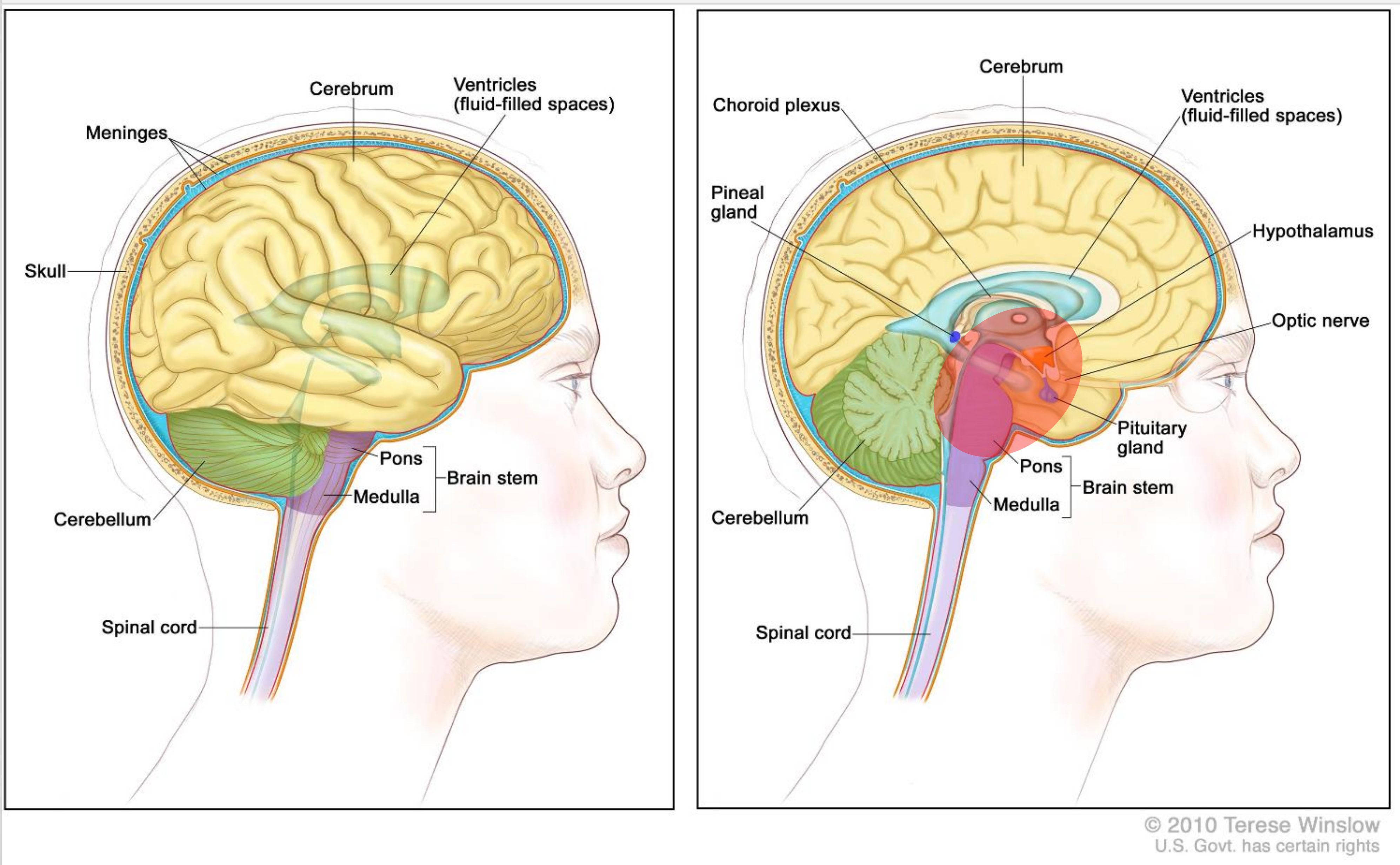
Post-treatment MR Imaging Changes and their Relation to Treatment Planning in Paediatric Proton Therapy

Jonathan B. Farr, D.Sc.

Outline

1. Brainstem toxicities in proton therapy review
2. Details of and LET calculations
3. Mitigations
    1. Treatment Planning
    2. Treatment

Anatomical Orientation



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● *Original Contribution*

RELATIVE BIOLOGICAL EFFECTIVENESS FOR DAMAGE TO THE CENTRAL NERVOUS SYSTEM BY NEUTRONS

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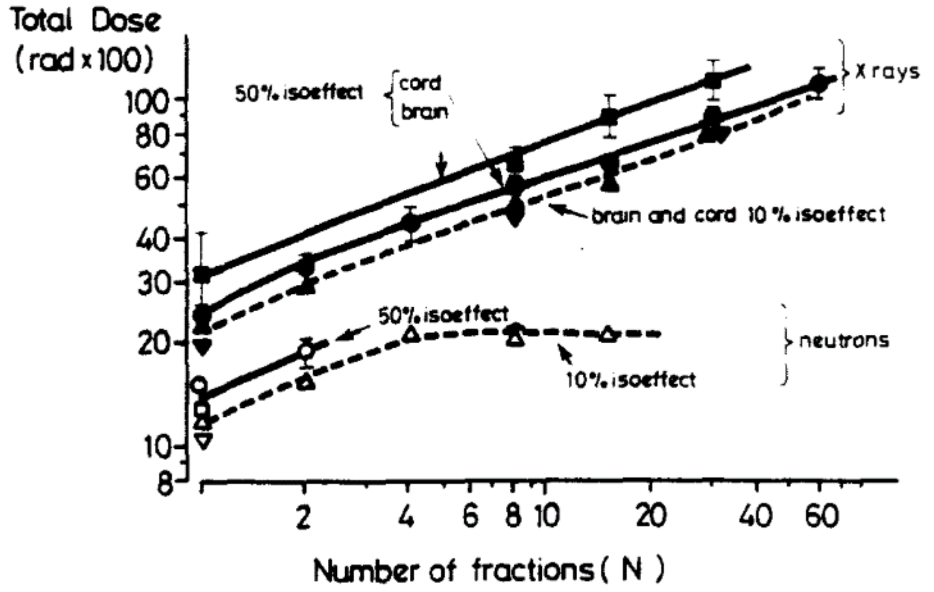

Fig. 1. Isoeffect curves for radiation damage to the spinal cord and to brain in rats for irradiation with 250 kV X-rays and fast neutrons (*Ed* = 16 MeV-Be).
Irradiation with X-rays: 50% isoeffect ● lumbar cord ■ brain, 10% isoeffect ▲ lumbar cord, ▼ brain.
Irradiation with neutrons: 50% isoeffect ○ lumbar cord, □ brain, 10% isoeffect △ lumbar cord, ▽ brain.

