Modelling Radiation Dose-Volume Tolerance based on data from Hypofractionated Head and Neck Retreatments

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CLINICAL SIGNIFICANCE

- The vast majority of stereotactic body radiation therapy (SBRT) treatments for head and neck lesions are currently re-treatments
- The new Tx would require a BED at least as high as the initial course (unless the intention is purely palliative).
- However, since the surrounding anatomical critical structures most likely have not fully recovered from the original radiation therapy treatment, they must be spared to even tighter tolerance doses than initially.

Treatment strategies using SBRT

SBRT boost is a potential strategy to achieve a higher BED in the original courses of radiation therapy.

This can be achieved by covering the large volume of the target and prophylactic regions with a conventionally fractionated treatment

followed by treatment of a smaller boost volume using the steep dose gradients and targeting accuracy of SBRT.

This approach has been used for years in other anatomical sites (e.g. brain, prostate) using protons or HDR brachytherapy

OARs involved

Numerous anatomical critical structures are normally involved and must be spared,

bone/mandible,
esophagus,
pharyngeal constrictor muscles,
oral mucosa,
pharynx,
submandibular gland,
carotid artery,
larynx,
parotid,
skin,
trachea

Cranial or thoracic structures may also be involved depending on the location of the tumor

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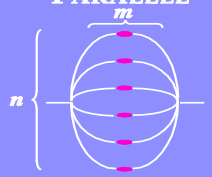
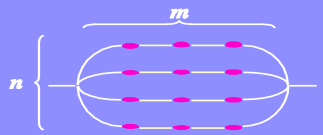
Influence Of Functional Organization Of Tissues On Dose Response Relation

Parallel



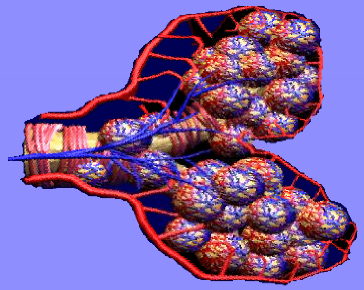
Mixed



Serial

Functional Organization

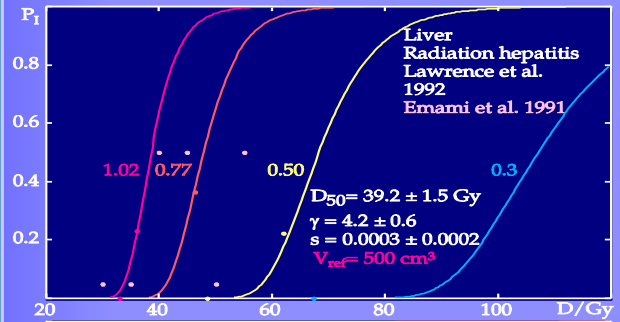
● = Functional Sub Unit

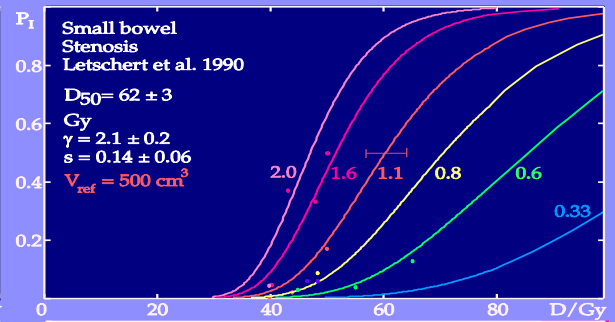


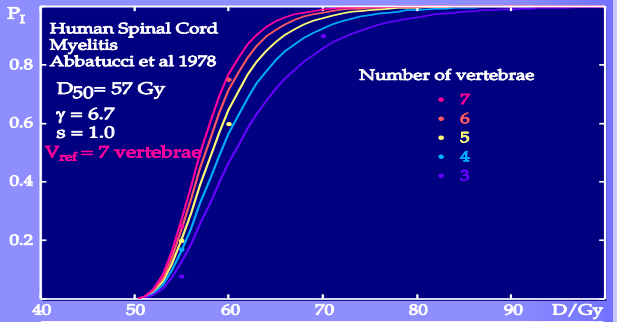
Relative Seriality:

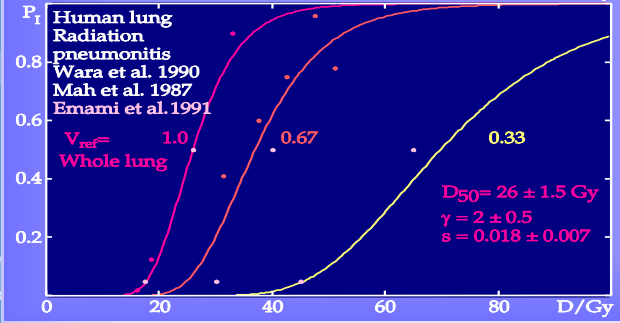
$s = \frac{m}{n*m} = 1/n$

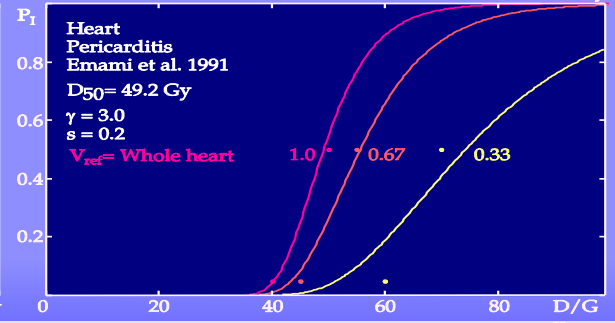
Organ	Relative Seriality
Tumors	0
Liver	0.0003
Kidney	0.004
Lung	0.018
Small bowel	0.14
Heart	0.20
Brain	0.64
Colon	0.69
Skin	0.86
Brain Stem	1.0
Small Intestine	1.5
Esophagus	3.4
Spinal Cord	4.0
Brachial Plexus	8.4

