



The Management of Locally Recurrent Nasopharyngeal Carcinoma

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Local Recurrence of NPC after Definitive Treatment



- **Local recurrence remains one of the most important modality of treatment failure after definitive RT for NPC**
 - 15~30% of NPC patients would develop LR after conventional (2D) RT
 - 5-year LC improved to > 90% after IMRT
- **Local recurrence alone can be treated with curative intent, but re-RT is challenging**
 - Post nasal space is adjacent to important OARs
 - High-dose RT to these OARs



Treatment for Locally Recurrent NPC

■ Different Treatment Modalities for LR-NPC

- Surgery – Nasopharyngectomy
- Conventional Radiation
- Brachytherapy/Stereotactic Radiosurgery
- Intensity-Modulated Radiation Therapy (IMRT)
- Particle therapy – Proton and Carbon Ion Radiation

■ Chemotherapy

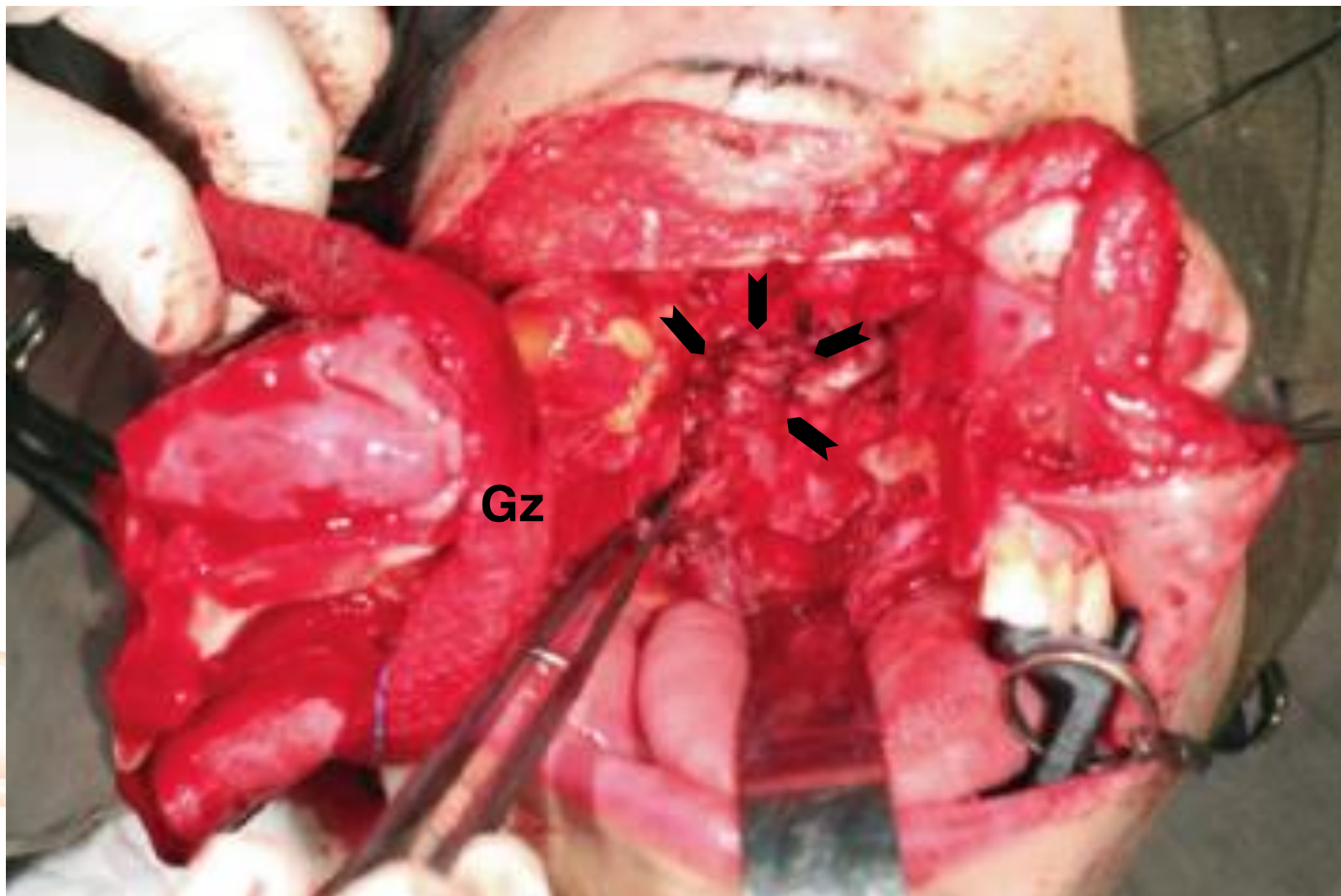
- Not for definitive purposes
- Effective adjuvant modality

Surgery for Locally Recurrent Nasopharyngeal Cancer



- **Nasopharyngectomy for locally recurrent NPC**
 - 5-year DFS can be as high as 55% in experienced hands
 - For highly selected patients with small disease
 - Experience in the procedure is critical

