The Clinical Application of Proton Pencil Beam Scanning for High-Dose Spatially Fractionated Radiation (GRID) Therapy

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July 18, 2019

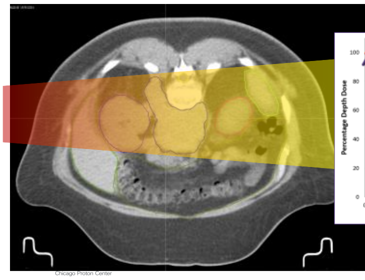
Disclosures

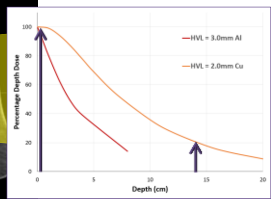
- Nothing to disclose

Learning Objectives

- To learn some of the historical background of high-dose spatially fractionated radiation therapy (GRID Therapy)
- To recognize the common clinical indications for GRID therapy.
- To appreciate how PBS protons can provide clinical effectiveness and improve patient safety in a sub-set of patients where GRID therapy is indicated.

The early problems of deep seated targets and Ortho-voltage X-Ray





PDD Data From Johns and Cunningham "The Physics of Radiobiology"

An alternative approach to space skin

- 1895 Roentgen discovers X-Ray
- In 1902 first reported treatment using X-ray
- In 1909 Kohler introduced a method to spare some skin in the irradiated field by using a perforated screen initially made of Pb and rubber.
- Produced a "Grid" pattern of X-Ray intensity over the field of 100-400kVp
- Able to increase doses 20X's higher with tolerable dose to the skin

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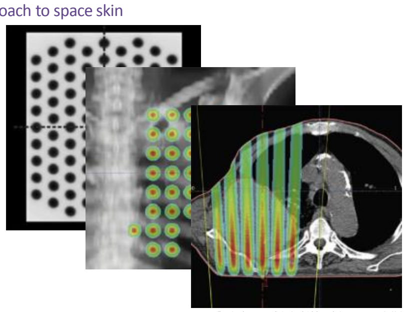

Billena C., Kahn, X. Int J Radiation Oncol Biol Phys, Vol. 104, No. 1, pp. 177-187, 2019

Treatment Planning : 101

- Rule #1 : Cover the target with dose to control disease
- Rule #2 : Limit dose to critical structures to minimize the probability of toxicities

Nevertheless GRID therapy produced good clinical outcomes

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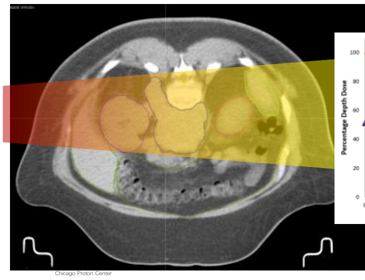
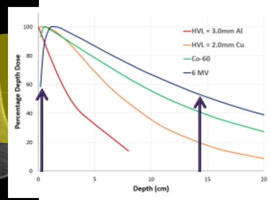
The early problems of deep seated targets and Ortho-voltage X-Ray

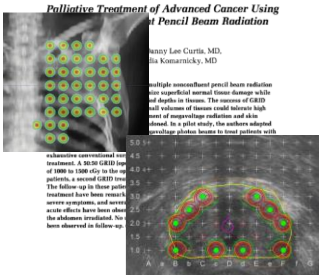




PDD Data From Johns and Cunningham "The Physics of Radiobiology"

A second look at GRID Therapy

- Renewed interest published by Mohiuddin in 1990.
- Spatially fractionated radiotherapy was similar to a brachytherapy boost
  - Goal : safe delivery of high doses without exceeding normal tissue tolerance
- 22 patients, already treated with:
  - maximal surgery
  - maximum conventional chemotherapy
  - maximum conventional radiotherapy
  - massive tumor bulk



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A second look at GRID Therapy

- Single GRID Field with 6MV Peak doses of 10 – 15Gy
- All patients were treated with intent of palliation
  - 6 had prior irradiation of $\geq$ 50Gy
  - 14 had EBRT in addition to GRID
  - 4 had GRID Tx repeated after a 4 week interval
- Reported complication
  - 1 Erythema, 2 Abdo cases and Nausea and Diarrhea
  - 1 late bowel obstruction, 70Gy + 10Gy GRID
- Excellent response rates
  - 20 of 22 achieved "dramatic relief of severe symptoms"

Palliative Treatment of Advanced Cancer Using

TABLE 3. Response Rate as a Function of the Four Most Common Symptoms

Symptoms	Total no.	CR (%)	PR (%)	Total response CR + PR	NR (%)
Pain	19	5 (26)	12 (67)	89%	2 (7)
Edema	3	—	3 (100)	100%	—
Bleeding	4	4 (100)	—	100%	—
Mass effect	5	—	4 (80)	80%	—

CR: complete response; PR: partial response; NR: no response.