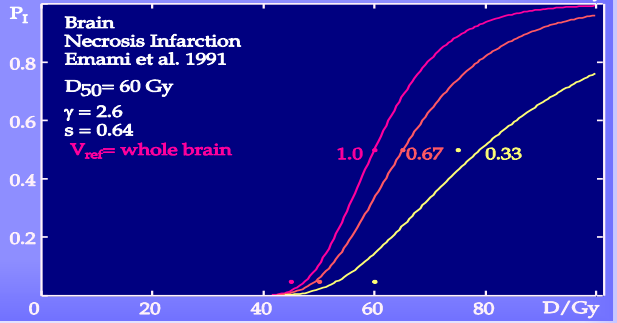




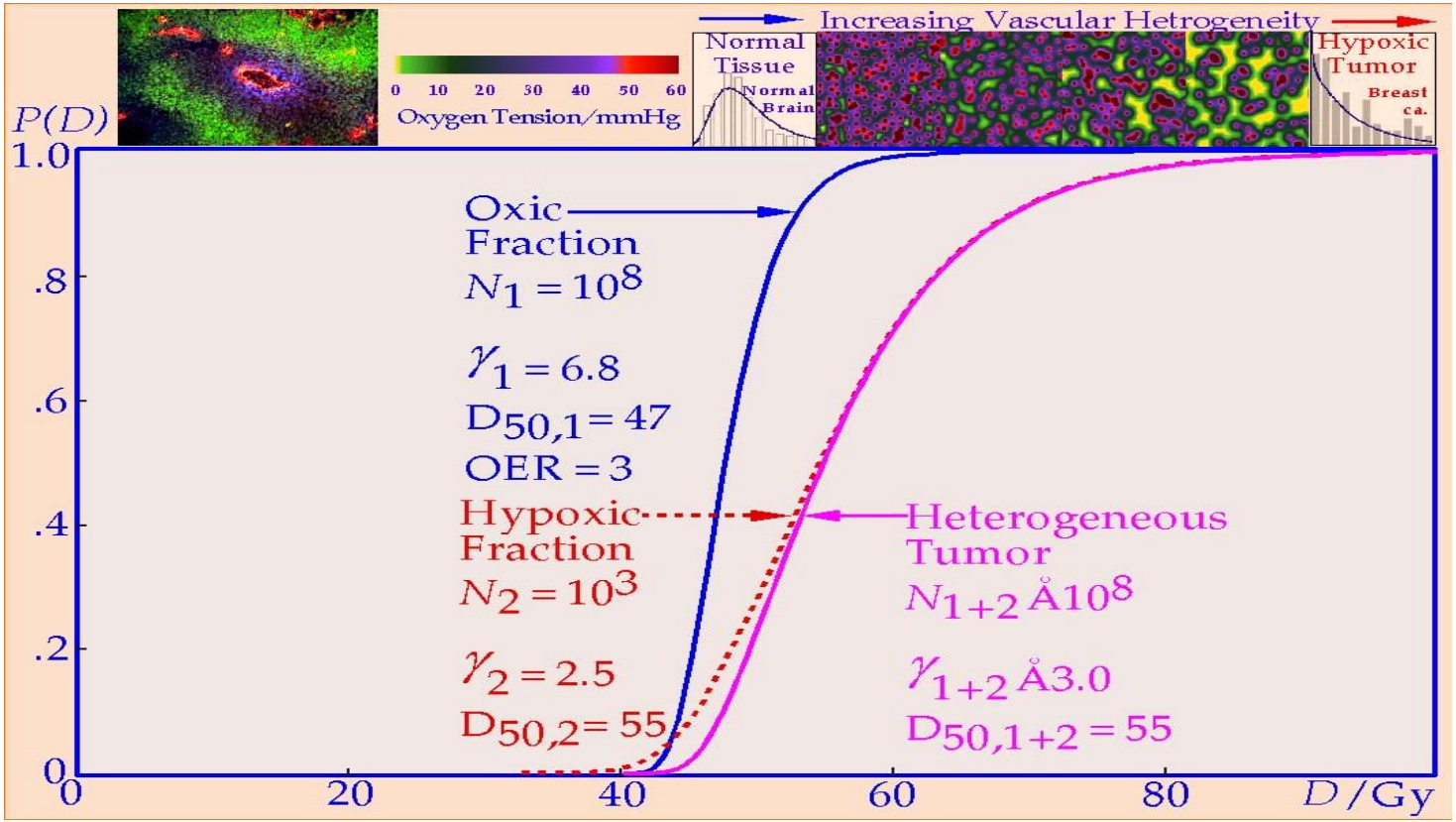








The impact of Hypoxia on the radiosensitivity of tumors



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Radiobiological Models

Survival functions

Simple multitarget model

$$S = 1 - \left(1 - e^{D/D_0}\right)^N$$

Multitarget, single hit model

$$S = e^{D/D_1}\left[1 - \left(1 - e^{D/D_2}\right)\right]^N$$

Linear-quadratic model

$$S = e^{-\alpha D - \beta D^2}$$

Statistical models describing dose-response relationships

Probit model

$$P(D) = \frac{1}{2}\left\{1 - Erf\left[\sqrt{\pi\gamma}\left(1 - \frac{D}{D_{50}}\right)\right]\right\}$$

Logit model

$$P(D) = \left[1 + \left(\frac{D_{50}}{D}\right)^{4\gamma}\right]^{-1}$$

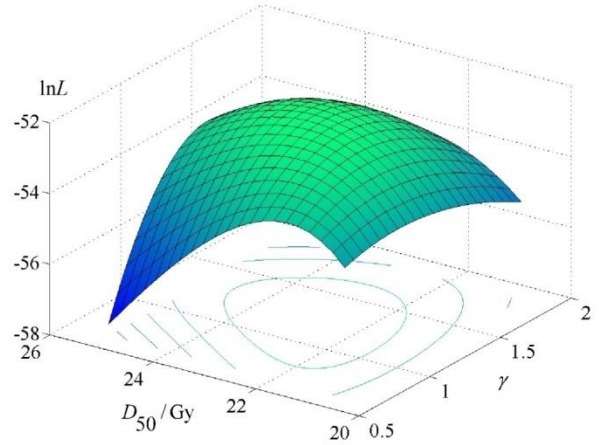
Poisson model

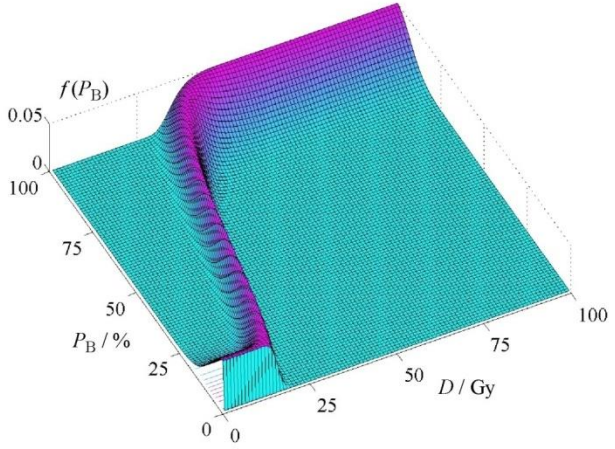
$$P(D) = 2 - e^{\left[e\gamma\left(1 - D/D_{50}\right)\right]}$$

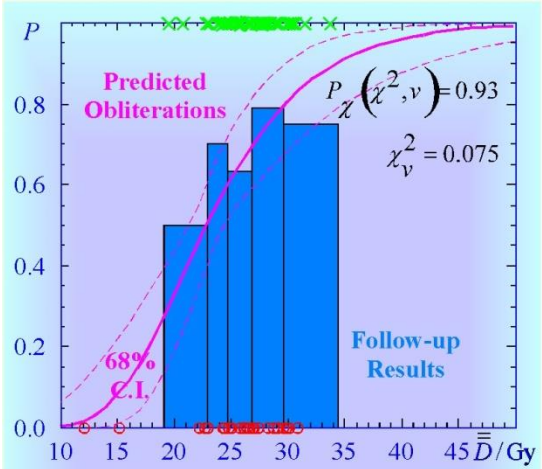
LQ-Poisson model

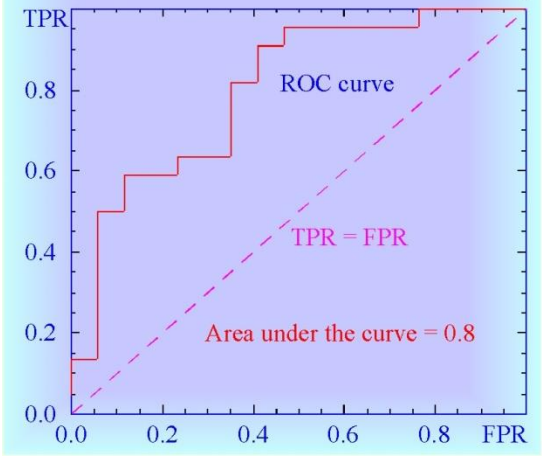
$$P(D) = e^{-N_0 e^{-\alpha nd - \beta nd^2}}$$

Derivation and clinical validation of model parameters









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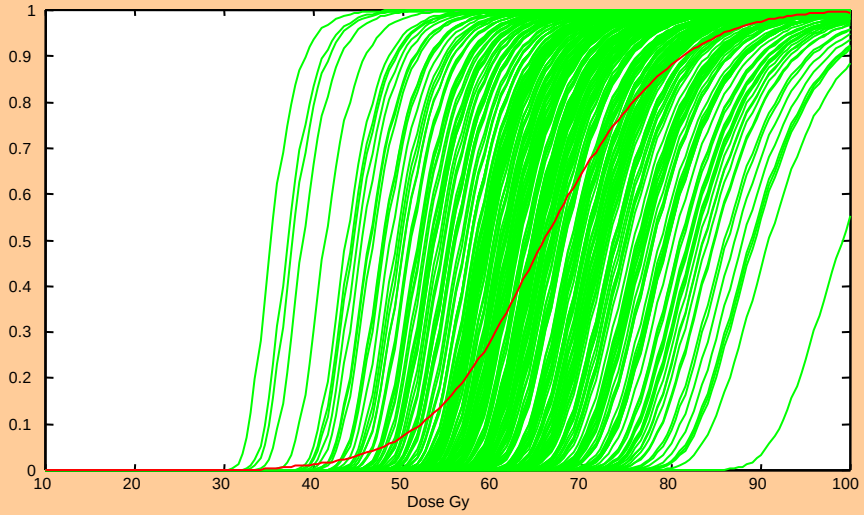
Individual and averaged dose-response curves