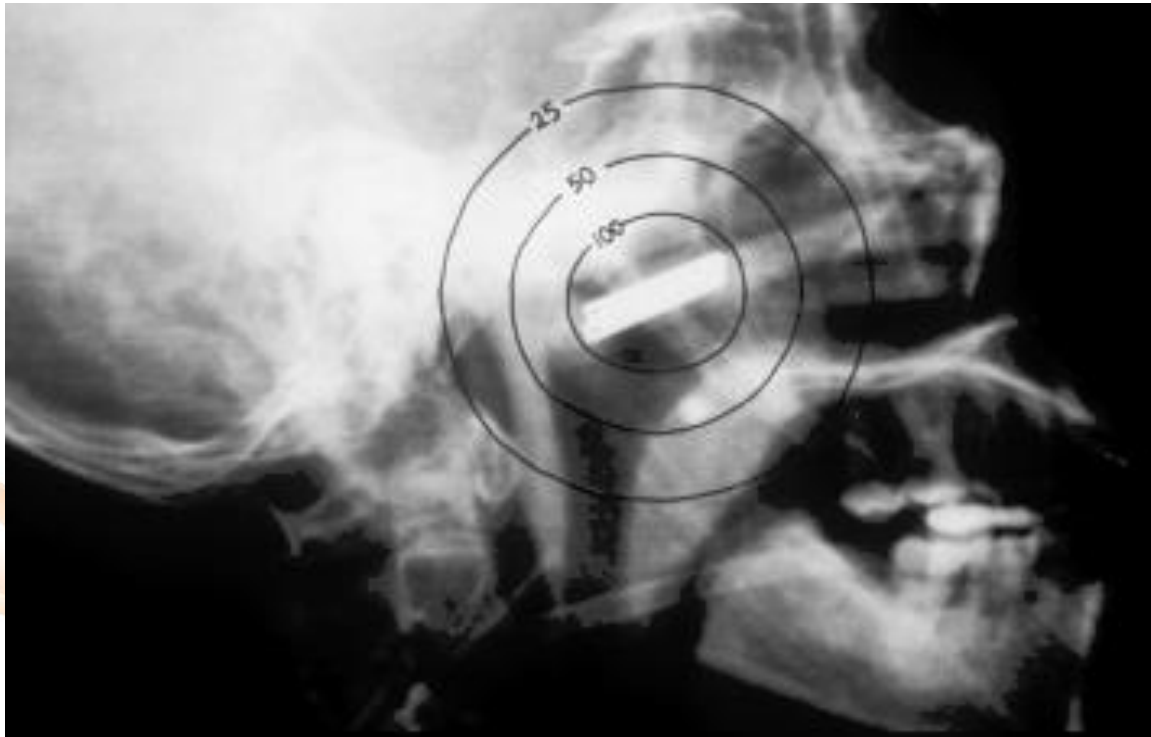
Surgery for Locally Recurrent Nasopharyngeal Cancer



Brachytherapy for Locally Recurrent Nasopharyngeal Cancer



- **Intra-Cavitary High Dose Rate Brachytherapy**
 - Range of effectiveness $< 1\text{cm}$ – small disease
 - Used with external beam radiation therapy
 - Brachytherapy facility needed





Treatment for Locally Recurrent NPC

■ Different Treatment Modalities for LR-NPC

- Surgery – Nasopharyngectomy
- **Conventional Radiation**
- Stereotactic Radiosurgery
- Intensity-Modulated Radiation Therapy (IMRT)
- Particle therapy – Proton and Carbon Ion Radiation

■ Chemotherapy

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Conventional RT for Locally Recurrent NPC



- **Re-irradiation with conventional RT**
 - Requires a total dose of 60 Gy or above
 - Produces poor results
 - 3-year LFFS for rT1~rT3 is less than 20%
- **High probability of developing SAE**
 - 5-year SAE rate is ~70%
 - 5-year brain/CN SAE rate is ~50%
 - Data presented were RT alone without chemotherapy



Treatment for Locally Recurrent NPC

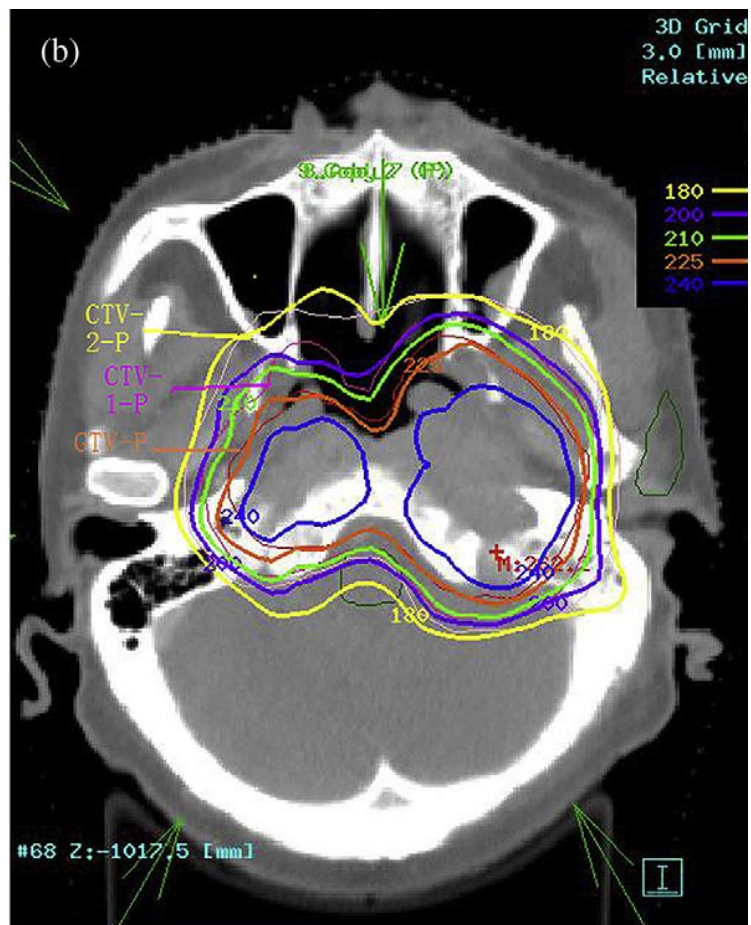
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■ Chemotherapy

- Not for definitive purposes
- Effective adjuvant modality

IMRT for Locally Recurrent NPC



IMRT for Locally Recurrent NPC

Publication	Pt. No./Dose	F/U (mos)	rT1/2 : T3/4	LC/OS (%)	G3 LT Toxicities
Qiu (2012)	70(70Gy)	25	43%:57%	66%/67% (2-yr LC/OS)	36% ³
Han (2012)	239(~67Gy)	29	24%:76%	45% (5-yr OS)	69% ⁴
Hua (2012)	151(~67Gy)	40	19%:71%	63~71%/30~36% (5-yr OS)	34%
Roeder (2011)	14(50.4Gy) ¹	20	24%:76%	76%/44% (2-yr LC/OS)	29%
Chua (2005)	31 ²	11	26%:74%	65%/63% (1-yr LC/OS)	19%