CONCLUSIONS

1. The RBE curve relating RBE and neutron dose/fraction for damage to the CNS was steeper than that for damage to skin. This reflected the steep isoeffect curves for X ray induced spinal cord and brain damage.

2. Fractionation of neutron dose had a minimal effect on tolerance levels.

3. The simplest method to convert an acceptable photon schedule to an acceptable neutron schedule is to use the RBE appropriate to the *photon* dose/fraction and convert it directly to total neutron dose.

4. For neutrons of *Ed* = 16 MeVd-Be, the RBE at a photon dose/fraction of 200 rad is 5.2; a photon dose of 6000 rad γ-rays/30*f*/6 wks is equivalent to a total dose of 1150 rad neutrons.

5. Doses used at Hammersmith to treat brain tumors were probably too high.

ORIGINAL RESEARCH
PEDIATRICS

Radiation Necrosis in Pediatric Patients with Brain Tumors Treated with Proton Radiotherapy

S.F. Kralik, C.Y. Ho, W. Finke, J.C. Buchsbaum, C.P. Haskins, and C.-S. Shih

- 60 pediatric patients with primary brain tumors treated with proton therapy.
- Double scattering/uniform scanning
- Radiation necrosis was assessed by examining serial MRIs and clinical records.

- Thirty-one percent of patients developed radiation necrosis with a median time to development of 5.0 months
- Risk factors included multiple chemotherapy agents (3 cytotoxic agents)
- Among patients with imaging findings of radiation necrosis, 25% demonstrated severe symptoms with medical intervention indicated.

- Pediatric patients with brain tumors treated with proton radiation therapy have a high incidence of radiation necrosis.
- The presence of multiple chemotherapeutic agents was found to be a statistically significant risk factor associated with radiation necrosis.
- Technique related?

ORIGINAL RESEARCH
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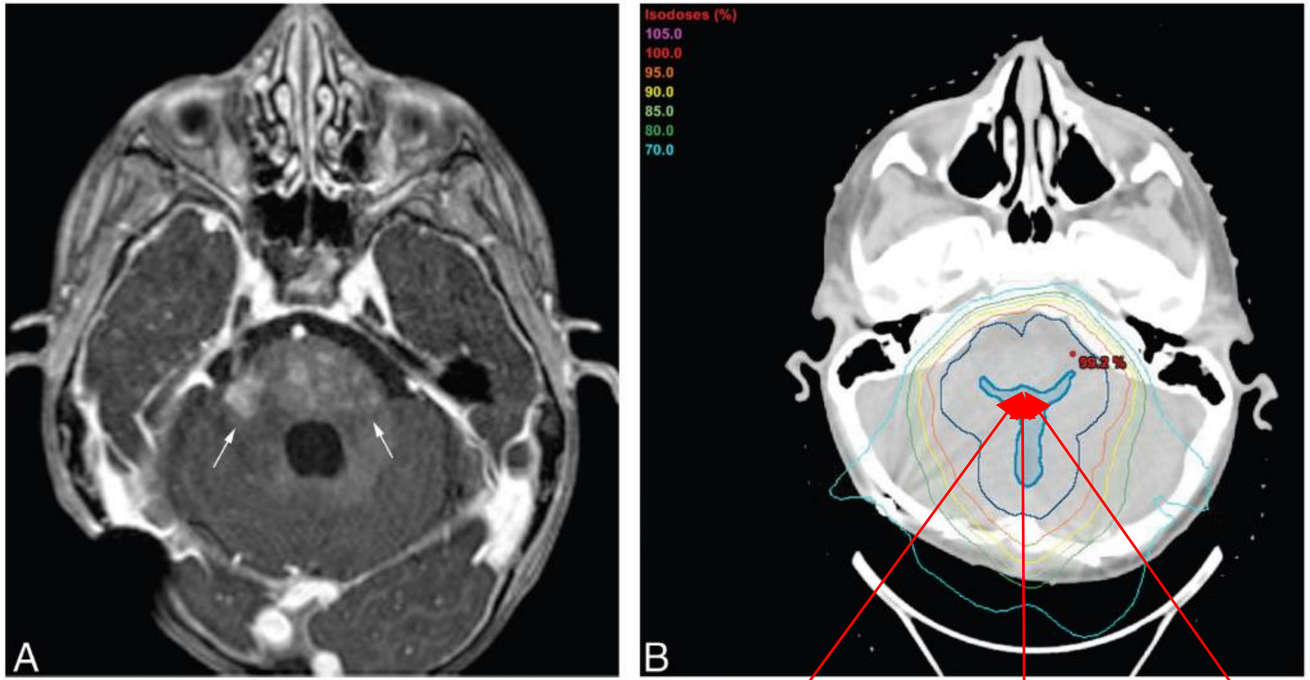


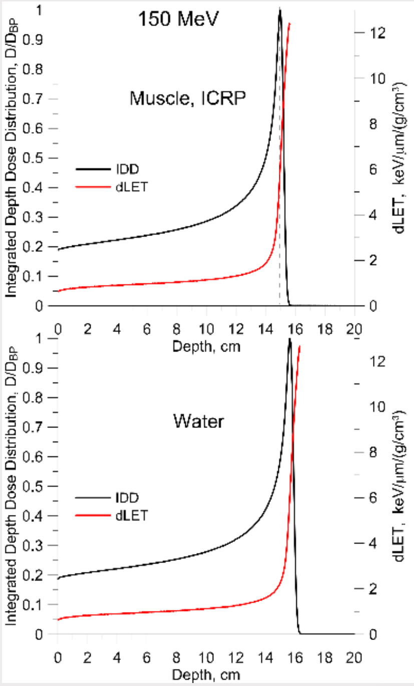
FIG 1. A 2-year-old child with a posterior fossa ependymoma status post gross total resection who developed multiple small foci of abnormal enhancement (*arrows*) in the pons and middle cerebellar peduncles, seen on an axial T1WI+C image (*A*), located within the radiation field (*B*) at 6 months following completion of PBT. Shown in the radiation treatment image (*B*) are the target structures of the gross tumor volume (dark blue filled) and the clinical target volume (darker blue, not filled). The dose lines of the proton beam treatment plan (analogous to the elevation lines of a topographic map) are shown as percentages of the prescription dose (59.4 Gy) in light purple (105%), red (100%), orange (95%), yellow (90%), light green (85%), forest green (80%), and cyan (70%).