If only D_{50} varies among the patients (inter-patient variation)

$$\bar{D}_{50} = 65\text{Gy}\ ;\ D_{50} = 64.6\text{Gy}$$
$$\sigma_{D50} = 10\text{Gy}\ ;\ \gamma_{50} = 2.2$$
$$\bar{\gamma}_{50} = 6$$



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Patient population

- Most patients in these re-treatment cohorts have already received conventionally fractionated regimens with prescription doses ranging from 60 to 74Gy
- Re-treatments bear the additional challenge that the different normal tissues have usually different rates of recovery
- Depending on the time that has elapsed from the previous treatment,
  - » certain organs may have recovered completely and can be treated using the same tolerance doses
  - » Other organs may show no recovery and the dose that they have already received should be considered in treatment planning

Summary of reported dose-volume limits from the literature

47 dose volume constraints

Organ	#Fx	Volume cc or %	Dose Limit Gy	Dmax Limit Gy	#AE ≥ G3	# Pts Rx this Dose	#Pts in Study	Endpoint (≥ G3)
Carotid Artery	5	1	34		2	8	35	Aortic Rupture
Carotid Artery	5	1	27		2	17	35	Aortic Rupture
Carotid Artery	5			20	0		87	Carotid blowout
Carotid Artery	5			23.3	0	1	22	Carotid blowout
Carotid Artery	5		30		10	10	80	Carotid blowout
Carotid Artery	5			34	11	37	75	Carotid blowout
Carotid Artery	5			31.7	1	1	34	Carotid blowout
Carotid Artery	5			30.7	1	1	34	Carotid blowout
Bone: TMJ	5			20	1		39	
Brain	1			5	1		18	Necrosis
Brain	5			20	0		87	Necrosis
Brain	5			19.2	0	1	22	Necrosis
Brainstem	1			5	0		18	Cranial neuropathy
Brainstem	3			24.3	0		32	Cranial neuropathy
Brainstem	5			37	0	1	37	Cranial neuropathy
Brainstem	5			16	0	18	37	Cranial neuropathy
Brainstem	5			9	0		87	Cranial neuropathy
Brainstem	5			9.1	0	1	22	Cranial neuropathy
Brainstem	5			8	0		39	Cranial neuropathy
Chiasma	1			4	0		18	Neuritis
Chiasma	3			24.3	0		32	Neuritis
Chiasma	5			10	0		87	Neuritis
Chiasma	5			8.2	0	1	22	Neuritis
Chiasma	5			7	0		39	Neuritis
Esophagus	5			40.1	1		34	Mucositis/disphagea/ucler/hemorrhage
Esophagus	5			37.7	1		34	Mucositis/disphagea/ucler/hemorrhage
Esophagus	5			26.2	1		34	Mucositis/disphagea/ucler/hemorrhage
Esophagus	5			20	1		87	Stenosis/fistula
Esophagus	5	1	10		1		12	Stenosis/fistula
Esophagus	5			19.3	1	1	22	Stenosis/fistula
Eyes: Lens	5			6	0		87	
Eyes: Lens	5			2	0	1	22	
Eyes: Retina	5			10	0		87	
Eyes: Retina	5			8.9	0	1	22	
Larynx	5			20	0		87	Stenosis/fistula
Larynx	5	1	10		0		12	Stenosis/fistula
Nerve: Optic	1			4	0		18	Neuritis
Nerve: Optic	3			24.3	0		32	Neuritis
Nerve: Optic	5			58	0	1	37	Neuritis
Nerve: Optic	5			15	0	18	37	Neuritis
Nerve: Optic	5			10	0		87	Neuritis
Nerve: Optic	5			9.1	0	1	22	Neuritis
Nerve: Optic	5			7	0		39	Neuritis

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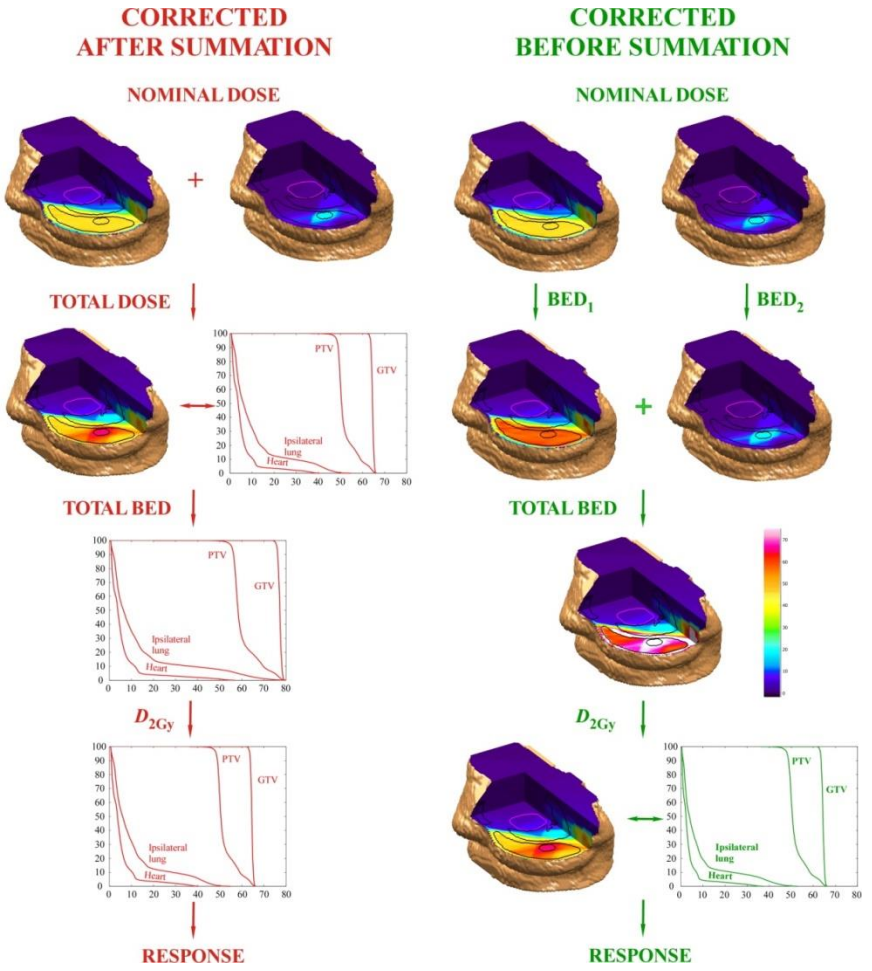
Composite dose

Leung 2011 proposed a method to account for composite doses for head and neck boost, with a single case study as an example [r005]. Dose tolerance limits in Hara 2008 and Seo 2009 were posed in terms of composite maximum point doses converted to 2Gy equivalent doses



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Volume definition using PET-CT segmentation

89 patients were reviewed with recurrent head and neck cancer treated with SBRT using no margin around the GTV

Radiotherapy and Oncology 106 (2013) 90–95

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Head and neck cancer

Target delineation in stereotactic body radiation therapy for recurrent head and neck cancer: A retrospective analysis of the impact of margins and automated PET-CT segmentation

Kyle Wang[a], Dwight E. Heron[a,b,*], David A. Clump[a], John C. Flickinger[a,c], Gregory J. Kubicek[a], Jean-Claude M. Rwigema[a], Robert L. Ferris[a,b], James P. Ohr[d], Annette E. Quinn[a], Cihat Ozhasoglu[a], Barton F. Branstetter[b,e]

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PET-CT planned GTVs were also recontoured by adding PET-standardized uptake values and signal/background ratio (SBR) to the original GTV.