Live	Tissue necrosis	0/22 (0%)
Squ	Lymphedema	0/22 (0%)
Ren	Neurologic	0/22 (0%)
Mel		
Ade		

* Twelve patients received abdominal fields.

Total	22	6	14

CA: carcinoma; XRT: radiation therapy; Adeno CA: adenocarcinoma.

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A slowing growing interest in SFRT

Table 2 Summary of clinical studies

Authors	Treated Sites (n)	Follow-up, median (range) (mo)	Histology	GRID dose, median (range) (Gy)	Prior RT	GRID only	Control rates	Side effects
Mohiuddin et al, 1990[9]	22	NR (1-18)	Diverse	NR (10-15)	27%	36%	Response rate: 91%	1 acute skin erythema, 2 N&V, 2 diarrhea, 1 late SBO
Mohiuddin et al, 1996[7]	72	4 (0.5-28)	Diverse	NR (10-25)	24%	44%	Response rate: 91%	No grade 2 or higher acute toxicity
Mohiuddin et al, 1999[18]	87	7 (3-42)	Diverse	15 (10-20)	9%	20%	Response rate: 91%	1 grade 3 acute mucositis, 1 fatal carotid blowout
Kudrimoti et al, 2002[19]	20	NR	Melanoma	15 (12-20)	25%	25%	Response rate: 80%	No grade 3 or higher toxicities
Huhn et al, 2006[22]	27	10 (3-44)	SCC of H&N	15 (15-20)	0%	0%	(1) Neck control rate: 93%; (2) neck control rate 92%	(1) acute G 2-3 skin toxicity, 10 late G 2 soft tissue and muscle fibrosis; (2) 3 poor postoperative wound healing, 4 fibrosis limiting neck movement
Mohiuddin et al, 2009[20]	44	9 (2-44)	Soft tissue sarcoma	15 (12-20)	NR	9%	Response rate 76%	2 G 3 acute skin reactions
Penagaricano et al, 2010[21]	14	19.5 (2-38)	SCC of H&N	20	0%	0%	Local control rate: 79%	1 fatal carotid blowout, 11 acute G 2-3 skin reaction, 13 acute G 2-3 mucosal reaction, 4 late G 2-3 skin fibrosis
Neuner et al, 2012[13]	79	2 (0-51.6)	Diverse	15 (10-20)	NR	20%	Pain response rate, block: 95%, pain response rate, MLC: 74%, mass effect response rate, block: 84%, mass effect response rate, MLC: 79%	4 G 3-4 acute skin reactions with block versus 10 G 3-4 acute skin reactions with MLC
Mohiuddin et al, 2014[23]	14	14 (3-43)	Soft tissue sarcoma	18	0%	0%	Local control rate: 100%	1 G 3 acute skin, 2 delayed wound healing
Edwards et al, 2015[24]	53	mean 34 (1-239)	SCC of H&N	15	NR	0%	Local control rate: 81%	2 late toxicities requiring feeding tubes

Abbreviations: G = grade; H&N = head and neck; MLC = multileaf collimator; N&V = nausea and vomiting; NR = not reported; RT = radiation therapy; SCC = squamous cell carcinoma.

Critical Review

A Current Review of Spatial Fractionation: Back to the Future?

Cole Billena, BS, and Atif J. Khan, MD

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

Received Dec 13, 2018. Accepted for publication Jan 15, 2019.

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So what is going on to make GRID therapy work??

- GRID treatments minimize the toxicity of high dose radiations by limiting the volume of normal tissues irradiated.
- Although the entire target is not covered by the high dose, GRID treatment remain clinically effective.
- For these extremely inhomogeneous radiation fields, there exists signal-mediated effects:
  - near the tumor (bystander effects)
  - at distance sites (abscopal effects)

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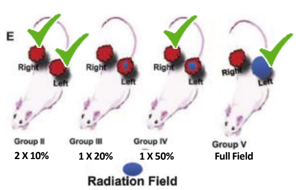
So what is going on to make GRID therapy work??