¹ 14 & 3 pts received IMRT and SRS

² Patients received IMRT \pm SRS per protocol

³ Moderate to severe adverse events

⁴ Including 34.7% Grade 5

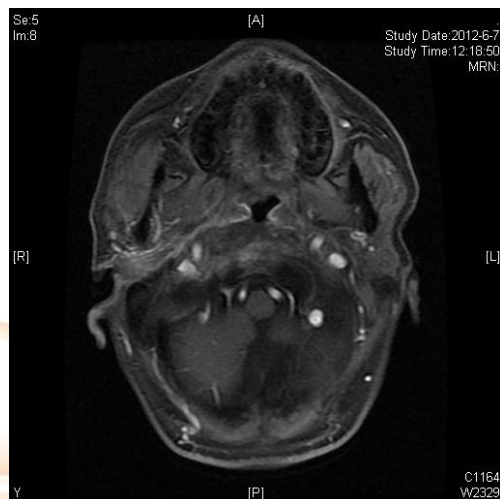
IMRT for Locally Recurrent NPC

- **IMRT for local regions with all stages**
 - $rT1/2 + rT3/4$
 - More suitable EBRT modality for extended lesions
- **Tolerated IMRT well but with short follow-up**
 - Median follow-up < 48 months
 - Potential late adverse effects with extended follow up
- **Various prognostic factors reported**
 - Original stage, rT-classification, time to recurrence, etc
 - Possibly due to small sample size, diff. in RT modality, and short follow-up time

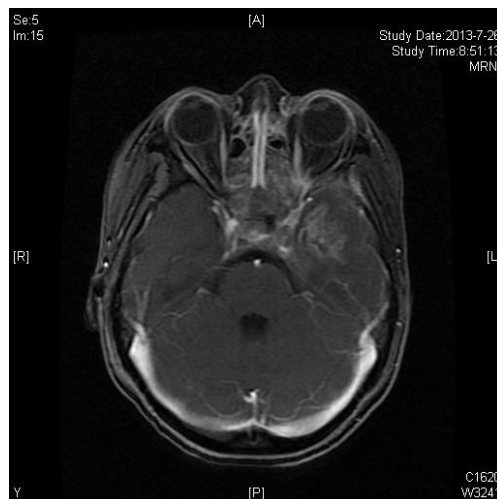
Cause of Death after Re-IMRT

Status at last follow-up		No. patients (percentage)	
Death 120 patients	Cause of death	Local recurrence	13 (10.8%)
		Regional recurrence	0 (0%)
		Distant metastasis	22 (18.3%)
		Radiation injuries	83 (69.2%)
		Others	2 (1.7%)

Radiation injuries include severe temporal lobe necrosis, injuries of lower cranial nerves and massive haemorrhage of nasopharyngeal mucosa due to necrosis and subsequent infection.



Mucosal necrosis



Temp lobe necrosis



CN neuropathy

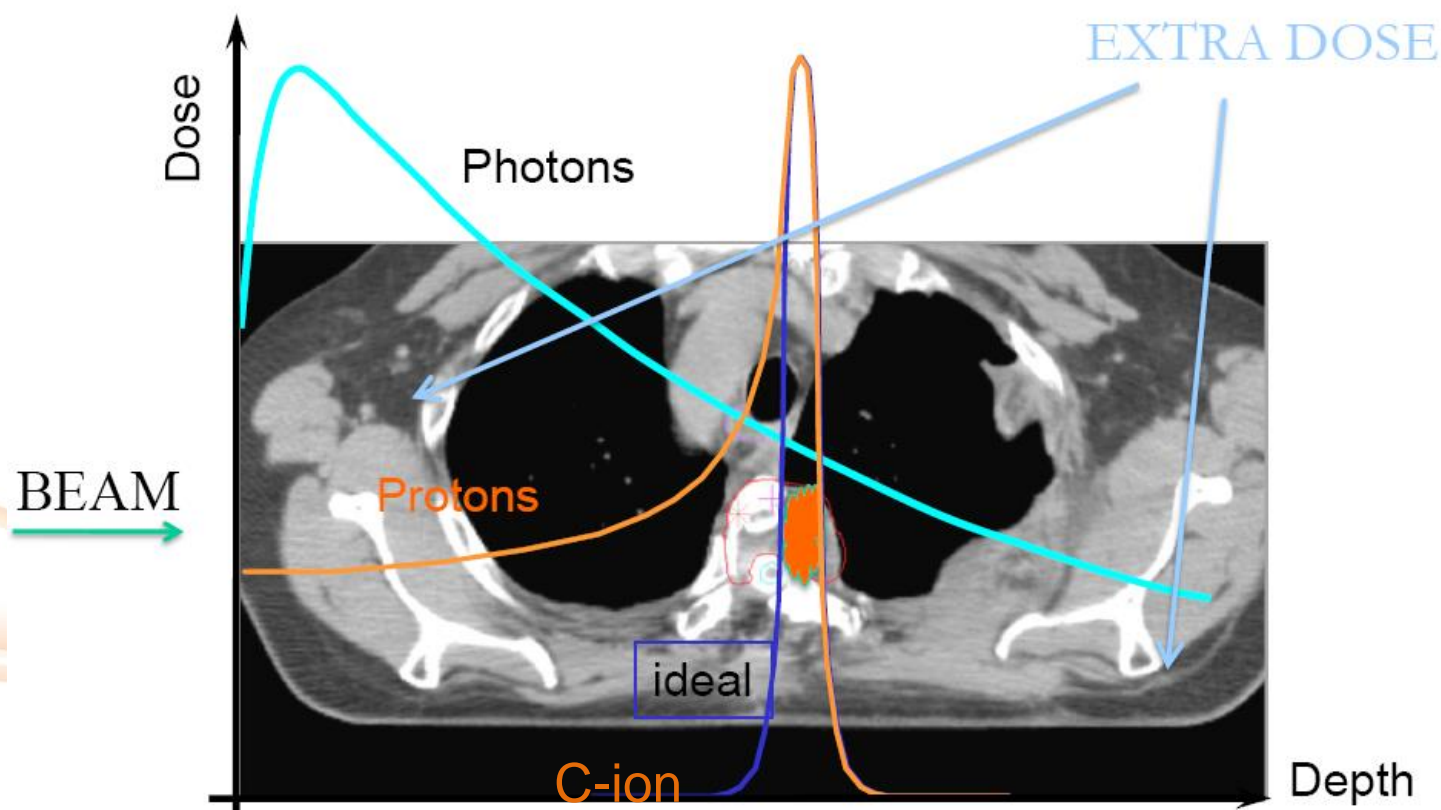
How to Solve the Issues?