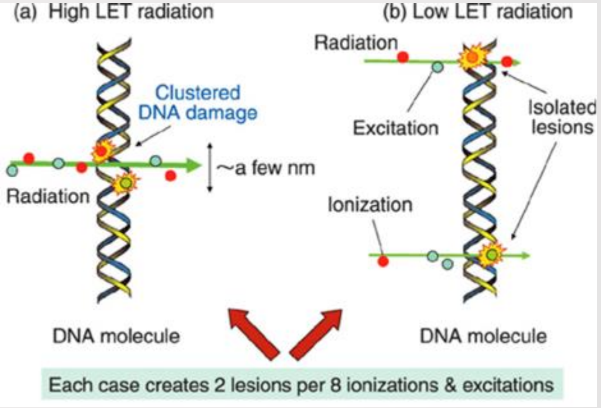
Linear Energy Transfer

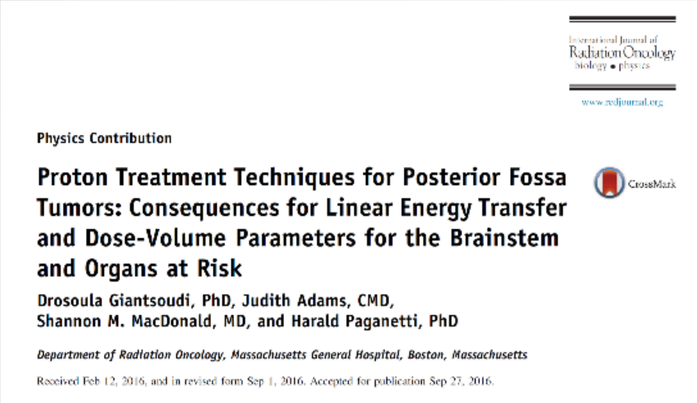
- Linear Energy Transfer (LET) = how much energy an ionizing particle transfers to the material traversed per unit distance.
- [keV/micro-meter]
- [MeV/cm]
- Radiation Dose [Gy=J/Kg]
- Dose weighted-LET =

$$\frac{\sum_{events} dE \times \left(\frac{dE}{dx}\right)\frac{1}{\rho}}{\sum_{events} dE}$$

protons







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Physics Contribution

Proton Treatment Techniques for Posterior Fossa Tumors: Consequences for Linear Energy Transfer and Dose-Volume Parameters for the Brainstem and Organs at Risk

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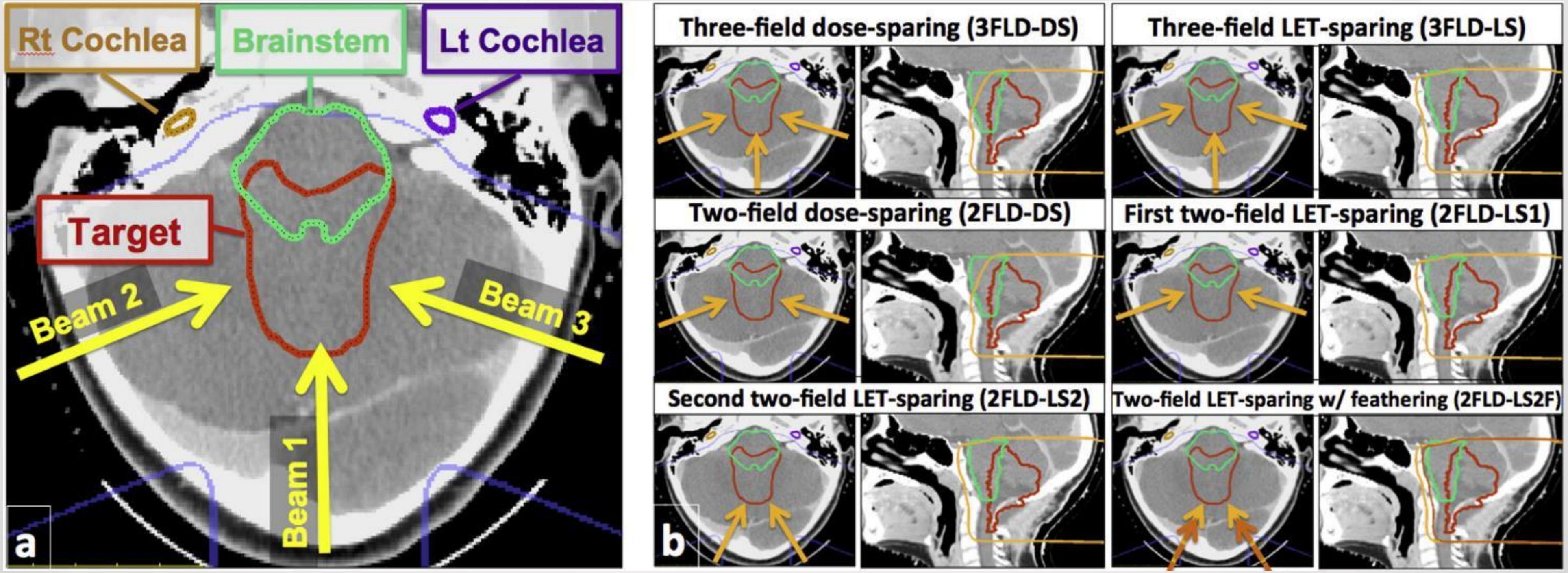
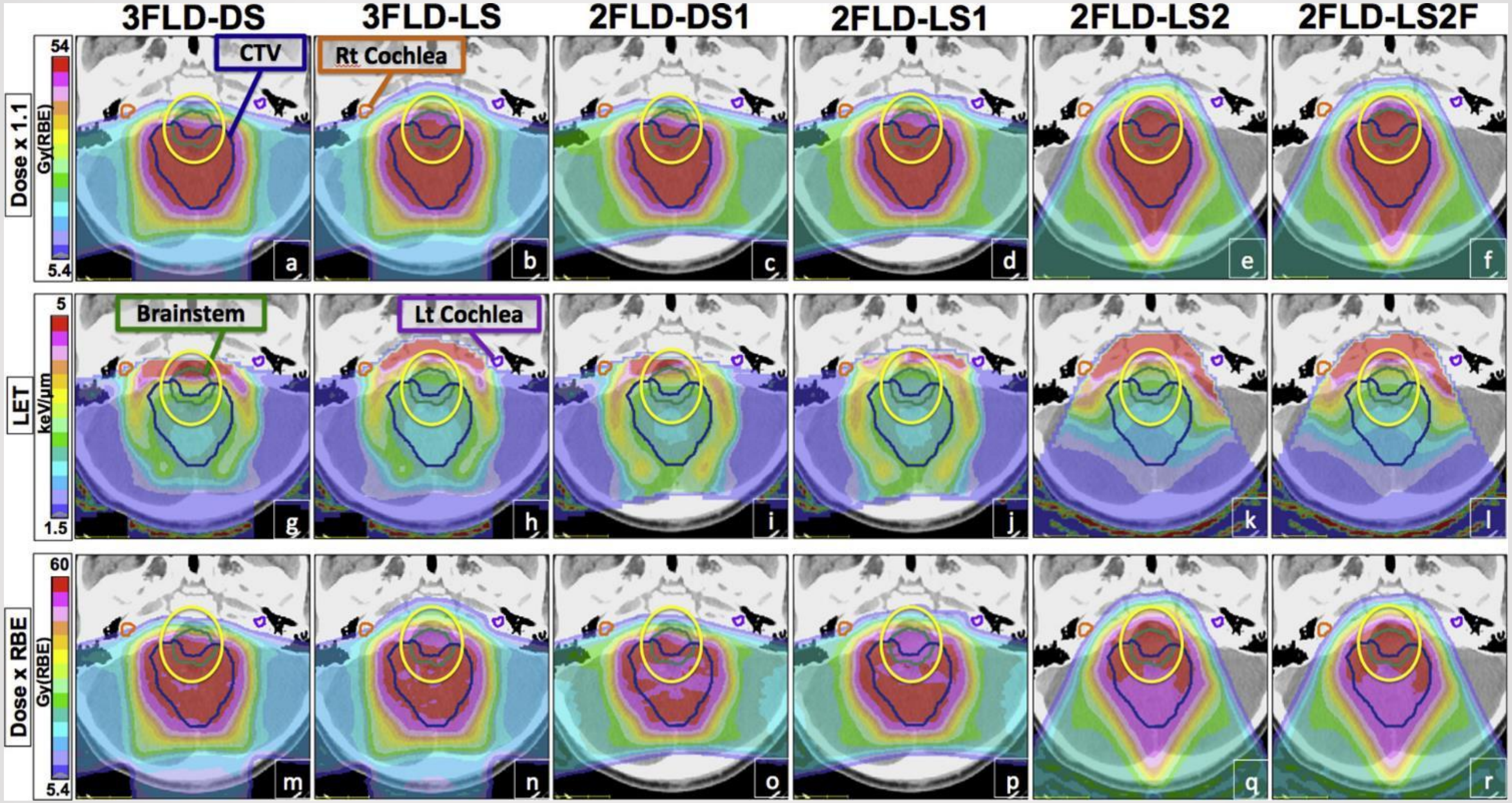
Received Feb 12, 2016, and in revised form Sep 1, 2016. Accepted for publication Sep 27, 2016.