- Bystander effects :
  - Cellular and biological effects occur on un-irradiated tumor cells (located in the valleys) in response to signals from irradiated cells within the peak portion of the radiation.
    - Cells survival in the valleys are much less than what is expected by the dose delivered in these regions
    - Overexpression of DNA repair, apoptosis, cell cycle control, heat shock protein and antioxidant/pro-oxidant genes
    - TNFa, a cytokine associated with tumor killing was increased from baseline levels in 32% of GRID patients and correlated with improved clinical response
- Abscopal effects :
  - An action at a distance from the irradiated volume, but within the same organism.



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Asur, R.S., et al. Spatially fractionated radiation induces cytotoxicity and changes in gene expression in bystander and radiation adjacent murine carcinoma cells. Radiat Res 2012;177:751-765.
Sathishkumar S, et al. The impact of TNF-alpha induction on therapeutic efficacy following high dose spatially fractionated (GRID) radiation. Technol Cancer Res Treat 2002;1:141-147.
Saravana K., et al. In Vivo Effects of Lattice Radiation Therapy on Local and Distant Lung Cancer: Potential Role of Immunomodulation, Radiation Research 182(2), 149-162, (18 July 2014)

A new need … in a new time… with new technology

- Skin sparing to treat deep targets is no longer the primary motivation
- Now treating large, bulky, poorly responding targets with limited alternative treatment options
- Spatial fractionation (spatial dose inhomogeneities) is the primary goal
- High energy linear accelerators are the X-ray source

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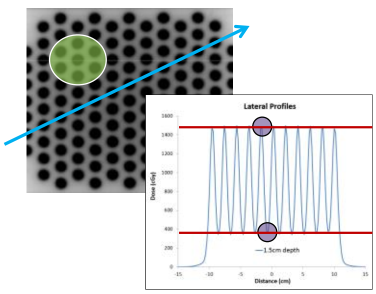
Linac Based GRID Therapy : Describing the beam

- How do we quantify the GRID Dose?
  - Hole Size and Spacing
    - Hexagonal pattern (Equidistant holes)
    - i.e. 1cm diam. holes spaced 2cm apart
  - Valley to Peak Ratio (VP)

$$VP(Depth, E, GRID) = \frac{Dose(valley)}{Dose(peak)}$$



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Linac Based GRID Therapy : Describing the beam

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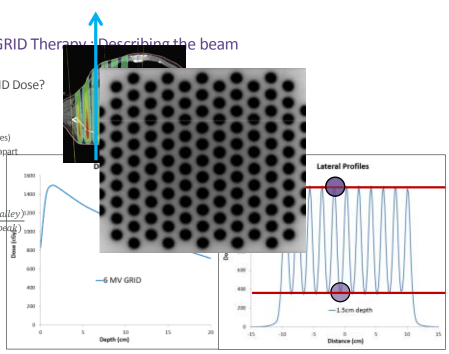
$$VP(Depth, E, GRID) = \frac{Dose(valley)}{Dose(peak)}$$

  - Dose prescribed a D(max) in the center of an open hole



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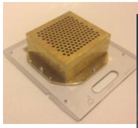
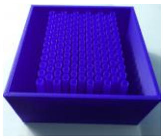
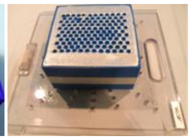
Linac Based GRID Therapy : Creating the GRID

- Physical Block
  - Cerrobend / Brass



- 3-D Printed *
  - Poured Cerrobend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* Zhu et.al. Fabricating Cerrobend grids with 3D printing for spatially modulated radiation therapy: A feasibility study. Med Phys. 42 (11) 2015

Linac Based GRID Therapy : Creating the GRID

- MLC Based GRID Patterns

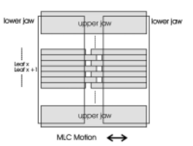
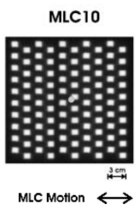


FIG. 1. Illustration of the MLC leaf positions in delivering one of the beams for a grid field.



