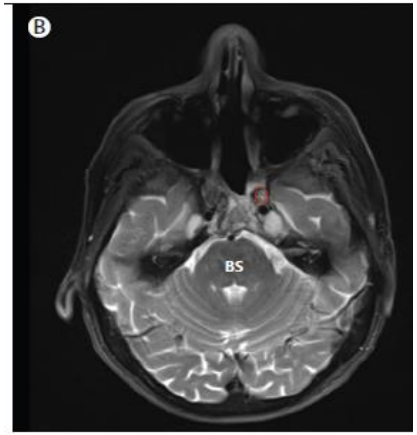
Surgery R1



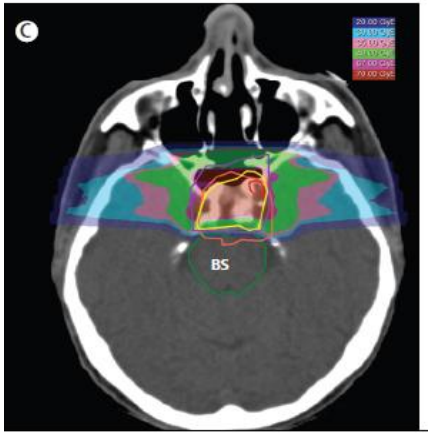
Postoperative PBT 74GyE (37 frs x 2Gy E in 7 week)s



Diagnosis



Surgery R2



Postoperative CIRT 70.4 GYE (16 frs x4.4 GyE in 4 week)s

Stacchiotti, 2015

Skull base cordoma and condrosarcoma

- 5-year Local control:70–100%, depending on histology, (median dose 74 GyE) ; high grade toxicity effects: 0-6%

  Munzenrider JE, 1999, Catton 1996Noel G, 2011Mc Donald 2016

- A D1cm(3) ≥74.5 Gy (RBE) represents a proposed treatment planning objective

  Mc Donald 2016

Adenoid cystic carcinoma

Unresectable disease or macroscopic residual disease after surgery

- **German experience** (COSMIC trial): a shrinking fields technique. CIRT boost to the GTV plus margin followed by photons IMRT to a wider volume that always included perineural spread. CIRT is delivered in 8 fractions of 3 Gy [RBE] each for a total of 24 Gy[RBE] with 5 or 6 fractions per week and was followed by 50 Gy of IMRT in fractions of 2 Gy. Jensen 2015

- **Japanese experience:** CIRT as exclusive therapy. Shrinking fields were used and a dose per fractions of 3.6–4 Gy [RBE] is employed with 4 fractions per week. The wider target volume received 9 fractions and included areas at risk of microscopic spread, perineuraland submucosal spread (paranasal sinuses that were partially infiltrated by the tumor were entirely included). In smaller target volume received 7 fractions and included GTV plus margins, and also perineural routes in cases of ACC at high risk of infiltration Mizoe JE 2012

Reirradiation (66-70. 2 GyRBE)

Tableau 2
Sélection d'études évaluant la protonthérapie en cas de réirradiation ORL.

Reference	Période	Technique	Type	Patients (*n*)	Chirurgie (%)	Histologie	Suivi médian (mois)	Résultat
McDonald et al. [54]	2004–2014	Protonthérapie conformationnelle[a]	Rétrospective	61	47,5	Carcinome épidermoïde (32) Autre (29)	29	À deux ans, récidive locale 19,7 %, survie globale 32,7 % Toxicité tardive : 8 de grade 3 (nécrose osseuse et muqueuse), 3 de grade 4 et 3 de grade 5
Phan et al. [55]	2011–2015	Protonthérapie conformationnelle[a] (*n* = 15), protonthérapie conformationnelle avec modulation d'intensité (*n* = 45)	Prospective	60	58	Carcinome épidermoïde (40) Autre (20)	13,6	À un an, survie sans rechute locorégionale 68,4 %, survie globale 83,8 % Toxicité tardive à un an 16,7 % ; trois de grade 5
Romesser et al. [56]	2011–2014	Protonthérapie conformationnelle[a]	Rétrospective	92	39	Carcinome épidermoïde (52) Autre (40)	13,3	À un an, récidive locorégionale 25,1 %, survie globale 65,2 % Toxicité tardive : de grade 3+ chez 10 patients. Trois de grade 5