†McNamara AL, Schuemann J, Paganetti H. A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. Phys Med Biol 2015;60: 8399-8416.

- Ependymoma and medulloblastoma
- Preferred beam directions to spare temporal lobes and cochlea place distal end of Bragg peak within brainstem
- Should planning extend Bragg peaks beyond brainstem?
- Using RBE model† calculate RBE plans based on differing beam arrangements
- 6 patients
- Double scattering plans
- 54 Gy (RBE) to CTV
- TOPAS calculated dLET
- Assign alpha/beta by tissue type, calc RBE-weighted dose





3FLD-DS
3FLD-LS
2FLD-DS1
2FLD-LS1
2FLD-LS2
2FLD-LS2F
Dose x 1.1
Gy(RBE)
54
5.4
CTV
Rt Cochlea
LET
keV/μm
5
1.5
Brainstem
Lt Cochlea
Dose x RBE
Gy(RBE)
60
5.4
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
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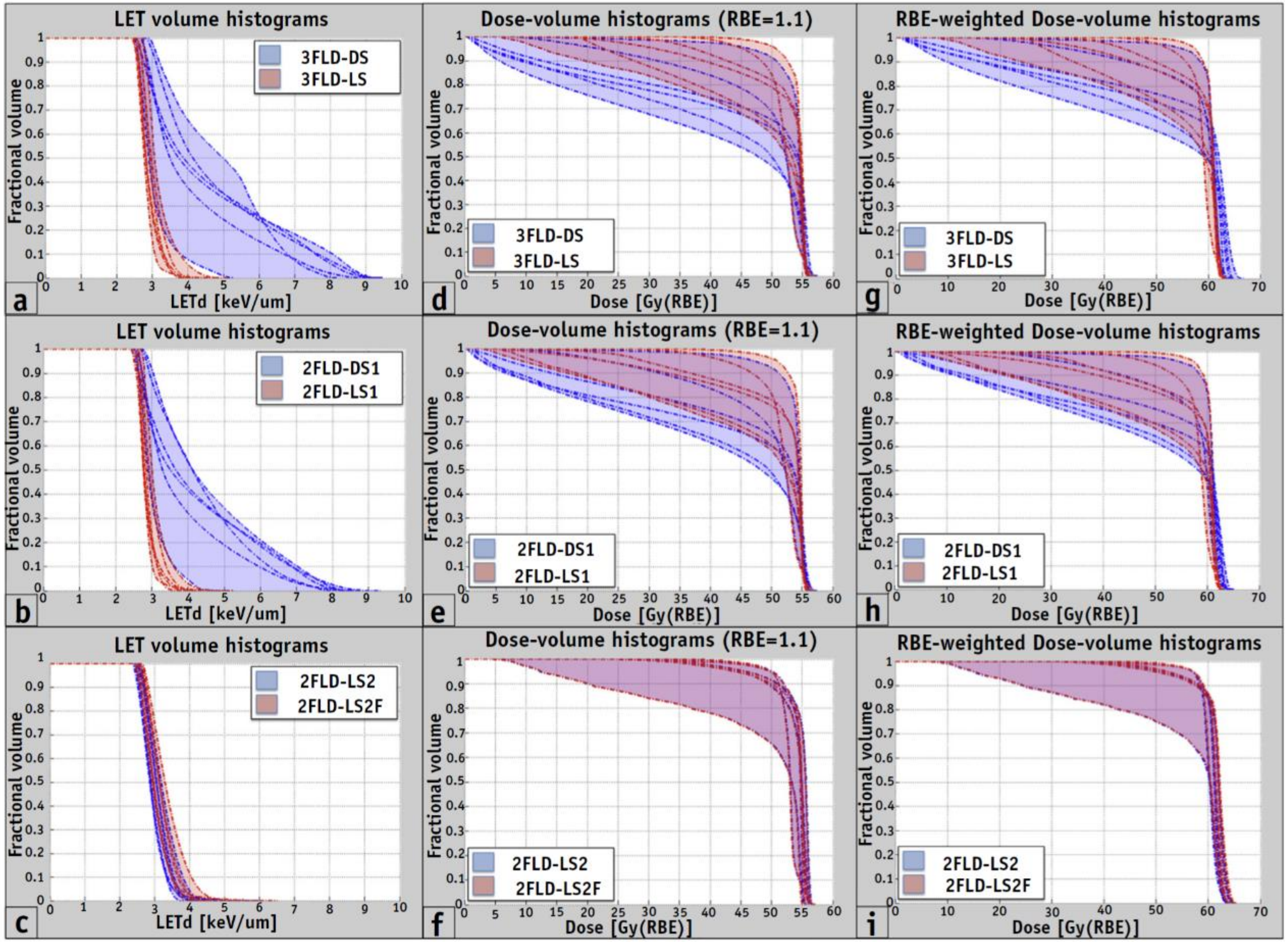

Fig. 4. (a-c) Linear energy transfer (LET), (d-f) constant relative biologic effectiveness (RBE) dose, and (g-i) variable RBE weighted dose-volume histograms for the brainstem for all 6 cases comparing pairs of techniques. Each curve corresponds to a specific patient and each color to a planning technique, showing 2 curves per patient in each graph. *Abbreviations:* 3FLD-DS = 3-field dose-sparing; 3FLD-LS = 3-field LET-sparing; 2FLD-DS1 = 2-field dose-sparing; 2FLD-LS1 = first 2-field LET-sparing; 2FLD-LS2 = second 2-field LET-sparing; 2FLD-LS2F = 2-field LET-sparing with feathering.