	MLC10			MLC5		
Depth (cm)	1.5	5	10	1.5	5	10
VP ratio$_{\parallel}$ (%)	11.5	15.1	17.6	17.8	19.5	25.6
VP ratio$_{\perp}$ (%)	10.3	13.6	16.3	18.9	21.9	24.7
$W^{\parallel}_{(30\text{-}80)}$ (cm)	0.26	0.26	0.34	0.22	0.26	0.31
$W^{\perp}_{(30\text{-}80)}$ (cm)	0.21	0.22	0.25	0.18	0.20	0.26
Output factor (%)	82	65	50	65	55	37

	BLOCK10			BLOCK5		
Depth (cm)	1.5	5	10	1.5	5	10
VP ratio$_{\parallel}$ (%)	13.2	15.9	19.1	20.7	24.3	31.7
VP ratio$_{\perp}$ (%)	15.0	16.3	19.8	20.1	24.4	30.6
$W^{\parallel}_{(30\text{-}80)}$ (cm)	0.25	0.25	0.30	0.19	0.22	0.33
$W^{\perp}_{(30\text{-}80)}$ (cm)	0.24	0.24	0.28	0.23	0.19	0.28
Output factor (%)	80	68	53	57	45	32

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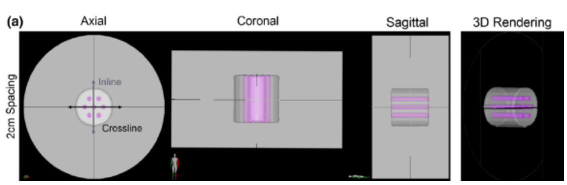
U of Maryland Ha, J., et al. Feasibility of delivering grid therapy using a multileaf collimator. Med. Phys. 33 (1), 2006

Linac Based GRID Therapy : Creating the GRID

- 3-D Conformal, VMAT or Tomotherapy methods



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Sheikh, K, et. al. Comparison of treatment planning approaches for spatially fractionated irradiation of deep tumors. J Appl Clin Med Phys 2019

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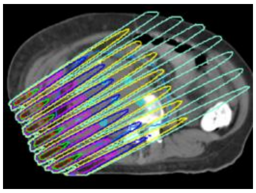
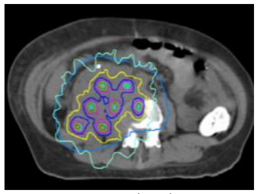


Standard GRID Block



TOMO (2.5cm)

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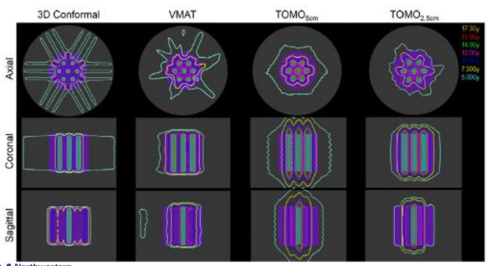
Linac Based GRID Therapy : Creating the GRID

- 3-D C
Tomo



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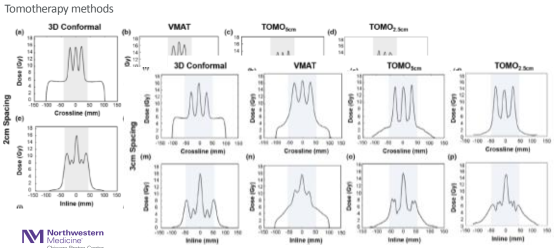

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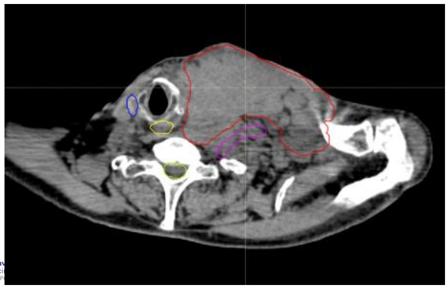
Upper Lip Carcinoma with prior XRT to 64Gy with recurrence



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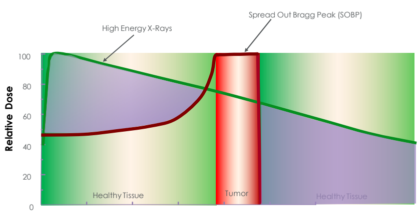
The Physics of Protons

Depth Dose Curves for Different Treatment Types



Depth in Tissue (cm)

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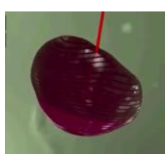
With protons, a few question arise.....