- **Purpose of the treatment for locally recurrent NPC: Minimize side effects, maximize tumor control**
 - All definitive treatment are local treatment modality
 - Chemotherapy used are for radio-sensitization
- **Re-irradiation for locally recurrent NPC**
 - Use proper dose and RT technique - Reduce RT induced SAE
 - More technically and biologically effective technology – for radio-resistant cancer cells



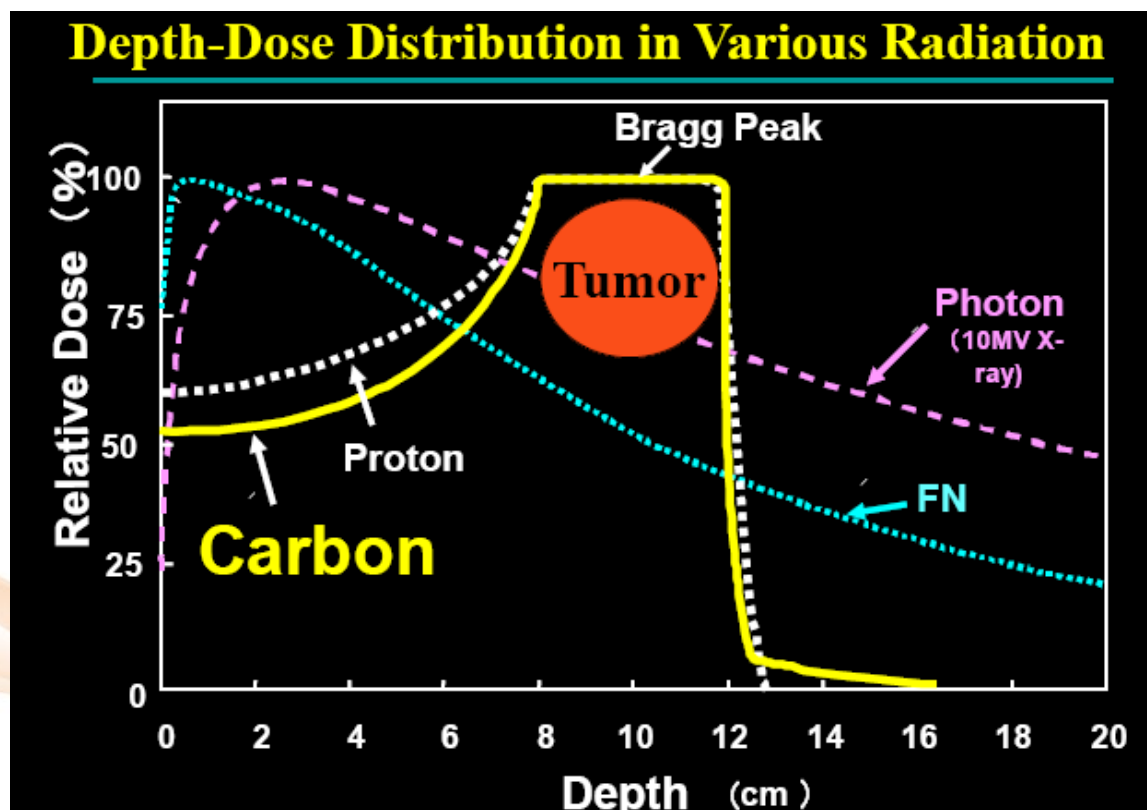
Radiation Therapy: What is Ideal?

- Curative dose delivered w/out causing substantial AE
- Esp. important for head and neck cancer
- Conventional photon vs. particle therapy

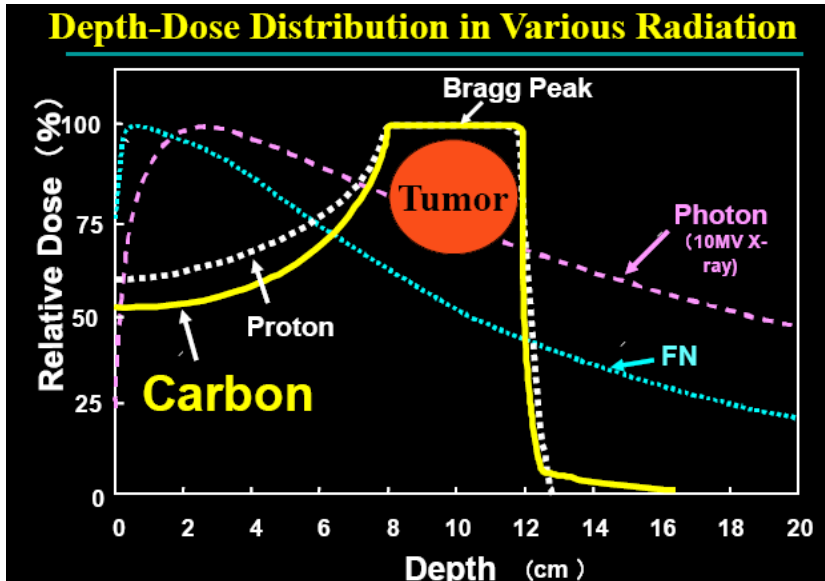


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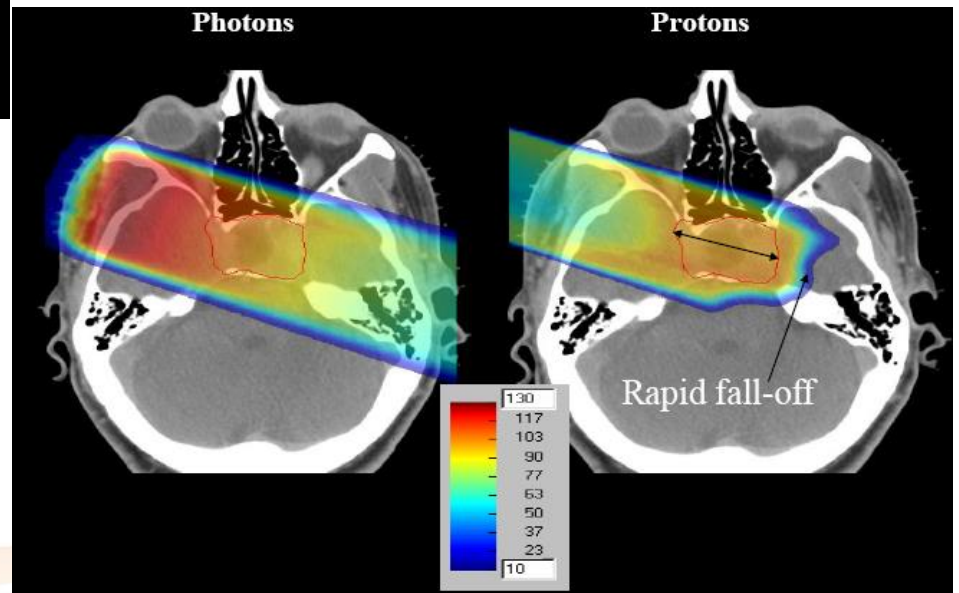