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Physics Contribution

Proton Treatment Techniques for Posterior Fossa Tumors: Consequences for Linear Energy Transfer and Dose-Volume Parameters for the Brainstem and Organs at Risk

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- Comparing the results from LET-sparing techniques 3FLD-LS, 2FLD-LS1, and 2FLD-LS2 points out the significance of selecting the appropriate number and directions of proton beams in the treatment of these patients.
- In an effort to better spare the brainstem and spinal cord of any unnecessary (relative biologically effective) dose, oblique beams in larger angles (relative to the PA direction) should be preferred because they potentially allow for both dosimetric and LET sparing of the brainstem.
- In conclusion, extending the end of range beyond the brainstem does not necessarily lead to favorable variable RBE-weighted doses, despite the decreased LET values in the brainstem.
- Considering all these factors, we can conclude that if the objective is to minimize the volume of the brainstem being treated, then the dose-sparing approach should be preferred.
- What about minimized LET and Dose?
- IMPT?

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Variable proton RBE

Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma

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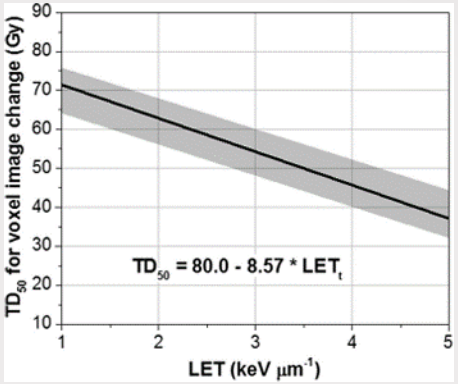


Table 2
Univariate and multivariate logistic regression analysis of clinical factors for all patients.

Variable	Odds ratio	95% CI	*P* value (univariate)	P value (multivariate)
Mean LET in CTV >1.5 keV μm^{-1}	8.67	0.94–80.0	0.06	0.63
Max LET in CTV >2.5 keV μm^{-1}	7.33	1.29–41.7	0.02	0.53
Mean CTV physical dose >52 Gy	0.61	0.15–2.43	0.49	
Max CTV physical dose >56 Gy	0.82	0.21–3.22	0.77	
Age at RT <3 years	2.50	0.58–10.7	0.22	0.65
Time before RT <3 months	7.00	0.75–65.2	0.09	0.30

Abbreviations: LET, linear energy transfer; CTV, clinical target volume; RT, radiotherapy; CI, confidence interval.

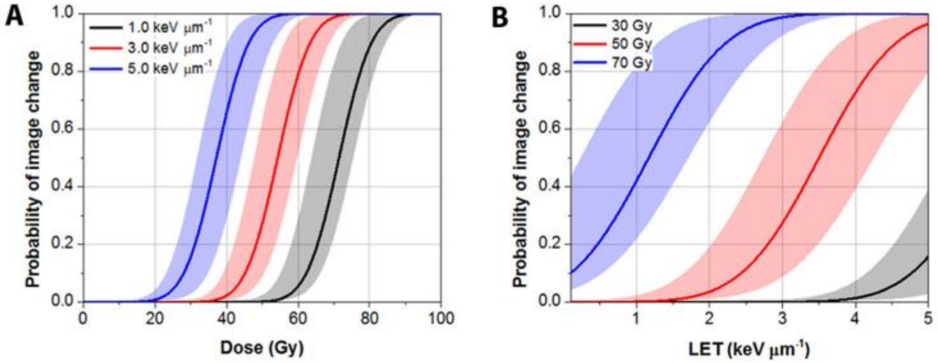


Fig. 2. Two-dimensional representations of the generalized linear model for predicting image change from constant LET_t or physical dose. Curves represent slices through the three-dimensional surface produced by the generalized linear model for (A) constant LET_t of 1, 3, and 5 keV μm^{-1} and (B) constant physical dose of 30, 50, and 70 Gy. Shaded bands indicate 95% confidence intervals.

- 34 pediatric patients with ependymoma treated with proton therapy.
- DS
- A subset of 14 patients exhibited post-treatment changes on MR images
- MRs registered, regions contoured
- MCNPX Monte Carlo modeled LETt track averaged LET
- LETt is the arithmetic mean value of the fluence spectrum of LET.
- Considered association of 6 factors

Challenge: Proton therapy target conformity

- Cohort of 7 H&N patients from clinical practice
- Tomotherapy and IMPT plans compared
- Dose fall off gradient determined by 1 mm expansion shells scoring mean dose
- **On average, Tomotherapy provided a steeper dose gradient from the target**

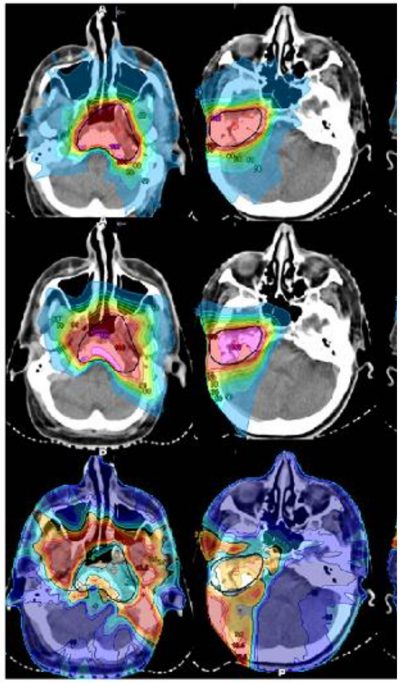
Stuschke *et al. Radiation Oncology* 2013, **8**:93
http://www.ro-journal.com/content/8/1/93

RADIATION ONCOLOGY

RESEARCH Open Access

Re-irradiation of recurrent head and neck carcinomas: comparison of robust intensity modulated proton therapy treatment plans with helical tomotherapy

Martin Stuschke[1,2*], Andreas Kaiser[2], Jehad Abu-Jawad[1], Christoph Pöttgen[1], Sabine Levegrün[1†] and Jonathan Farr[2,3†]