Blanchard 2017

Ongoing and planned trials

	Institution	Inclusion	Treatment	Primary endpoints	Study start
NCT02923570	MSKCC	Unilateral head and neck targets (salivary, skin tumours)	Randomised to proton beam therapy vs intensity modulated radiotherapy	Acute toxicity	October, 2016
NCT02736786	Mayo Clinic	Resected oropharyngeal tumours by TORS	Mucosal sparing proton beam therapy	Local control at 2 years	March, 2016
NCT02663583	MDACC	Stage 1–3 previously untreated oropharyngeal squamous cell carcinoma	Intensity modulated proton therapy or transoral surgery	Functional outcome measured with patient reported outcomes and longitudinal digital wristband activity monitoring of study participants	January, 2016
NCT01973179	Technische Universitat Dresden	Previously irradiated head and neck cancer	Proton beam therapy	Late toxicity (24 months after therapy)	July, 2015
NCT01893307	MDACC, MGH, NCI, NIDCR	Stage 3–4 squamous cell carcinoma of the oropharynx	Randomised to intensity modulated radiotherapy vs intensity modulated proton therapy	Incidence of severe late toxicity 90 days to 2 years after RT	August, 2013
NCT01346124	MGH, MDACC, NCI	Sarcoma of the spine, sacrum, or base of skull	Intensity modulated proton therapy	Local control at 3 years	December, 2012
NCT01586767	MGH, NIH, NCI, Mayo clinic	Locally advanced sinonasal tumours	Proton beam therapy or intensity modulated radiotherapy	Local control at 2 years	July, 2011
NCT01228448	MGH, NCI	Brain, head and neck, and skull base tumours	Proton beam therapy	Effectiveness of in-room PET	October, 2010
NCT02130427	University of Pennsylvania	Multiple tumour sites, including head and neck	Proton beam therapy	Number of adverse events at 4–6 weeks	September, 2010
NCT00797043	University of Florida	Carcinoma of the skin of the head and neck with perineural invasion	Combined intensity modulated radiotherapy/proton beam therapy	Grade 3 or higher xerostomia at 1 year	September, 2008
NCT00592501	MGH, DFCI, BWH	Squamous cell carcinoma of the nasopharynx, non-metastatic, T2b and/or N+	Proton beam therapy	Acute toxicity, treatment compliance, quality-of-life measures	October, 2006
NCT00496119	MDACC	Skull base chordoma	Proton beam therapy	Time to local recurrence	September, 2006
NCT00797498	University of Florida	Cancer of the nasal cavity and/or paranasal sinuses	Proton beam therapy	Incidence of grade 3 or worse xerostomia at 1 year	August, 2006
NCT00496522	MDACC	Skull base chondrosarcoma	Proton beam therapy	Time to local recurrence	April, 2006
..	MSKCC	Cancer of the nasal cavity and/or paranasal sinuses	Endoscopic surgical resection and proton beam therapy	Local control at 2 years	Planned 2017 start
..	MSKCC	Recurrent or second primary head and neck cancer, previously treated with radiation	Proton beam therapy	Locoregional control	Planned 2017 start

MSKCC= Memorial Sloan Kettering Cancer Center. MDACC=MD Anderson Cancer Center. MGH=Massachussets General Hospital. NCI=National Cancer Institute. NIDCR=National Institute of Dental and Craniofacial Research. PET=positron emission tomography. DFCI=Dana-Farber Cancer Institute. BWH=Brigham and Women's Hospital. TORS=transoral robotic surgery.

Leeman JE 2017

Patient selection strategies for PBT

➢Evidence based medicine: randomization of the study population into photon and proton treatment ("all- or -none" question).

➢Model based approach: to estimate the potential clinical benefit for protons over photons in terms of reduction in normal tissue complication probability (NTCP) for each individual patient and assign the patient to PBT only if the reduction in toxicity is above a specified threshold (precision medicine).