Proton and Carbon Ion RT



Dose distributions of proton or carbon ion RT (CIRT) are significantly superior than X-ray RT

CIRT also has improved biological effectiveness as compared to proton or X-ray RT



Dosimetry Advantages of IMPT



Journal of X-Ray Science and Technology 18 (2010) 443–450
DOI 10.3233/XST-2010-0265
IOS Press

443

A treatment planning comparison between proton beam therapy and intensity-modulated x-ray therapy for recurrent nasopharyngeal carcinoma

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Dosimetry Advantages of IMPT

- 2004~2007: 7 例复发性鼻咽癌
- Proton Beam Therapy (PBT)

Characteristics of the seven patients and their tumors

Case	Sex	Age(y)	Pathology	Location	rT classification
1	Male	60	NKSCC	Left wall of the nasopharynx	rT1
2	Male	37	NKSCC	Right wall of the nasopharynx	rT1
3	Male	68	KSCC	Left wall of the nasopharynx	rT1
4	Male	55	BSCC	Right oropharynx	rT2
5	Male	53	NKSCC	Base of skull(abutting the brainstem)	rT3
6	Male	42	NKSCC	Left wall of the nasopharynx	rT1
7	Male	54	NKSCC	Oropharynx	rT2

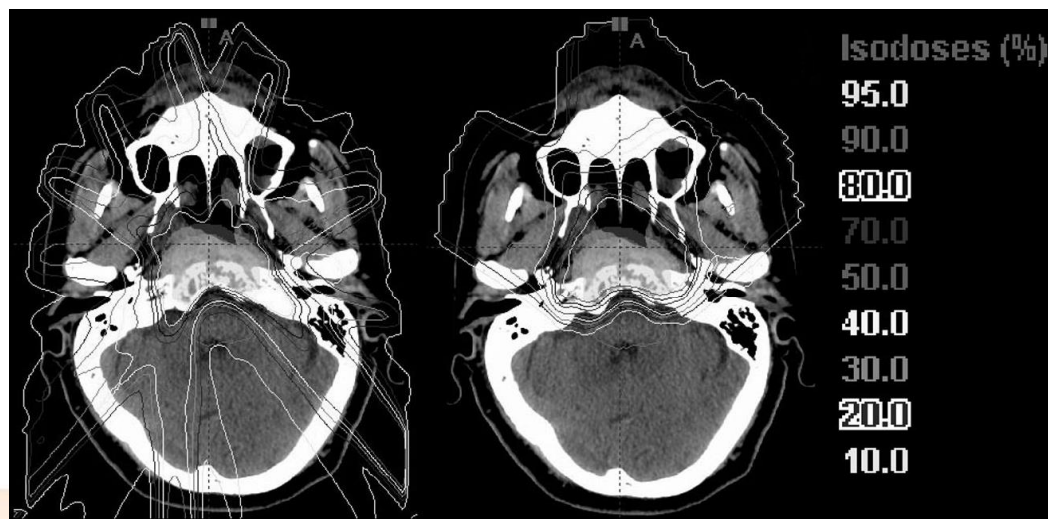
Abbreviations: BSCC, basaloid squamous cell carcinoma; KSCC, keratinizing squamous cell carcinoma; NKSCC, non-keratinizing squamous cell carcinoma.

Dosimetry Advantages of IMPT



Proton Beam Therapy (PBT) vs. Intensity Modulated Xray Therapy (IMXT)

- Eclipse proton treatment planning system
- Eclipse inverse treatment planning system for IMXT
- Dose (2CGE/F): GTV 66CGE; PTV 62.7CGE;



Dosimetry Advantages of IMPT

- Gross Tumor Vol. dose comparison (PBT vs. IMXT)
 - GTV 66CGE ; PTV 62.7CGE

Comparison of dose to GTV between PBT and IMXT

	Median maximal dose (\pm SE)	Minimum dose (\pm SE)	Mean dose (\pm SE)
PBT (CGE)	71.27 \pm 5.58	63.21 \pm 5.62	66.32 \pm 1.21
IMXT(Gy)	71.11 \pm 2.75	63.53 \pm 1.67	67.17 \pm 1.12
<i>t</i> value	0.610	0.710	0.415
<i>p</i> value	0.54	0.94	0.71

Dosimetry Advantages of IMPT

- Planning Target Vol. dose comparison (PBT vs. IMXT)
 - GTV 66CGE ; PTV 62.7CGE

Comparison of dose to PTV between PBT and IMXT

	Median maximal dose (\pm SE)	Minimum dose (\pm SE)	Mean dose (\pm SE)
PBT(CGE)	72.57 \pm 3.12	61.37 \pm 1.41	64.90 \pm 1.23
IMXT(Gy)	71.31 \pm 3.58	63.28 \pm 4.49	65.37 \pm 1.28
<i>t</i> value	2.36	0.585	1.121
<i>P</i> value	0.06	0.58	0.31

Dosimetry Advantages of IMPT



- 正常组织剂量比较 (PBT vs. IMXT)
 - GTV 66CGE ; PTV 62.7CGE

Comparison of dose to OARs between PBT and IMXT

		PBT (CGE)	IMXT (Gy)	<i>t</i> value	<i>p</i> value
Spinal cord	Median Maximal	8.38 ± 2.49	22.91 ± 2.75	4.469	< 0.004
	D5	2.18 ± 1.17	13.62 ± 2.17	5.828	< 0.001
	D 10	1.22 ± 0.86	12.28 ± 2.16	5.273	< 0.002
Brainstem	Median Maximal	27.89 ± 3.18	42.45 ± 4.45	3.666	< 0.01
	D5	12.83 ± 1.72	19.47 ± 1.01	3.885	< 0.001
	D10	9.00 ± 1.24	15.18 ± 0.51	5.160	< 0.002
Optic nerve and chiasm	Median Maximal	0.48 ± 0.27	2.28 ± 0.75	11.511	< 0.001
	D5	0.26 ± 0.16	2.05 ± 1.47	23.8	< 0.001
	D 10	0.21 ± 0.13	1.97 ± 0.14	30.52	< 0.001
Temporal lobes	Mean dose	2.77 ± 0.78	10.63 ± 1.45	4.67	< 0.003
Parotid glands	Mean dose	1.23 ± 0.36	3.63 ± 0.88	3.72	< 0.01