The recontoured GTVs were deformably registered to post-SBRT scans and the fraction of recurrence volume (RV) falling within the GTV, the "RV-GTV overlap“ was assessed

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Volume definition using PET-CT segmentation

RESULTS

- With non-PET-CT planning, median RV-GTV overlap increased from 11.7% to 48.2% using 5mm margins, and median GTV size increased by 41.8 cc (156%).
- With PET-CT planning, RV-GTV overlap increased from 45% to 93.6% using 5mm margins, and GTV size increased by 34.8 cc (140%).

So, the impact of volume definition between different studies reporting outcome data may be a significant factor to be considered

Composite dose

35 patients with locally recurrent NPC treated using FSRT with CyberKnife.

Radiotherapy and Oncology 93 (2009) 570–574

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Re-radiation in head and neck

Robotic system-based fractionated stereotactic radiotherapy in locally recurrent nasopharyngeal carcinoma

YoungSeok Seo[a], HyungJun Yoo[a,*], SungYul Yoo[a], ChulKoo Cho[a], KwangMo Yang[a], Mi-Sook Kim[a], ChulWon Choi[a], YoungJu Shin[a], DongHan Lee[b], GukHang Lee[c]

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Radiation doses were prescribed at the isodose line (75-84% of the maximum dose).

The prescribed dose of FSRT ranged from 24 to 45 Gy (median, 33 Gy) in three or five fractions.

Cumulative $NTD_{2Gy,\ \alpha/\beta=10}$ of FSRT and the previously treated RT ranged from 57 to 193 Gy (median, 130.0 Gy)

The cumulative $NTD_{2Gy,\ \alpha/\beta=3}$ of brainstem, optic nerve, chiasm was limited to < 54Gy and that of spinal cord to < 45Gy

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Results

The overall survival (OS) rate, local failure-free survival (LFFS) rate, and disease progression-free survival (DPFS) rate at 5 years were 60%, 79%, and 74%, respectively.

Twenty-three patients achieved complete response after FSRT.

Five patients exhibited severe late toxicity (Grade 4 or 5).

Most studies do not report fractionation corrected cumulative doses. This makes the comparison of different studies less accurate if not incompatible.

Deformable registration

Furthermore, possible patient deformation during the course of the treatment is currently not accounted for. Typically during SBRT, pre-treatment imaging is performed in each fraction and a rigid setup correction is applied. However, when deformation is present, to properly determined the total dose distribution delivered to the patient from all the fractions the fractional CBCTs should be registered (through deformable registration) to the planning CT and their corresponding dose distribution be summed up. The produced composed dose distribution is the one that should be correlated to the treatment outcome.

Impact of tissue densities

The nasopharyngeal region has varying tissue densities and air cavities which can affect dose calculations, by as much as 5-8% in the Kan 2011 comparison of two dose calculation algorithms and it is possible that other dose calculation methods could be more susceptible to these effects.

IOP Publishing — Physics in Medicine and Biology

Phys. Med. Biol. **56** (2011) 397–413 — doi:10.1088/0031-9155/56/2/008

The accuracy of dose calculations by anisotropic analytical algorithms for stereotactic radiotherapy in nasopharyngeal carcinoma

M W K Kan[1,2,3], J Y C Cheung[1], L H T Leung[1], B M F Lau[1] and P K N Yu[2]

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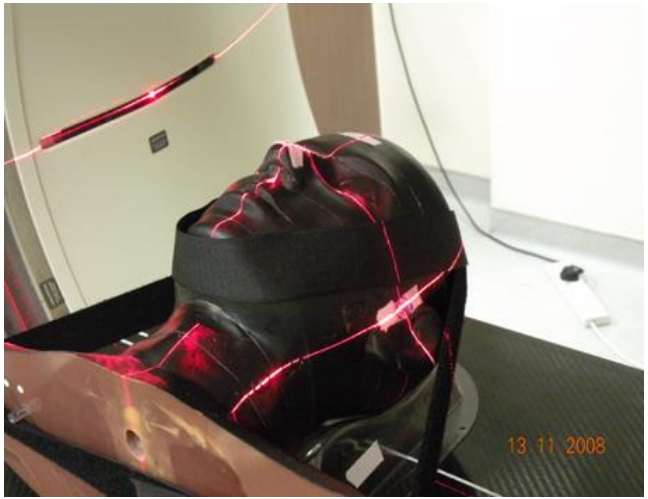
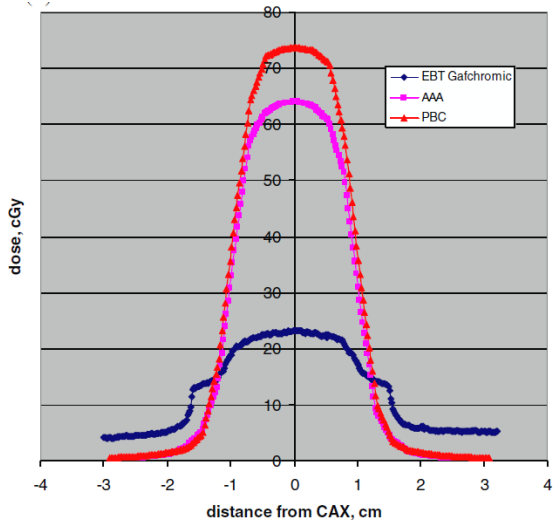
Impact of tissue densities

Testing of the algorithms using the anthropomorphic phantom showed that the maximum overestimation by the PBC algorithm was 20.7%, while that by the AAA was 8.3%.

When multiple fields were used in a patient geometry, the dose prediction errors of the AAA would be substantially reduced compared with those from a single field. However, **overestimation of more than 3% could still be found** at some points at the air–tissue interface.





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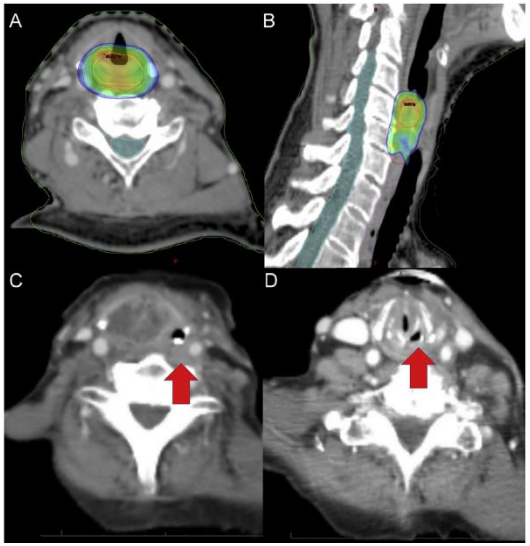
Recent report

A retrospective review was performed on 291 patients treated with SBRT for recurrent, previously irradiated head and neck cancer over a period of 10y.

Median time to death or last clinical follow-up was 9.8 months among the entire cohort and 53.1 months among surviving patients. Overall, 33 patients (11.3%) experienced grade ≥3 acute toxicity and 43 (18.9%) experienced grade ≥3 late toxicity.



CME ASTRO

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Risk of Severe Toxicity According to Site of Recurrence in Patients Treated With Stereotactic Body Radiation Therapy for Recurrent Head and Neck Cancer

Diane C. Ling, MD,* John A. Vargo, MD,* Robert L. Ferris, MD, PhD,*,† James Ohr, DO,‡ David A. Clump, MD, PhD,* Wai-Ying Wendy Yau, BS,* Umamaheswar Duvvuri, MD, PhD,† Seungwon Kim, MD,† Jonas T. Johnson, MD,† Julie E. Bauman, MD, MPH,‡ Barton F. Branstetter, MD,§ and Dwight E. Heron, MD, MBA, FACR, FACRO*,†

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Recent report

Of the entire cohort, 33 (11.3%) experienced grade ≥ 3 acute toxicity. Grade 3 acute toxicities included dysphagia in 13 patients, mucositis in 8, skin toxicity in 5, trismus in 3, xerostomia in 2, and fatigue in 2.

Of the 227 patients included in late toxicity analysis, 43 (18.9%) experienced grade 3 late toxicity. Grade 3 late toxicities included dysphagia in 20 patients, osteonecrosis in 6, laryngeal edema in 2, trismus in 2, and tracheae esophageal fistula in 2.