- **Can PBS spot patterns be configured to deliver GRID type dose distributions?**
  - Similar peak to peak (hole) positioning
  - Similar valley to peak (VP) ratios
  - Some different assumptions would need to be made depth dose shape



Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation

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(Received 14 September 2017; revised 10 January 2018; accepted for publication 25 January 2018;

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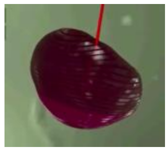
With regards to PBS protons, a few question arise.....



- Feasibility Study
  - Phantom plans of simple shapes
  - Dosimetric verifications
  - Common GRID parameters compared
- Early report on clinical implementation
  - Two of the first four cases are presented

Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation

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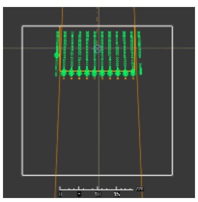
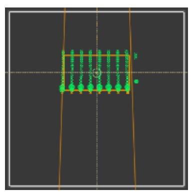
Shallow Depth and a Deep Depth Simulation

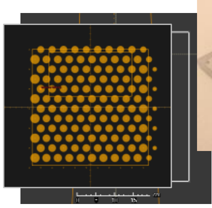


Shallow Target : 20cm X 20cm X 12cm
Central depth 6cm
Proximal depth at surface



Deep Target : 15cm X 15cm X 8cm
Central depth 14cm
Proximal depth = 10cm

Shallow Depth and a Deep Depth Simulation



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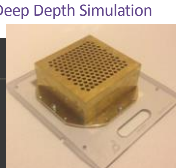
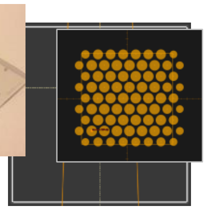
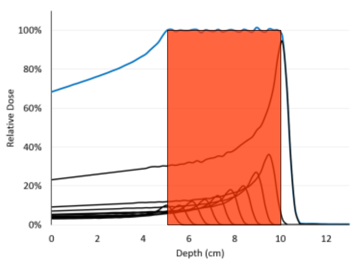


Spot Spacing
Match GRID Block
2cm spacing

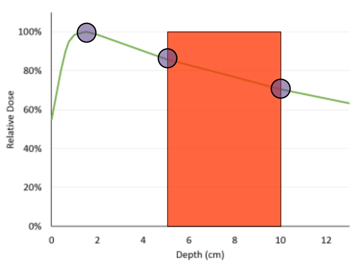


Deep Target : 15cm X 15cm X 8cm
Central depth 14cm
Proximal depth = 10cm

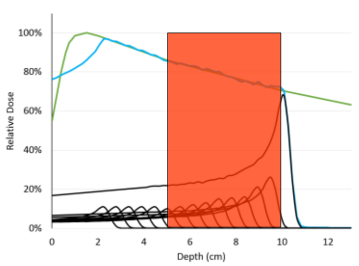
PBS Protons : Energy Stacking to create the SOBP



Dose gradient with depth on traditional GRID



PBS energy stacking can be optimized to match photon PDD's



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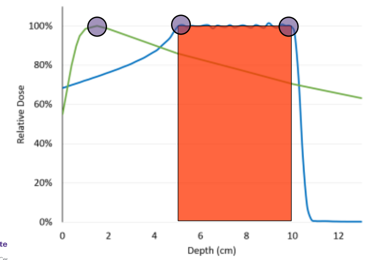


PDD optimizations for the Shallow and Deep targets

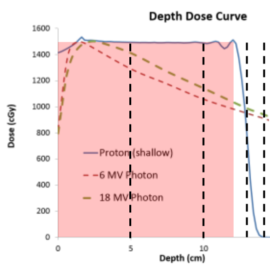


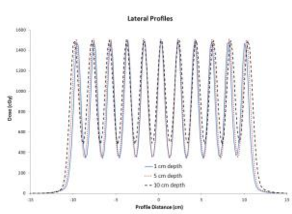
TABLE I. Comparison of the calculated percentage depth dose normalized to the prescribed dose for the proton PBS and photon GRID plans[10] for the shallow phantom target.

Depth	Description	Percentage depth dose Photon 6 MV	Photon 18 MV	Proton PBS
5.0 cm	Inside target	86%	94%	100%
10.0 cm	Inside target	70%	76%	98%
12.9 cm	0.9 cm beyond target	63%	66%	50%
14.0 cm	2 cm beyond target	61%	63%	0.5%

Gao, M., et. al. Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation. Med. Phys. (45), 4, 2018.