复发性鼻咽癌：质子治疗的临床结果

- **Loma Linda**质子治疗复发性鼻咽癌的回顾性研究(1999)
 - 收治了16例局部复发鼻咽癌患者
 - T1/T2 —4例；T4—12例
 - 曾接受50~88.2Gy的光子治疗
 - 再程质子放疗（非IMPT）：60~70GyE
 - 没有现代影像学的支持
- **研究结果**
 - OARs的剂量：0~22GyE
 - 2年OS为50%
 - 黏膜或颞骨坏死各一例—Salvaged



Results from Re-RT with Neon or Helium

- Neon/Helium ion re-irradiation for locally recurrent nasopharyngeal cancer
 - UCSF and Lawrence Berkley Lab 1992
 - **Not supported with MRI and PET CT scans**

RECURRENT LOCALLY ADVANCED NASOPHARYNGEAL CARCINOMA TREATED WITH HEAVY CHARGED PARTICLE IRRADIATION

PATRICK E. FEEHAN, D.O., JOSEPH R. CASTRO, M.D., THEODORE L. PHILLIPS, M.D.,
PAULA PETTI, Ph.D., J. MICHAEL COLLIER, Ph.D.,
INDER DAFTARI, Ph.D. AND KAREN FU, M.D.

University of California San Francisco, University of California Lawrence Berkeley Laboratory

Results from Re-RT with Neon or Helium

- 11 patients with locally recurrent NPC
 - Most patients had rT3 or rT4 disease
 - Included patients with M1 disease
 - Re-irradiation dose: 32~62GyE

Table 1. Characteristics of patients with locally extensive recurrent nasopharyngeal carcinoma re-irradiated with helium and neon ions

Patient	Age	Sex	Tumor extent	TTR from previous XRT [mo]	Chemotherapy
1	59	M	Parapharyngeal Space, BOS	108	MTX several years prior
2	37	M	Clivus, Sphenoid Sinus	36	DDP, Bleo. prior & concurrent
3	39	M	MCF, Petrous Bone	35	DDP, 5-FU prior & post
4	66	F	Maxillary Sinus, Sphenoid Sinus	11	DDP, 5-FU prior
5	48	M	Sphenoid Sinus, Ethmoid Sinus, Pterygoid Fossa	8	MTX prior
6	46	M	BOS, Ethmoid Sinus	36	DDP, MTX, 5-FU prior
7	67	M	Cavernous Sinus, Temporal Lobe	13	Bleo. concurrent, MTX post
8	48	M	BOS, Sphenoid Sinus	0	5-FU, DDP, IL-2 prior
9	42	M	MCF, Frontal Sinus, Oropharynx	20	5-FU, DDP, IL-2 prior
10	41	M	Orbit, Ethmoid Sinus, Frontal Sinus, Maxillary Sinus	22	5-FU, DDP prior
11	63	F	Temporal Bone Erosion, External Auditory Canal	20	

MCF = middle cranial fossa, BOS = base of skull, MTX = Methotrexate, Bleo. = Bleomycin, 5-FU = Fluorouracil, DDP = cis-Platinum, IL-2 = interleukin-2, TTR = time to relapse.



Results from Re-RT with Neon or Helium

■ Results

- Median survival time = 40 months
3-year OS = 59%
- 6 patients deceased with local recurrence; 3 with distant metastasis
- With a median F/U of 50 months, 5/11 patients remained NED
- Side effects: xerostomia -2 ; visual impairment, trismus and pituitary dysfunction – 1 each

Results from Re-RT with Neon or Helium

Table 2. Previous radiation dose, beam characteristics and survival for patients re-irradiated for locally recurrent nasopharyngeal carcinoma with helium and neon ions

Patient	Initial XRT dose [cGy]	Helium dose [cGyE]	Neon cGyE	Total dose cGyE	Survival months—alive
1	6100	5600		5600	110—NED
2	7000	600	3600	4200	42.4—NO
3	7020	4400		4400	62.0—NED
4	6860	4400		4400	56.5—NO
5	6940	3200	2800	6000	11.4—NO
6	8100	1950	3400	5350	48.7—NED
7	6720	5400		5400	28.0—NO
8	7000	1000	100	3180*	9.1—NO
9	7020		2700	5523*	13.6—NO
10	7200	5000		5000	25.0—NED
11	7000	1730		6230*	9.0—NED

NED = no evidence of disease, cGy = centigray, cGyE = centigray equivalent, XRT = radiation, * = includes photon dose.