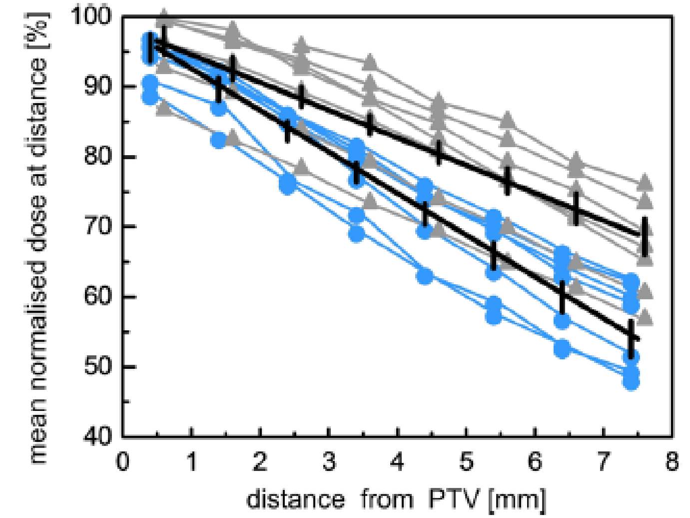


Figure 3 Dose fall-off. Dose fall-off outside planning target volume for helical tomotherapy (HT) (blue) and intensity modulated proton therapy (IMPT) (grey). Mean doses in adjacent shells of 1 mm width around the planning target volume (PTV) within the respective patient's body are given normalized to the prescribed dose. The slopes of the average dose fall-off differed between HT and IMPT (p< 0.0001). In addition, the 95% confidence intervals for the predicted dose values at a given distance are indicated by vertical bars.

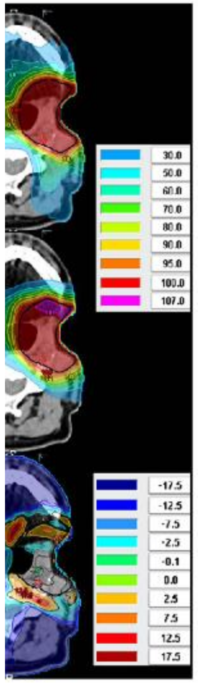


Figure 1 Dose distribution. Dose distribu... dulated proton therapy (IMPT) plans are shown in row 1 a... ird row for the respective patients.

Beam quality - Penumbra

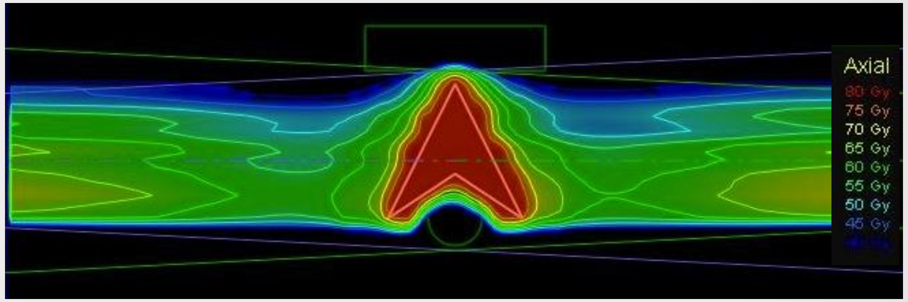
- Effect on dose conformity and delivery efficiency of intensity modulated proton therapy (IMPT) by varying physical proton beam dimensions (beam σ using the Gaussian profile).
- A 3-12 mm range of beam σ in air was simulated.
- A series of treatment plans on simple phantoms were generated with variable spot size.
- The following metric was used to grade the plans: Target Conformity = (D10-D95)/(D10-D95)3mm,OAR Hit = DOR50/DOR503mm, Quality Index (QI) = Target Conformity/OAR Hit.
- Lower QI scores (1-2) indicate potentially superior plans.

J. Farr, D. Geismar, A. Kaiser, M. Stuschke, Westdeutsches Protonentherapiezen trum and Universitätsklinikum Essen, “Gaussian beam sigma and field number effects on dose conformity in intensity modulated proton therapy,” PTCOG, October 2009, Heidelberg, Germany.

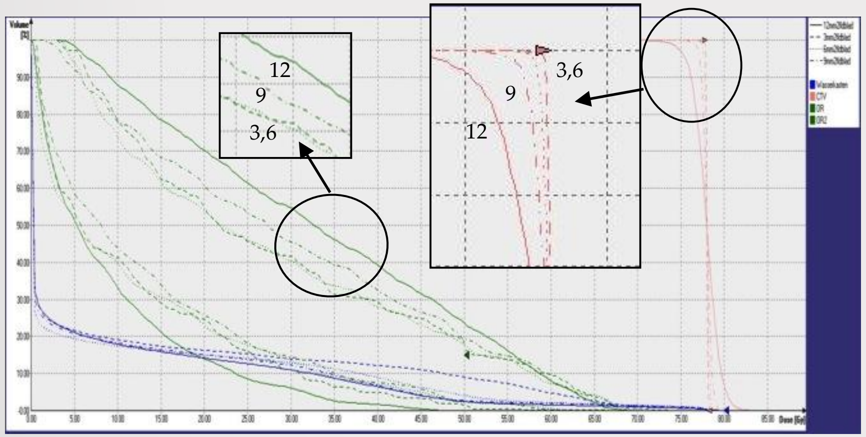
Beam quality - Penumbra

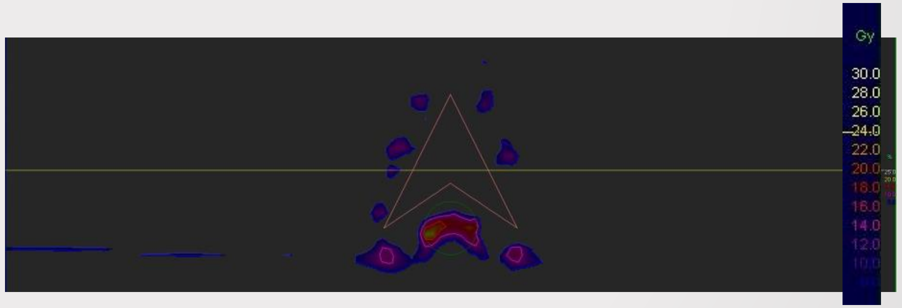
- The phantom QI's indicated a significant sensitivity to beam size.
- A reasonable QI was only achieved by the 3 and 6 mm σ beams.