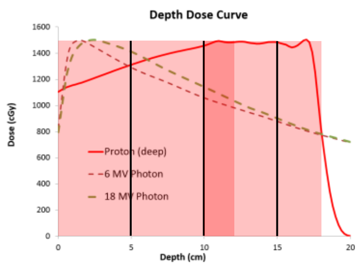
Valley to Peak Ratios : Comparison to photon block GRID

- PBS plan were created using RayStation treatment planning system (RaySearch Labs, Sweden) and IBA Universal Nozzle proton machine (IBA, Belgium).
- Valley / Peak Ratios (VP) are a function of :
  - Depth
  - Spot/Hole spacing
  - Local scatter conditions
- Gold standard : 6MV and 18MV commercially available Photon GRID blocks. (1cm holes spaced at 2cm)
- Our evaluation of the VP ratios of the different modalities demonstrates that the proton GRID distributions are clinically equivalent to photon GRID.



Gao, M., et. al. Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation. Med. Phys. (45), 4, 2018.

Profile optimizations for the Shallow and Deep targets



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Valley to Peak Comparisons

TABLE II. Comparison of the calculated valley-to-peak ratios for the proton PBS and photon GRID plans at 5 cm and 10 cm depths for the shallow phantom target and at 10 cm and 15 cm depths for the deep phantom target. Values for the photon GRID plan were taken from published data.[10,12]

		Valley-to-peak ratio		
Depth	Description	Photon 6 MV	Photon 18 MV	Proton PBS
5.0 cm	Shallow target	0.23	0.34	0.23
10.0 cm	Shallow target	0.27	0.38	0.34
10.0 cm	Deep target	0.29	0.37	0.21
15.0 cm	Deep target	0.36	0.40	0.30

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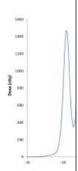
Verification of Valley to Peak Ratios : Measured vs. Calculated

- Beamlet distributions were calculated using Raystation using MC algorithm with 1mm calc point spacing.
- Profiles measured with IBA Dosimetry Lynx and MatrixPT
- Lynx (Scint plate coupled to CCD) was used for relative, high spatial resolution (0.5mm)
- MartixPT used as absolute dosimeter. Ion chamber array chamber size 4.5mm spaced 7.6mm apart
- Lynx data was down sampled into spatial resolution of the Matrix PT chamber volumes an absolute dose correction to the Lynx data was obtained using a least squares method.



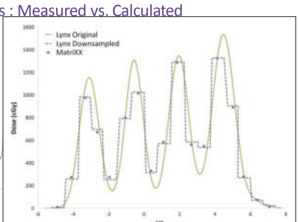


FIG. 5. Comparison of the dose profiles measured with MatriXX and Lynx detectors. Both the full-resolution Lynx measurement and the Lynx measurement downsampled to the MatriXX resolution are shown. The Lynx readings were converted to absolute doses using a dose conversion factor obtained by fitting the downsampled Lynx data with MatriXX data using the least squares method.

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Verification of Valley to Peak Ratios : Measured vs. Calculated

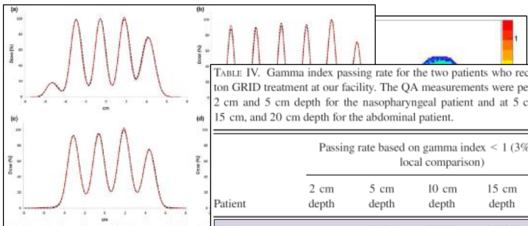

Fig. 6. Comparison of dose profiles measured by the Lynx detector (dashed lines) and ... 5 cm depth, (b) superior–inferior direction at 10 cm depth, (c) left-right direction at 15 ...

Table IV. Gamma index passing rate for the two patients who received proton GRID treatment at our facility. The QA measurements were performed at 2 cm and 5 cm depth for the nasopharyngeal patient and at 5 cm, 10 cm, 15 cm, and 20 cm depth for the abdominal patient.