Compared with larynx/hypopharynx, treatment of nodal recurrence was associated with a lower risk of severe acute toxicity (P=0.03), with no significant differences in severe acute toxicity among other sites.

Patients treated for a recurrence in the larynx/hypopharynx experienced significantly more severe late toxicity compared with those with oropharyngeal, oral cavity, base of skull/paranasal sinus, salivary gland, or nodal site of recurrence (P<0.05 for all).

Sixteen patients (50%) with laryngeal/hypopharyngeal recurrence experienced severe late toxicity, compared with 6-20% for other sites.

Radiobiological modelling

To date only one NTCP dose response model has been published for SBRT head and neck boost treatments, for the probability of dysphagia as a function of mean dose to the superior constrictor muscle

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 4, pp. 1119–1127, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2008.02.061

CLINICAL INVESTIGATION **Head and Neck**

TREATMENT TECHNIQUES AND SITE CONSIDERATIONS REGARDING DYSPHAGIA-RELATED QUALITY OF LIFE IN CANCER OF THE OROPHARYNX AND NASOPHARYNX

David N. Teguh, M.D.,* Peter C. Levendag, M.D., Ph.D.,* Inge Noever, R.T.T.,* Peter van Rooij, M.Sc.,* Peter Voet, R.T.T.,* Henrie van der Est, R.T.T.,* Dick Sipkema, R.T.T.,* Aniel Sewnaik, M.D., Ph.D.,† Robert Jan Baatenburg de Jong, M.D., Ph.D.,† Daniël de la Bije, R.T.T.,* and Paul I. M. Schmitz, Ph.D.‡

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Teguh et al 2008

This study includes 81 patients who completed quality of life surveys, including IMRT boost, brachytherapy boost, SBRT boost with CyberKnife, and no boost.

Only 6 of the 81 cases received SBRT, and 27 of the cases were scored as Grade 3-4 complications.

From this small amount of data it is impossible to say whether SBRT is significantly better or not – even if none of the SBRT cases had the complications

All oropharynx (Gy)	IMRT/3D-CRT $n = 12$	BT $n = 42$	CBK $n = 6$
scm	67	44	50
mcm	65	38	45
icm	48	27	32
cphm	34	22	25
eim	32	20	23

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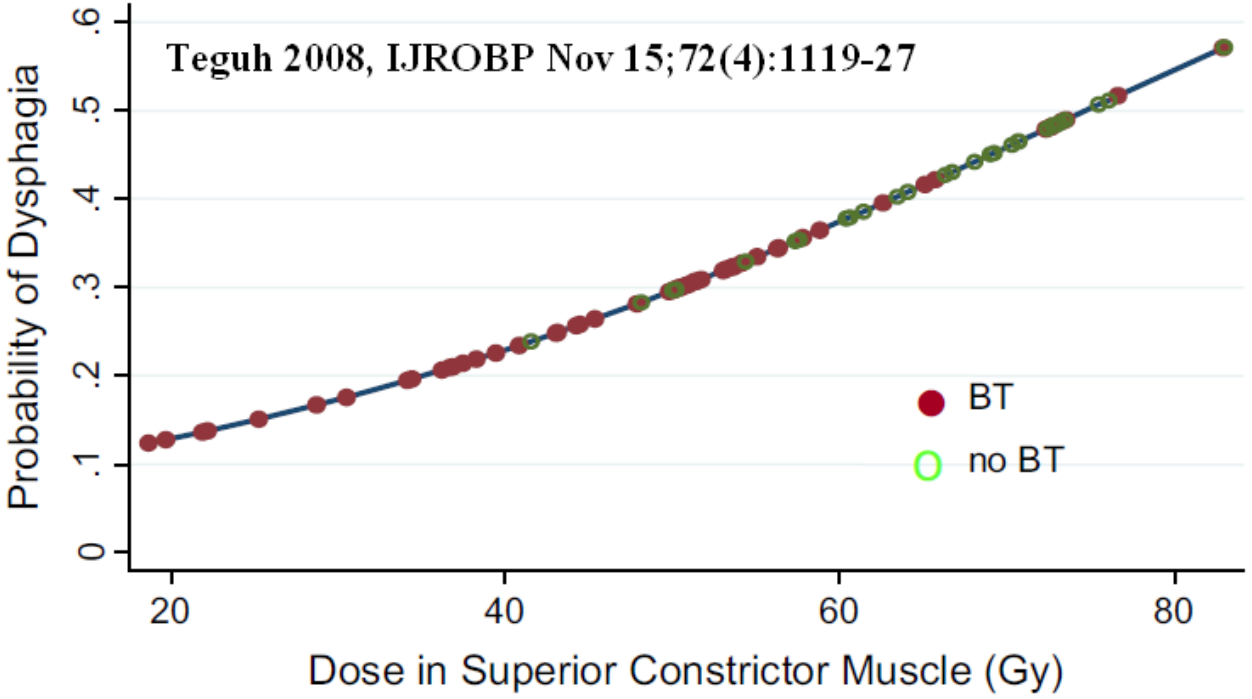
Dysphagia



Logistic dose response model for dysphagia as a function of mean composite boost dose to superior constrictor muscle, TD50=74.7Gy, γ50=0.6588 (γ50=k/4).

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SBRT Boost

The SBRT boost concept has clinical potential since: “the mean dose to the superior and middle constrictor muscles was significantly lower in patients treated with the SBRT compared with those treated with an IMRT boost (50 and 45 Gy vs. 67 and 65 Gy, respectively)”.

51 patients with Stage I to IV biopsy-proven primary oropharyngeal cancers. 46Gy with IMRT followed by 5.5 with SBRT. The 3-year actuarial rates of Local Control, Disease-Free Survival, and Overall Survival were 70%, 66%, and 54%, respectively. The 2-year cumulative incidence of Grade ≤2 dysphagia and xerostomia was 15% and 28%, respectively.

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 4, pp. 1494–1500, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.05.019

CLINICAL INVESTIGATION **Head and Neck Cancer**

STEREOTACTIC BODY RADIOTHERAPY: A PROMISING TREATMENT OPTION FOR THE BOOST OF OROPHARYNGEAL CANCERS NOT SUITABLE FOR BRACHYTHERAPY: A SINGLE-INSTITUTIONAL EXPERIENCE

Abrahim Al-Mamgani, M.D., Ph.D.,* Lisa Tans, M.D.,* David N. Teguh, M.D., Ph.D.,* Peter van Rooij, M.Sc.,† Ellen M. Zwijnenburg, M.D.,* and Peter C. Levendag, M.D., Ph.D.*

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Carotid blowout

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0360-3016/S–see front matter

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CLINICAL INVESTIGATION **Head and Neck**

SALVAGE REIRRADIATON WITH STEREOTACTIC BODY RADIOTHERAPY FOR LOCALLY RECURRENT HEAD-AND-NECK TUMORS

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46 patients were treated using the CyberKnife.

The median tumor dose with SBRT was 30 Gy (range, 18–35 Gy) in a median of 5 (range, 1-5) fractions.

In their primary treatment, patients were administered a total median dose of 61Gy (range, 30–70 Gy) with fractional doses of 1.8 to 2 Gy.

UNC SCHOOL OF MEDICINE

Carotid blowout

- Of 37 patients whose response to therapy was evaluated, 10 patients (27%) had complete tumor regression.
- Ultimate local disease control was achieved in 31 patients (83.8%).
- The overall survival was 11.9 months in median (ranged, 11.4 – 17.4 months), and the median progression free survival was 10.5 months.
- One-year progression-free survival and overall survival were 41% and 46%, respectively.
- **On follow-up, 8 (17.3%) patients had carotid blow-out syndrome, and 7 (15.2%) patients died of bleeding from carotid arteries.**
- **This fatal syndrome occurred only in patients with tumor surrounding carotid arteries and carotid arteries receiving all prescribed dose.**

Carotid blowout

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 3, pp. 1083–1089, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.029

CLINICAL INVESTIGATION **Head-and-Neck Cancer**

RISK OF CAROTID BLOWOUT AFTER REIRRADIATION OF THE HEAD AND NECK: A SYSTEMATIC REVIEW

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A literature search identified 27 published articles on H&N reirradiation involving 1554 patients, and a pooled analysis was performed to determine the rate of CB. Treatment

UNC SCHOOL OF MEDICINE

Carotid blowout

- Among 1554 patients receiving salvage H&N reirradiation, there were 41 reported CBs, for a rate of 2.6%; 76% were fatal.
- In patients treated in a continuous course with 1.8–2-Gy daily fractions or 1.2-Gy twice daily fractions, the rate of CB was 1.3%.
- In patients treated with 1.5 Gy twice daily in alternating weeks or with delayed accelerated hyperfractionation, the rate of CB was 4.5%.
- There was no statistically significant difference in the rate of CB between patients treated with or without concurrent chemotherapy, or between patients treated with or without salvage surgery before re-irradiation.
- Carotid blowout is an infrequent complication of salvage reirradiation for H&N cancer, with a rate of 2.6% among
- 1554 patients. Seventy-six percent of CBs were fatal.