The Treatment of Locally Recurrent NPC using Carbon Ion Radiotherapy

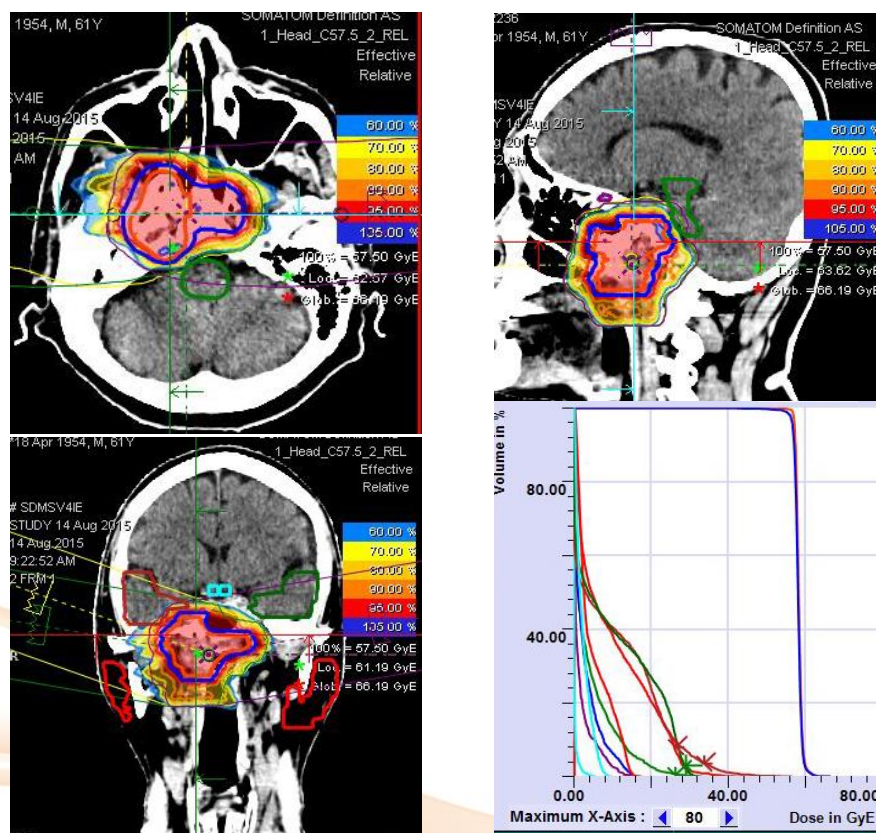


IMCT for Locally Recurrent NPC

- **20 cases have been treated with intensity modulated carbon radiation therapy (IMCT) since 5/2015**
 - Most are locally advanced disease
 - Most are resistant to chemotherapy
- **All received IMCT to 50~57.5GyE (daily dose of 2.0/2.5GyE)**
- **Early results**
 - All completed planned treatment
 - No Grade 2 or higher AE
 - All patients achieved SD, PR, or CR at 1~6 mo

A Typical Case of CIRT for LRNPC

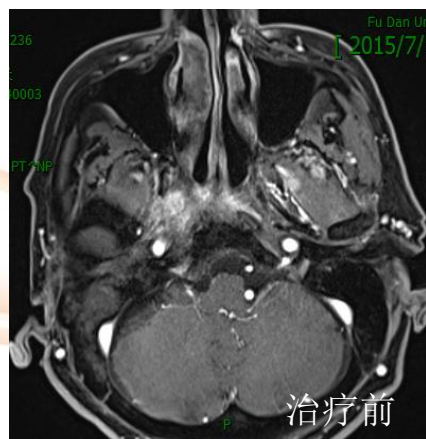
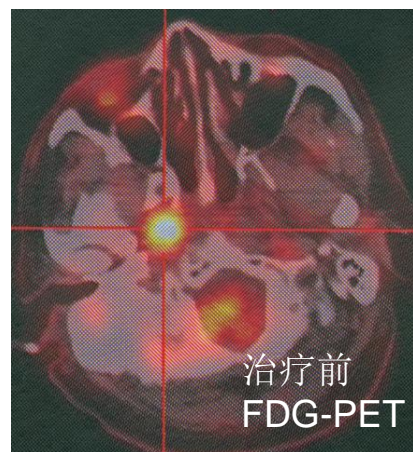
3-Field IMCT to 57.5GyE in 23F



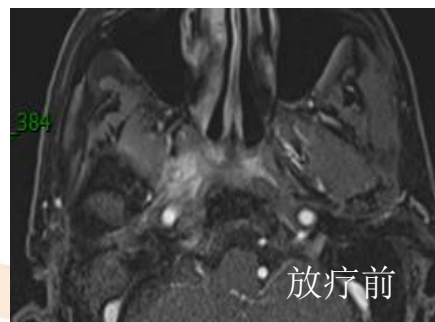
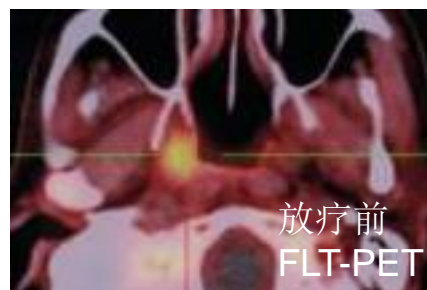
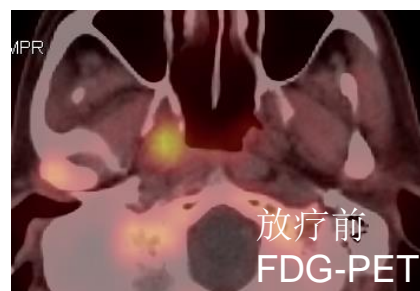
	Max dose (GyE)	Mean dose (GyE)
brain stem	32.17	3.77
spinal cord	5.61	0.16
Rt temporal	56.2	9.82
Lt temporal	32.79	9.8
Rt eye	0.01	0
Lt eye	0.09	0
Rt len	0	0
Lt len	0	0
Rt optical N.	16	1.49
Lt optical N.	15.92	2.55
Rt parotid	43.55	9.4
Lt parotid	17.36	4.68
Rt inner ear	49.6	32.38
Lt inner ear	24.96	18.51

A Typical Case of CIRT for LRNPC

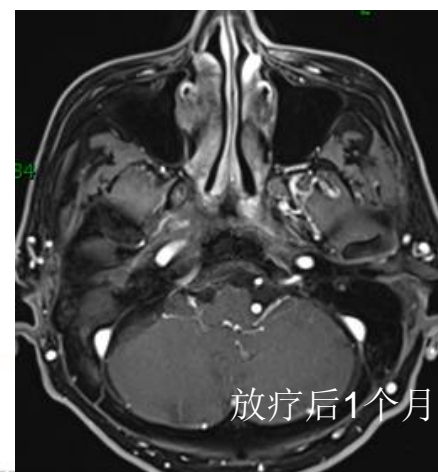
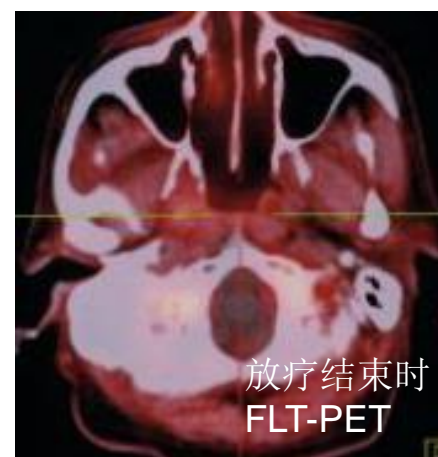
Before Induction
Chemotherapy