	Passing rate based on gamma index < 1 (3%/3 mm, local comparison)				
Patient	2 cm depth	5 cm depth	10 cm depth	15 cm depth	20 cm depth
Abdomen		98.6%	97.7%	95.6%	96.6%
Nasopharynx	98.7%	99.1%			

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Real patient Proton GRID Planning Strategies

- Start with spots centered 2 cm apart and verify VP ratios in the target are ~0.25 – 0.30 . If needed, open spot spacing. Attempt to place spots only inside the target.
- Because of the high single fraction doses (15-20 $Gy_{(RBE)}$), maximum MU/spot constraints may be exceeded. A simple fix on our IBA system was to force layer repainting.
- Keep spots away from very critical OAR's. Consider dosimetiric consequences of :

  Set-up errors
  Proton Range errors
  Potential proton RBE variations
  Intra-fraction motion

  → Thorough assessment of OAR doses via of robustness evaluation
- Remember, it is **not necessary** to cover the entire target! Plan conservatively.
- Do not use extremely low energy proton layers to provide some skin sparing (max ~95% at surface)

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GRID Therapy at our center

- 14 patients treated thus far using the methods described here
- Doses ranged for 15-20$Gy_{(RBE)}$, most patients receive and additional short course of Std Fx RT.
- Retrospective analysis of first 10 patents has been submitted for publication and was presented at the "Workshop on Understanding High-Dose, Ultra-dose rate, and Spatial Fractionated Radiotherapy" held on August 21, 2018 in Bethesda, MD.
  - Response rates very consistent with previously published works with a 90% local response rate and a similar side-effect profile.
- We are considering a Phase I study to determine optimal Proton GRID Doses / VP Ratios

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Case Studies

Case 1

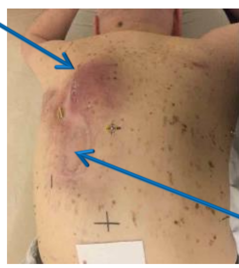
68 yo male, recurrent sarcoma of the back

50Gy XRT 2 years prior followed by a re-resection

1 year after RT had another resection

- Aortic value replacement
- Hypertension
- Bowel perforation

Referred for Proton GRID of 18Gy(RBE)
+ 15 x 2.5Gy(RBE) = 37.50Total

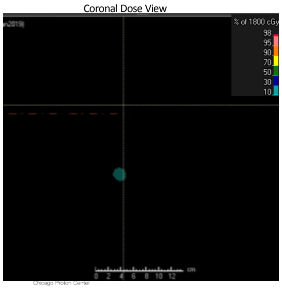


Case 1

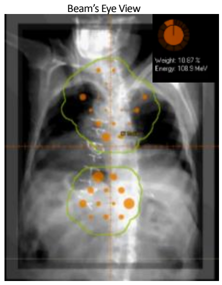
Case 1

Case 1

Coronal Dose View



Beam's Eye View



Case 2

85 yo male, 3 years ago diag with head/neck undifferentiated carcinoma Rt Lip possible salivary primary

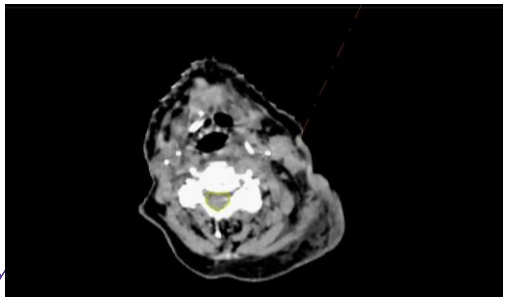
Resection. 24 of 38 +LN Rt side, and 2 of 16 + Lt side Chemo + 64Gy to upper lip and Bilateral neck, Lt side treated to 45-50Gy

2 years later recurrence in Lt Neck, metastatic to the skin. De-bulking surgery and Chemo.

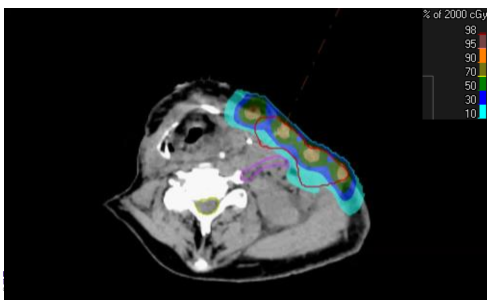
Trouble swallowing and speaking, PET showed involvement encasing the carotid and brachial plexus

Referred for 20Gy(RBE) GRID + XRT Boost of ~30Gy

Case 2



Case 2



Case 2 : Complete Local Response

Before Proton GRID

After Proton GRID

In conclusion…..

- Modern GRID Therapy can be a clinically effective treatment for some advanced, bulky tumors
- Pencil Beam Scanned Proton Beamlets can be used to generate the inhomogeneous GRID doses with similar properties to historical photon GRID blocks.
- The use of a PBS Proton GRID can be provide a safe and effective treatment option in cases where photon GRID treatments may be difficult.

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