Carotid blowout

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Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 1, pp. 164–170, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01623-6

CLINICAL INVESTIGATION Head and Neck

FRACTIONATED STEREOTACTIC RADIOSURGERY FOR 50 PATIENTS WITH RECURRENT OR RESIDUAL NASOPHARYNGEAL CARCINOMA

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50 patients were treated with FSRS with 6 MV of photons.

The total FSRS dose was 14–35 Gy (median dose 24) prescribed on the 60–90% isodose curves in multiple fractions of 6–8, 12, or 15 Gy, with interfraction intervals of 4–6 days.

Results: Thirty-eight patients (76%) had a complete tumor response, 9 (18%) had a partial response.

The overall rate of survival was 65.0% at 2 years, and 59.6% at 3 years.

The overall disease-free survival rate was 74% at 2 and 3 years.

8 of 50 patients die of hemorrhage

Carotid blowout

Carotid rupture has been a known risk in head and neck re-treatment with conventional fractionation for more than 15 years.

Although the risk had been reported for hypofractionation more than 10 years ago, it was not until publication of several recent articles that full attention was given to this issue for SBRT.

No publication to date has quantitatively described the dose-volume effects of carotid artery re-treatment dose tolerance.

So the values from the literature could only include Dmax data, and this data was used to construct a dose response model,

Carotid blowout

Yazici et al. 2013 have provided the Dmax dose to the carotid artery for each case that suffered the complication (11 pt), and these represent the most detailed data available.

Additionally, Yazici et al. provided the median Dmax dose among the 64 cases that did not have a carotid blowout.

Yazici *et al. Radiation Oncology* 2013, **8**:242
http://www.ro-journal.com/content/8/1/242

RADIATION ONCOLOGY

RESEARCH Open Access

A simple strategy to decrease fatal carotid blowout syndrome after stereotactic body reirradiaton for recurrent head and neck cancers

Gozde Yazici, Tolga Yusuf Sanlı, Mustafa Cengiz, Deniz Yuce, Melis Gultekin, Pervin Hurmuz, Ferah Yıldız, Faruk Zorlu, Fadil Akyol, Murat Gurkaynak and Gokhan Ozyigit*

Carotid blowout

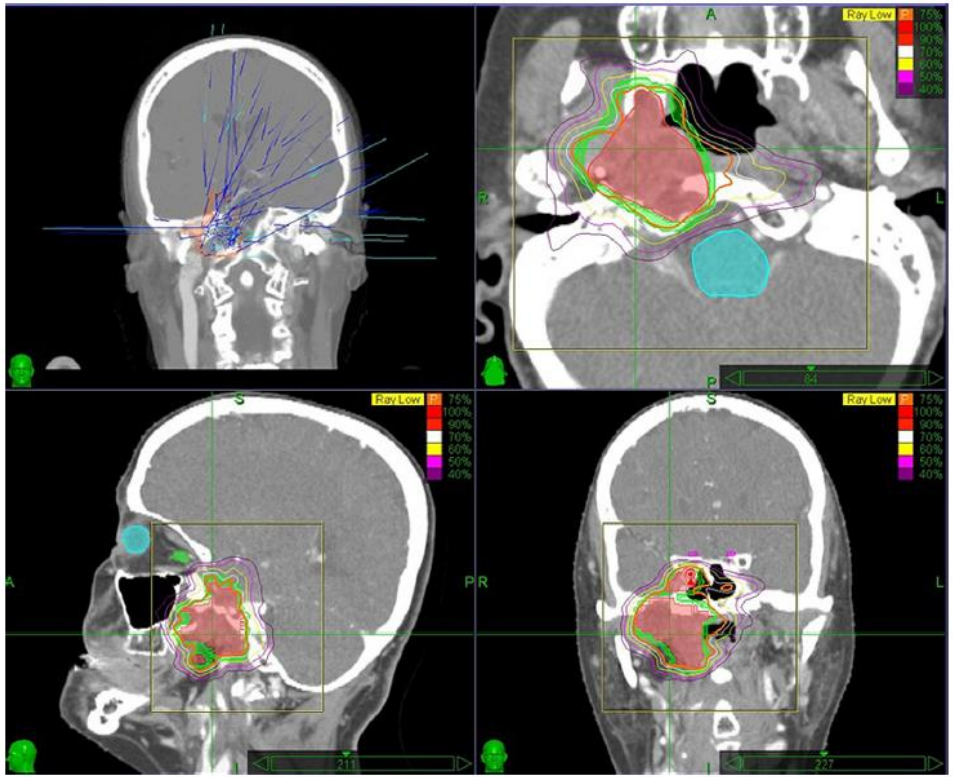
Yamazaki 2015 reported the median Dmax carotid artery dose in the 12 cases with blowout and for the 60 cases without complication, as well as the highest and lowest Dmax in each group

Maximum likelihood parameter estimation of the logistic model was used by replicating the median values into repeated binary outcomes, and the 95% confidence intervals were generated via the profile likelihood method

Carotid blowout

Experience now dictates that circumferential irradiation of the carotid artery should be avoided

Cengiz 2011, Int J Radiat Oncol Biol Phys. 81(1):104-9



UNC SCHOOL OF MEDICINE

Carotid blowout

34 patients with head and neck tumors were treated with CyberKnife SBRT.

21 patients had prior radiotherapy.

The prescribed dose ranged from 19.5 to 42 Gy (median, 30 Gy) in 3–8 fractions in consecutive days.

The median follow-up was 16 months.

The overall survival rates were 70.6% and 58.3% at 12 and 24 months

6 patients suffered severe late complications.

J. Radiat. Res., 52, 24–31 (2011)

Regular Paper

Stereotactic Body Radiation Therapy for Head and Neck Tumor: Disease Control and Morbidity Outcomes

Naohiro KODANI[1]*, Hideya YAMAZAKI[1], Takuji TSUBOKURA[1], Hiroya SHIOMI[2], Kana KOBAYASHI[1], Takuya NISHIMURA[1], Norihiro AIBE[1], Hiroyasu IKENO[1] and Tsunehiko NISHIMURA[1]

Carotid blowout

Several other Dmax values were obtained from other publications

Kodani et al. J Radiat Res. 2011;52(1):24-31

Voynov et al. Technol Cancer Res Treat. 2006 Oct;5(5):529-35.