Before IMCT



After IMCT &
1 month after IMCT



Phase I/II Trial to Evaluate CIRT for LRNPC Re-Treatment



ClinicalTrials.gov

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Trial record **1 of 1** for: recurrent nasopharyngeal carcinoma carbon

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Trail Evaluating Carbon Ion Radiotherapy for Locally Recurrent Nasopharyngeal Carcinoma

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified October 2015 by Shanghai Proton and Heavy Ion Center

Sponsor:

Shanghai Proton and Heavy Ion Center

Information provided by (Responsible Party):

Jiade J. Lu, Shanghai Proton and Heavy Ion Center

ClinicalTrials.gov Identifier:

NCT02569788

First received: October 1, 2015

Last updated: October 6, 2015

Last verified: October 2015

[History of Changes](#)

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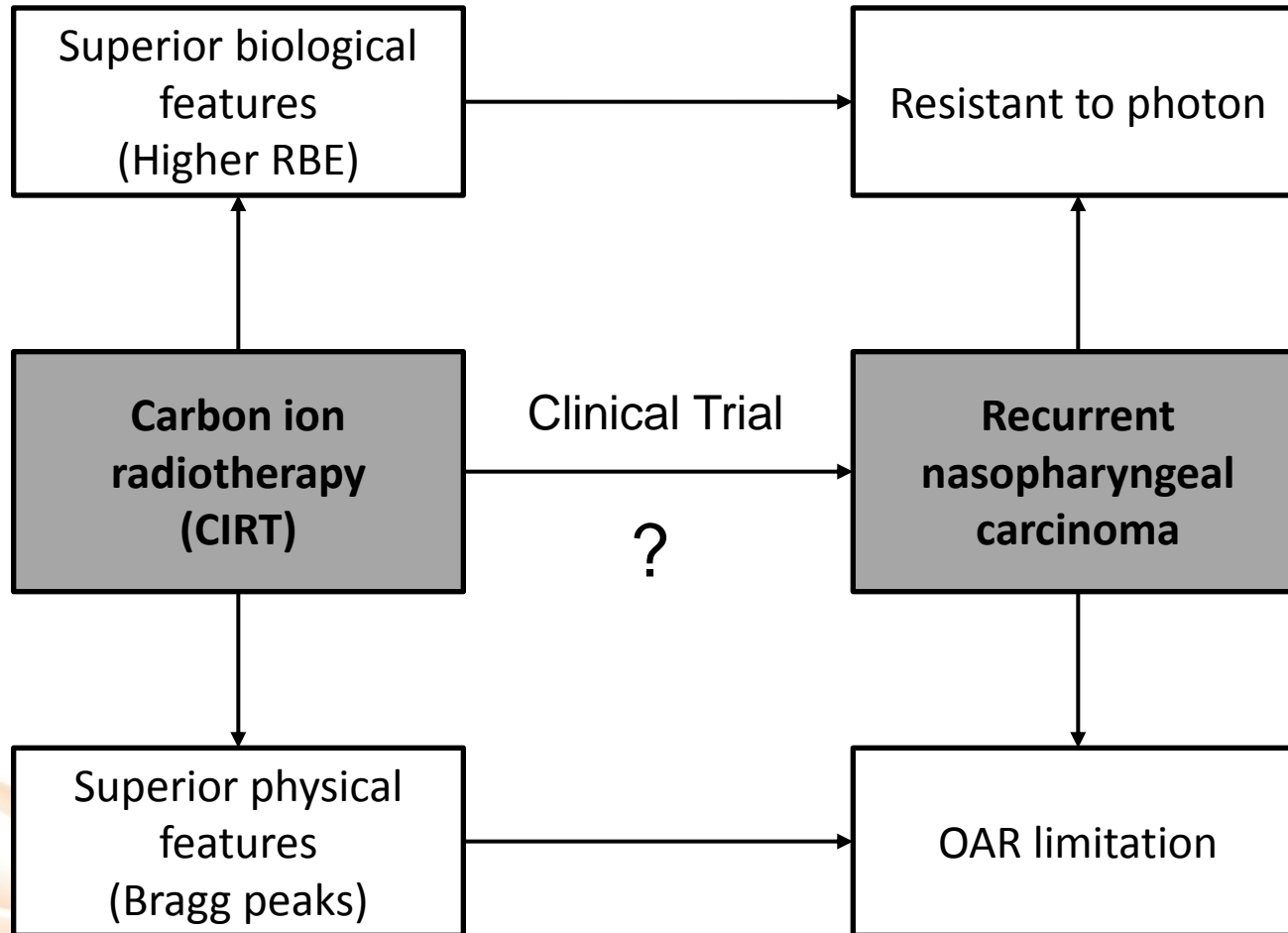
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Background



Trial Design & Schedule



9/2017

**Primary Endpoint:
Grade 4 AE at 6 mo**

Phase II trial Initiated

**Primary Endpoint:
2-year OS**

Phase I, dose escalation study, 2 years

Phase II, efficacy study, 2 years

9/2015

9/2019

Phase I study

- Define the Maximal Tolerated Dose (MTD) for Phase II study (Grade 4 or above AE).
- 5 dose regimens (55GyE/22Fx-65GyE/26Fx, start at 57.5GyE/23Fx).
- Time-to-Event Continuous Reassessment Method (TITE-CRM).
- A maximum of 25 patients for 5 dose levels.

Phase II study

- The MTD defined by Phase I study or 65GyE/26Fx (if MTD not defined) will be used.
- The primary endpoint is the OS after re-irradiation at 24 months.
- An exact single-stage phase II study design is used.
- A total of 40 patients will be recruited.

Dose Escalation Schedule



Dose Level	Dose and Fractionation	Total Dose	pDLT*	BED2 (GyE)	BED9 (GyE)
1	22 x 2.5 GyE	55 GyE	<5%	123.8	70.3
2	23 x 2.5 GyE (Starting Dose)	57.5 GyE	10%	129.4	73.5
3	24 x 2.5 GyE	60 GyE	20%	135.0	76.7
4	25 x 2.5 GyE	62.5 GyE	30%	140.6	79.9
5	26 x 2.5 GyE	65 GyE	40%	146.3	83.1

* pDLT, probability of dose limiting toxicity

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Thanks for
your attention