Ramaekers, 2012
Blanchard 2017
Lagendjik 2013

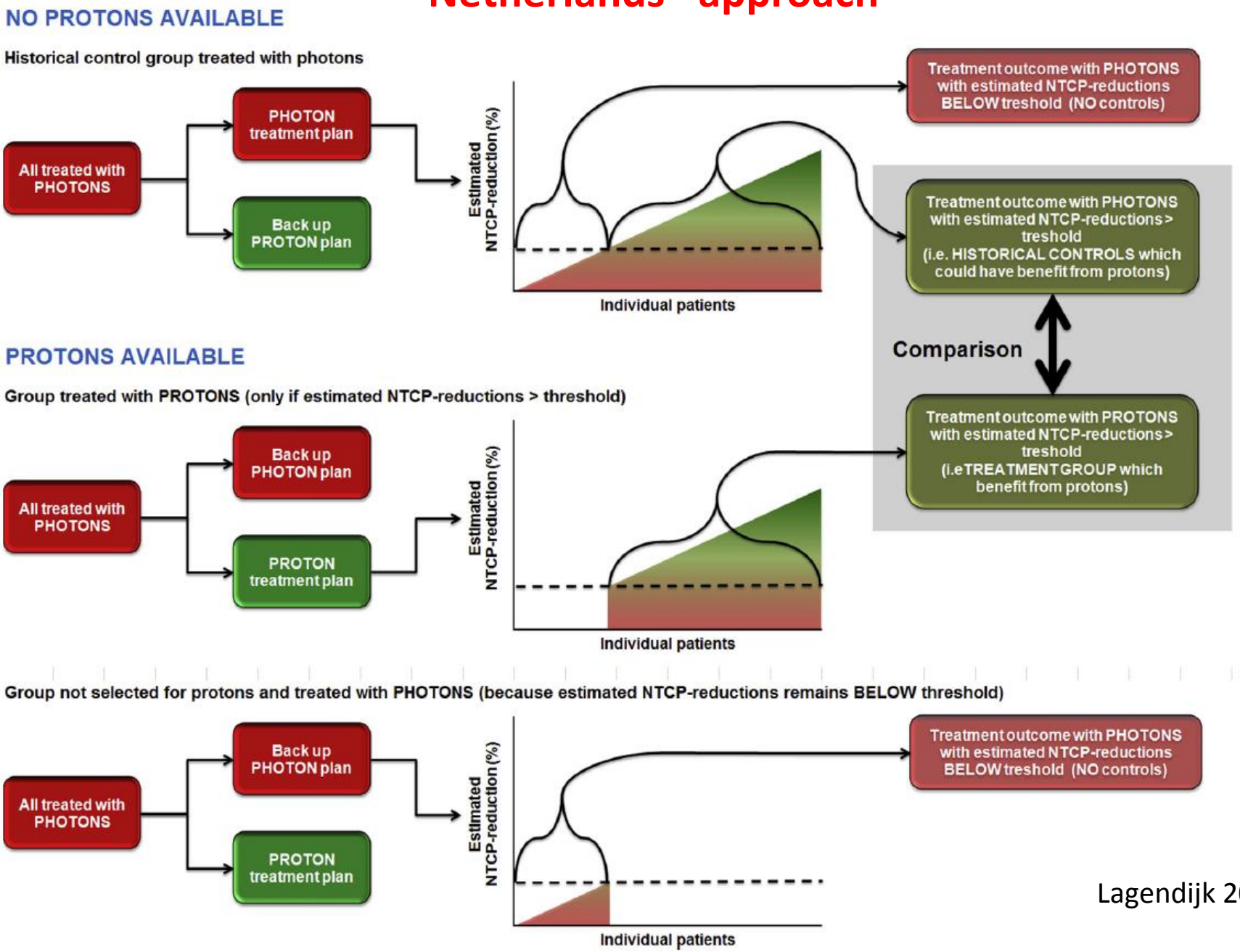
Patient selection strategies for PBT

➢Randomised controlled trials (RCT): when dose escalation can be expected to improve tumor control.

➢ RCT's investigating the added value of protons compared to photons with regard to reduction of side effects, run the risk of being ethically compromised.