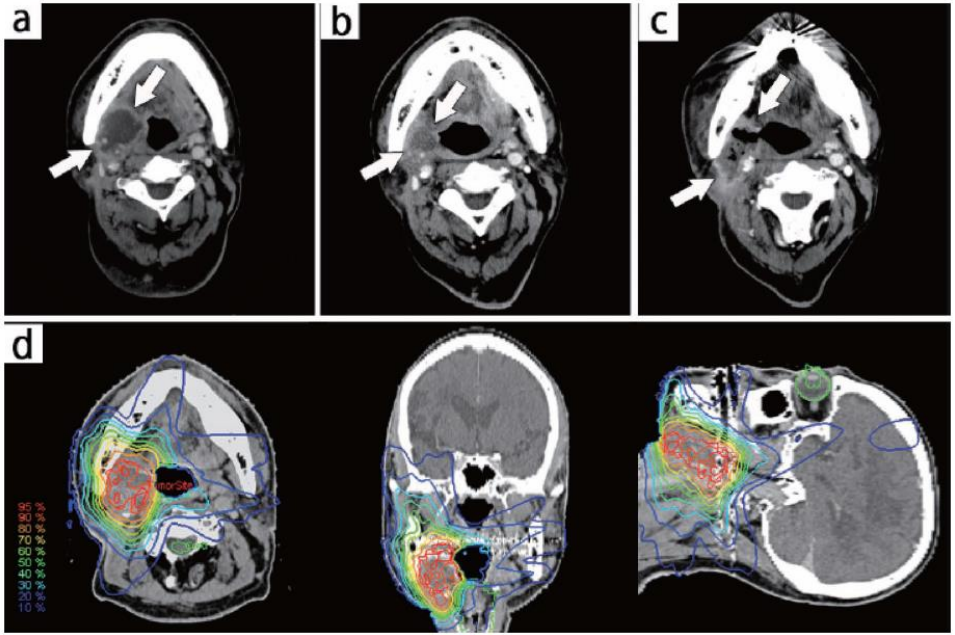
Rwigema et al. Am J Clin Oncol. 2010 Jun;33(3):286-93.

Maximum likelihood parameter estimation of the logistic model was used by replicating the median values into repeated binary outcomes, and the 95% confidence intervals were generated via the profile likelihood method

Carotid blowout

Experience now dictates that circumferential irradiation of the carotid artery should be avoided

Kodani 2011, J Radiat Res. 2011;52(1):24-31



Necrosis and carotid artery blowout after CyberKnife SBRT. (a) arrow indicates recurrent lymph node involvement. He had irradiation at 60 Gy as initial therapy. CyberKnife SBRT at 30 Gy in 5 fractions was prescribed (d) and achieved partial response (b). After 18 months of the treatment, tissue necrosis and pharyngocutaneous fistula were observed very close to the right carotid artery (c). He died of massive hemorrhage in this area after 28 months of the treatment.

UNC SCHOOL OF MEDICINE

Re-treatment tolerance of carotid artery
Modeling data extracted from the literature

#Fractions	Dmax (Gy)	Assigned AE ≥ G3	Assigned Weight	# Pts in Study	Refs.	Notes
5	20	0	87	87	033,034,036	Limit is for Carotid Artery
5	23.3	0	1	22	033	Highest Dmax used in 22 cases
5	42.5	0	1	75	181	Highest Dmax among Group 1 cases
5	2.5	0	1	75	181	Lowest Dmax among Group 1 cases
5	39.1	0	1	75	181	Highest Dmax among Group 2 cases
5	6.8	0	1	75	181	Lowest Dmax among Group 2 cases
5	34.7	0	60	75	181	Median Dmax among 64 non-CBOS cases
5	41.8	1	1	75	181	CBOS case 1
5	59	1	1	75	181	CBOS case 2
5	39.4	1	1	75	181	CBOS case 3
5	46.6	1	1	75	181	CBOS case 4
5	38.5	1	1	75	181	CBOS case 5
5	37.5	1	1	75	181	CBOS case 6
5	40.7	1	1	75	181	CBOS case 7
5	42.6	1	1	75	181	CBOS case 8, 5-fraction equiv dose
5	37.5	1	1	75	181	CBOS case 9
5	41	1	1	75	181	CBOS case 10
5	38.5	1	1	75	181	CBOS case 11
3-8, median 5	47.7	1	1	72	232	Highest Dmax among 12 CBOS cases
3-8, median 5	14.1	1	1	72	232	Lowest Dmax among 12 CBOS cases
3-8, median 5	30.2	1	10	72	232	Median Dmax among 12 CBOS cases
3-8, median 5	43.8	0	1	72	232	Highest Dmax among 60 non-CBOS cases
3-8, median 5	7.5	0	1	72	232	Lowest Dmax among 60 non-CBOS cases
3-8, median 5	26.8	0	58	72	232	Median Dmax among 60 non-CBOS cases
5	31.7	1	1	34	102	
5	30.7	1	1	34	102	

NTCP models

The Lyman-Kutcher-Burman (LKB),

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \qquad \text{where} \qquad t = \frac{gEUD_{2Gy} - TD_{50}}{m \cdot TD_{50}}$$

Relative Seriality (RS),

$$P_I(\vec{D}) = [1 - \prod_{i=1}^{M} (1 - P(D_i)^s)^{\Delta v_i}]^{1/s} \text{ where } P(D_i) = \exp[-e^{e\gamma - (EQD^i_{2\mathrm{Gy}} / D_{50}) \cdot (e\gamma - \ln\ln 2)}]$$

Logit

$$P(D) = \frac{1}{1 + \left(\frac{D_{50}}{gEUD_{2\mathrm{Gy}}} \right)^k}$$

Relative Logit (RL)

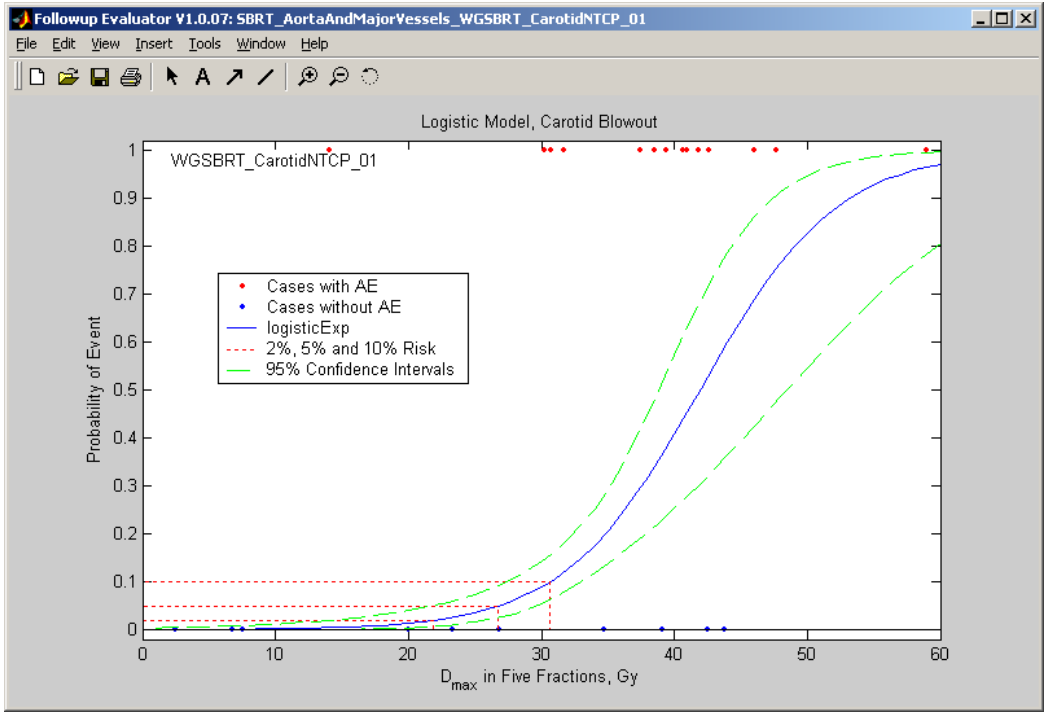
$$P_I(\vec{D}) = \left\{ 1 - \prod_{i=1}^{M} \left[1 - \left(\left(1 + \left(\frac{D_{50}}{gEUD^i_{2\mathrm{Gy}}} \right)^k \right)^{-1} \right)^s \right]^{\Delta v_i} \right\}^{1/s}$$

UNC SCHOOL OF MEDICINE

Carotid blowout

According to the model, the 2%, 5%, and 10% risk levels are 21.9, 26.8, and 30.6 Gy, respectively.

Note that only one event occurred with Dmax less than 30 Gy, but that several of the events occurred very close to 30Gy.



Logistic model of carotid blowout. Model parameters for Dmax carotid dose in five fractions are TD50=41.9Gy, γ50= 2.0394 (γ50=k/4).