	Conformity	OAR Hit	QI
Prostate Phantom			
3mm - 2 Field	1	1.0	1
6mm - 2 Field	2	1.1	2
9mm - 2 Field	5	1.1	5
12mm - 2 Field	17	1.2	14



Highly conformal 3 mm σ plan result





% dose difference between 3 mm and 12 mm σ plans indicating excess dose to the simulated OAR

Beam quality - Penumbra

Is there a single spot size and grid for intensity modulated proton therapy? Simulation of head and neck, prostate and mesothelioma cases

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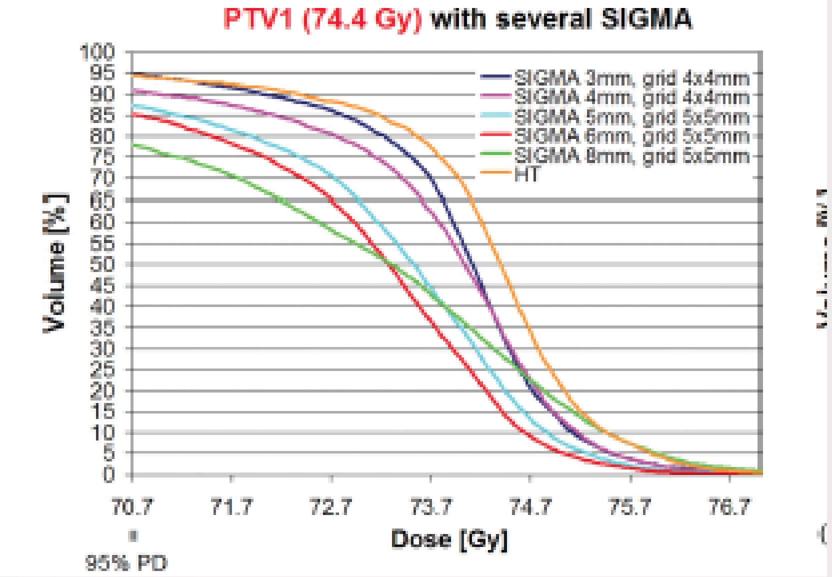
Med. Phys. 39 (3), March 2012



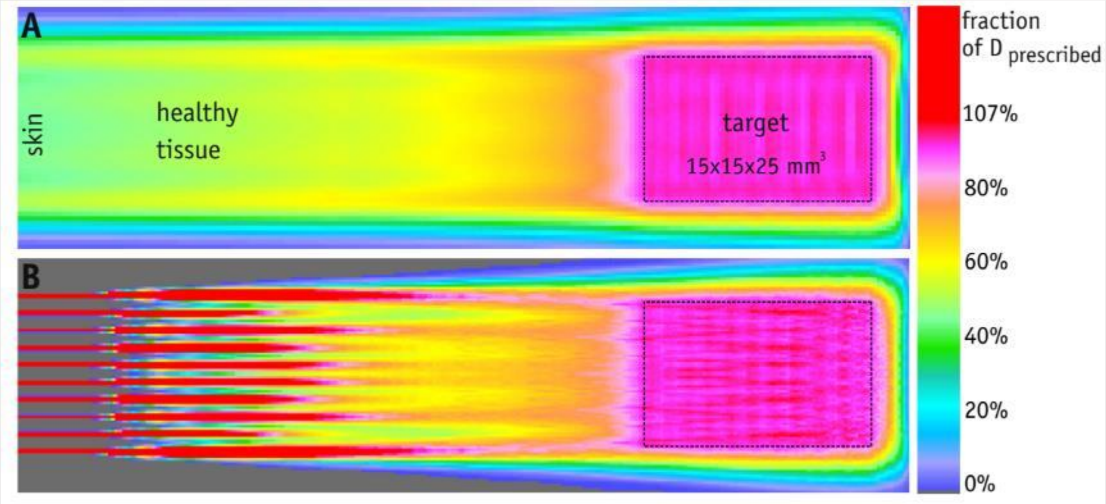
V. CONCLUSIONS

We determined the dependence of the maximum σ that obtains comparable target coverage and sparing of OARs to advanced photon techniques for three clinical cases. σ must be ≤ 4 mm for the head and neck cancer, ≤ 3 mm for the prostate cancer and ≤ 6 mm for the malignant pleural mesothelioma. Furthermore, the spot spacing was optimized for

Scanned minibeams

Charged Particle Therapy with Mini-Segmented Beams

F. Avraham Dilmanian[1,2,3]*, John G. Eley[4], Adam Rusek[5,6] and Sunil Krishnan[7]



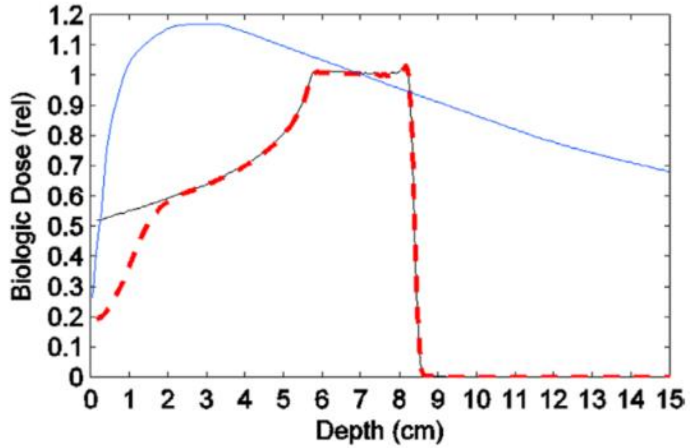
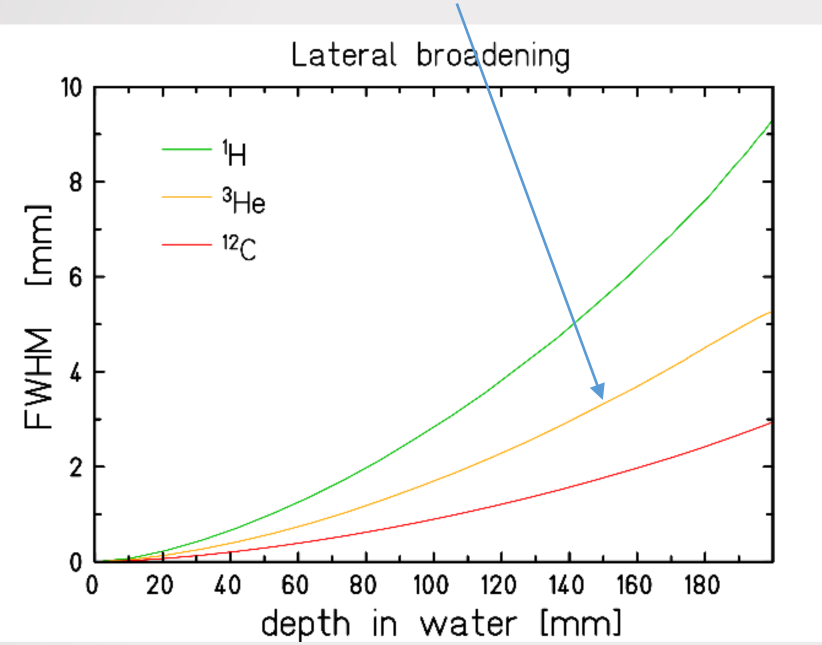
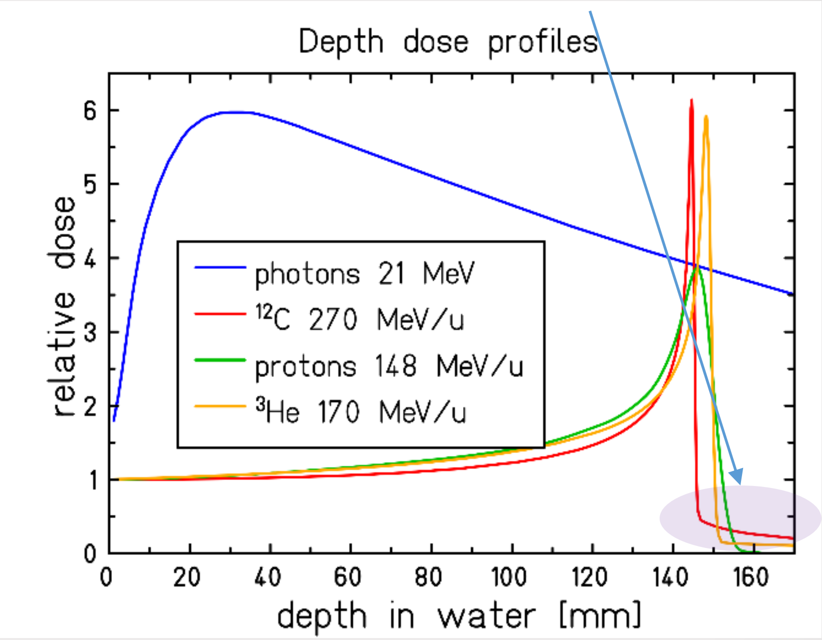