Lagendijk 2013
Bentzen 2012

Netherlands ' approach



Lagendijk 2013

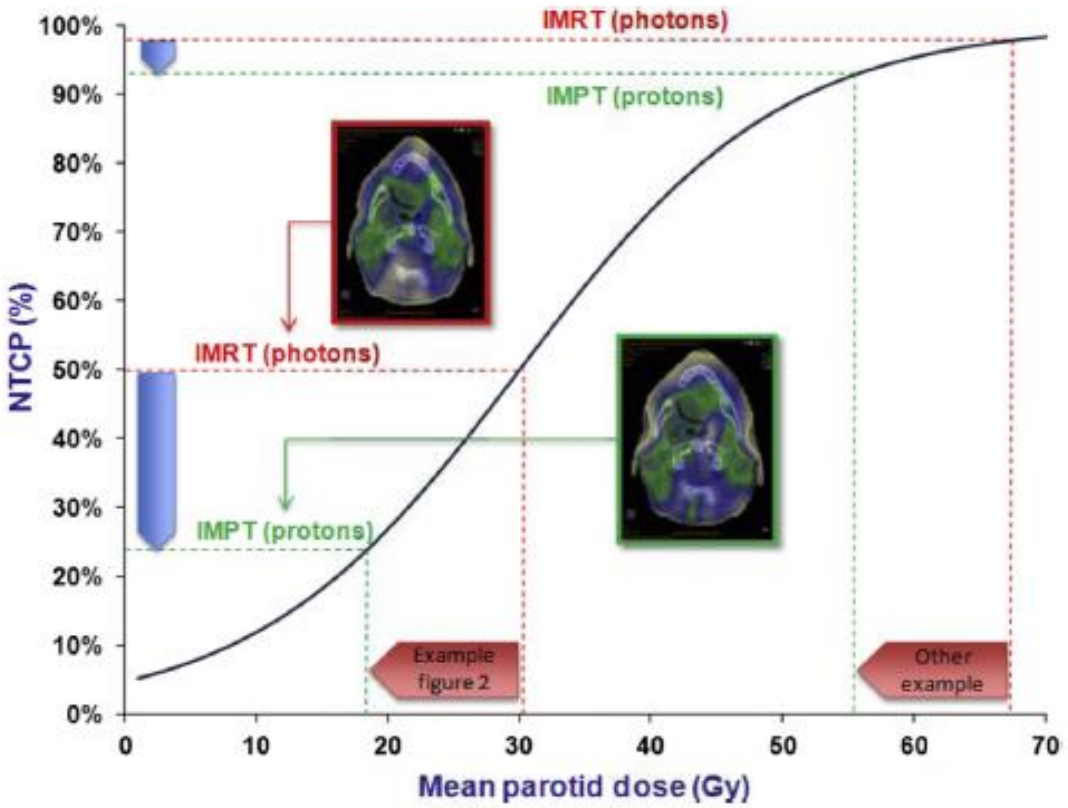


Fig. 3. Translation of the results of the individual ISPC-study depicted in Fig. 2 with regard to xerostomia. The reduction of the mean parotid dose from 30.1 Gy to 18.4 Gy (red arrow: example Fig. 2) corresponds with an estimated NTCP-value reduction for severe xerostomia from 50% to 24% according to the NTCP-model published by Semenenko. However, exactly similar absolute dose reductions (red arrow: other example) result in a minimal estimated NTCP-value reduction when the initial dose is much higher, due to the shape of the NTCP-curve.

Lagendijk 2013

Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort

Pierre Blanchard [a,c], Andrew J. Wong [a], G. Brandon Gunn [a], Adam S. Garden [a], Abdallah S.R. Mohamed [a], David I. Rosenthal [a], Joseph Crutison [a], Richard Wu [b], Xiaodong Zhang [b], X. Ronald Zhu [b], Radhe Mohan [b], Mayankkumar V. Amin [b], C. David Fuller [a], Steven J. Frank [a,*]

[a] Department of Radiation Oncology; [b] Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, USA; [c] Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France

Table 2
Discrimination properties of photon-derived NTCP models in proton-treated patients.

Model		Development set	IMPT validation	IMPT cross-validation
Persistence of feeding tube 6 months after treatment [9]	N patients	355	89	89
	N events	38	4	4
	AUC [95% CI]	0.88	0.947 [0.85–1.00]	0.90 [0.75–1.00]
	Model fit (HL)	0.70	0.43	
Physician-rated grade 2 + dysphagia 6 months after treatment [10]	N patients	354	89	89
	N events	NA	27	27
	AUC [95% CI]	0.8	0.708 [0.59–0.82]	0.697 [0.58–0.80]
	Model fit (HL)	NR	0.23	
Patient-rated dry mouth 6 months after treatment [12]	N patients	161	94	94
	N events	83	36	36
	AUC [95% CI]	0.68	0.735 [0.63–0.83]	0.704 [0.59–0.81]
	Model fit (HL)	0.84	0.05	
Hypothyroidism 12 months after treatment [11]	N patients	105	58	58
	N events	35	40	40
	AUC [95% CI]	0.85	0.743 [0.57–0.91]	0.728 [0.55–0.90]
	Model fit (HL)	NR ("good")	0.01	
Acute mucositis [8]	N patients	148	113	113
	N events	NP	40	40
	AUC [95% CI]	0.85	0.700 [0.60–0.80]	0.68 [0.58-.78]
	Model fit (R^2)	0.8	0.22	

Abbreviations: AUC, area under the ROC curve; HL, Hosmer-Lemeshow test; NR, no value reported; ROC, receiver operator characteristics. The Hosmer-Lemeshow test evaluates the model fit, a p-value of 0.05 or lower indicates a poor fit to the data. The R^2 is another measure of goodness of fit, and values close to one a good fit.

CONCLUSIONS

- PT could broaden the therapeutic window for patients with HNC

- Need of applying strategies to account for all uncertainties : robust treatment planning techniques, multicriteria optimization, CT-based image guidance, adaptive proton therapy,etc..

- Need to define the optimal target population for PT: RCTs vs model based approach (according to primary endpoint?)


That's all Folks!