FIGURE 10 | Comparing the depth-dose distributions in a phantom of (a) a 10-MV x-ray beam, (b) an incident solid proton beam with its spread-out Bragg-peak, and (c) estimated biological dose from an incident proton minibeam array undergoing the same pattern of Bragg-peak spreading as above.

Frontiers in Oncology | www.frontiersin.org 2 December 2015 | Volume 5 | Article 269

Higher Target Conformity: He++





- Proton MCS leads to degradation at depth in media loosing its high dose conformity in comparison to IMXT
- Due to greater mass, He and C do not experience as much MCS, retaining their physical dose distribution advantage in comparison to IMXT

- Carbon beams are associate with an undesirable fragmentation “tail”
- The fragmentation tail is not observed for protons
- The Helium fragmentation tail is much lower in magnitude in comparison to carbon

Source: *Helium ions for radiotherapy? Physical and biological verifications of a novel treatment modality. Michael Krämer, et al. Med. Phys. 43 (4), April 2016*

Higher Target Conformity: He++

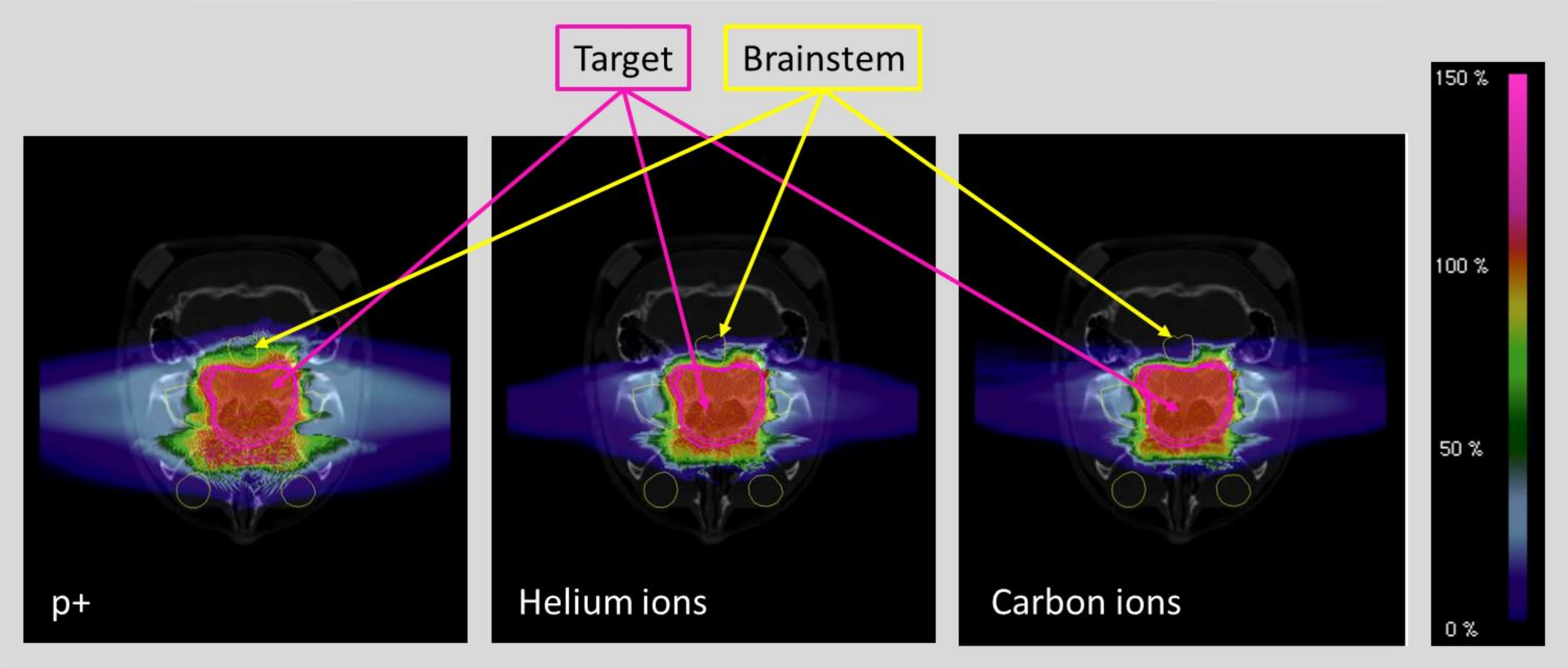


TABLE I. Mean brain stem RBE-weighted dose according to the patient plan in Figs. 7 and 8.

Ion type	Mean $D_{\text{brainstem}}$/ fraction [Gy (RBE)]
^{12}C	0.48
^{4}He	0.65
^{1}H	1.48

Helium and Carbon show significant physical and biological dose sparing to the brainstem

Assessment of potential advantages of relevant ions for particle therapy: A model based study.
R. Grün, et al. Med. Phys. 42 (2), February 2015