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Carotid blowout

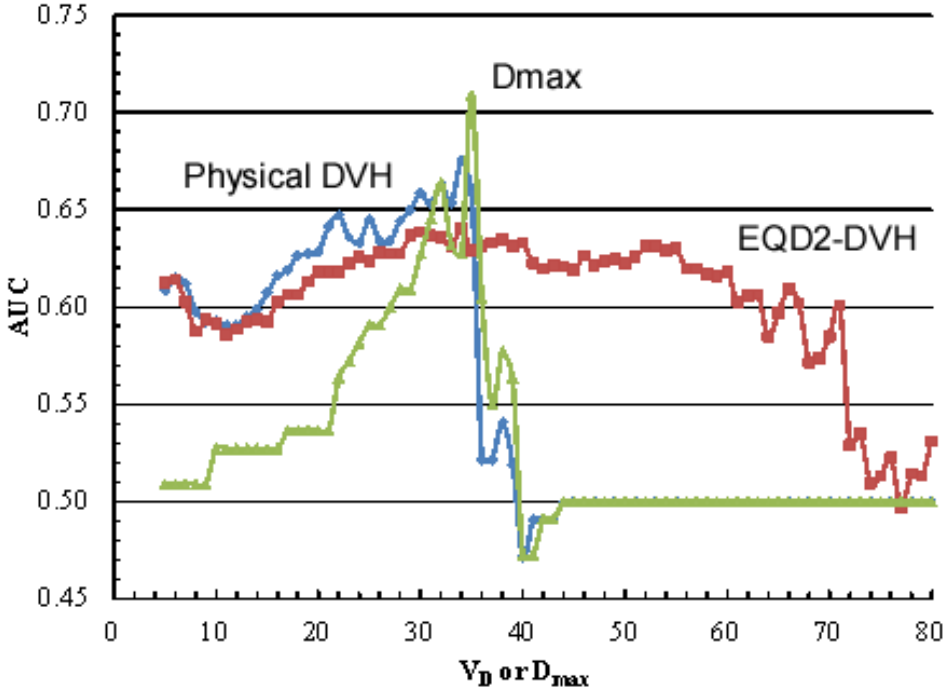
Yazici et al. concluded that:

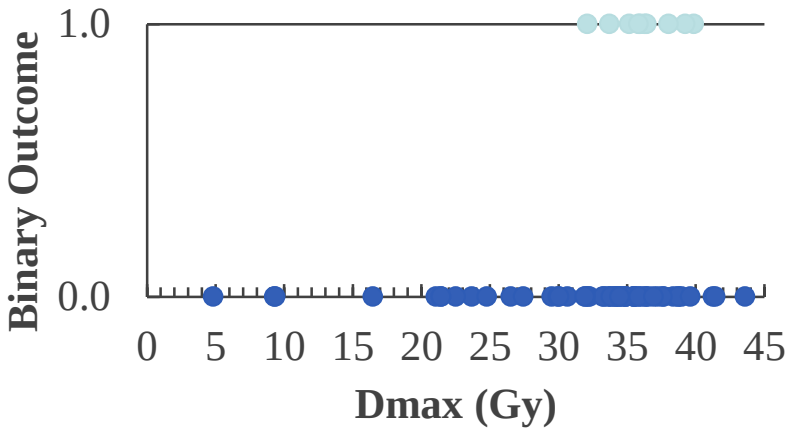
Carotid blowout did not occur in any of the patients with a maximum carotid artery radiation dose <34 Gy.

Every other day SBRT protocol for re-irradiation of recurrent head and neck cancer is promising in terms of decreasing the incidence of fatal carotid blowout.

Carotid blowout

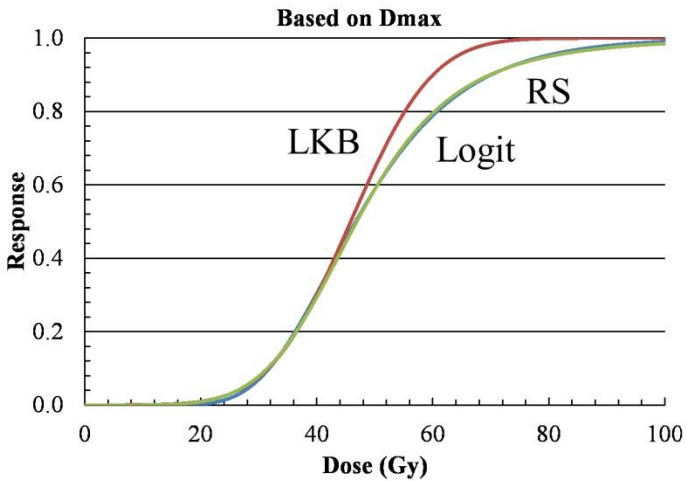
Yazici et al. concluded that:

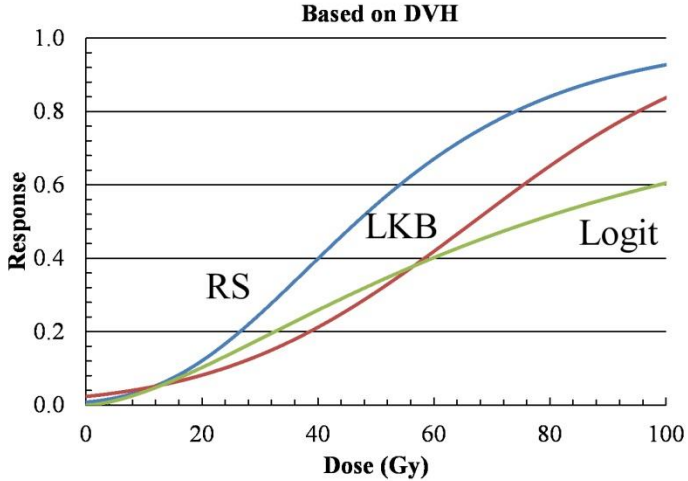




Carotid blowout

Calculations performed on the data published by Cengiz et al.





		LKB model	
Parameters	**D_{50} (Gy)**	***m***	***n***
Based on EQD_2-DVHs	66.88	0.50	0.20
Based on Dmax	45.83	0.24	0.01
		Logit model	
Parameters	**D_{50} (Gy)**	***k***	***n***
Based on EQD_2-DVHs	76.77	1.61	0.30
Based on Dmax	46.88	5.51	0.01
		Relative Seriality model	
Parameters	**D_{50} (Gy)**	**γ**	***s***
Based on EQD_2-DVHs	46.77	0.58	1.0
Based on Dmax	46.69	1.25	1.0

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Five-fraction dose tolerance limits

Rwigema 2010, Am J Clin Oncol. 33(3):286-93

Structure	Dmax Limit, Gy
Brain	20
Brainstem	9
Carotid Artery	20
Chiasm	10
Esophagus	< 20
Larynx	< 20
Lens of the Eye	6
Optic Nerves	10
Retina	10
Spinal Cord	12
Pharyngeal Constrictor Muscles*	20

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Conclusions

Many of these limits are intended for every-other-day treatments.

Those treatment planning constraints are intended to be conservative enough to accommodate retreatment of most initial courses of 60-74Gy prescriptions in conventional fractionation.

But if the dose-volume distributions of the initial course or the retreatment plan are particularly high, these estimated maximum tolerance doses may in some cases need to be reduced.

As most of these normal tissues are not considered to be ‘serial’ from a radiobiological standpoint, small portions were allowed to reach the maximum tolerance dose.

Many of the recent SBRT boost regimens use preliminary treatment planning constraints that are comparable to the highest known IMRT dose constraints, with the boost doses converted to conventionally fractionated doses and summed to the initial course .

FUTURE STUDIES

Phase I and II institutional studies have achieved preliminary safety and efficacy goals for retreatment of head and neck cancers with SBRT, but multi institutional cooperative trials to refine the technique and more fully analyze outcomes are desperately needed.

REPORTING STANDARDS FOR OUTCOMES

The true dose tolerance in the retreatment setting cannot be statistically analyzed until we have:

- reported outcomes
- dose distributions from the initial course
- dose distributions from the retreatment course
- composite dose distributions
- the time interval between the different courses

REPORTING STANDARDS FOR OUTCOMES

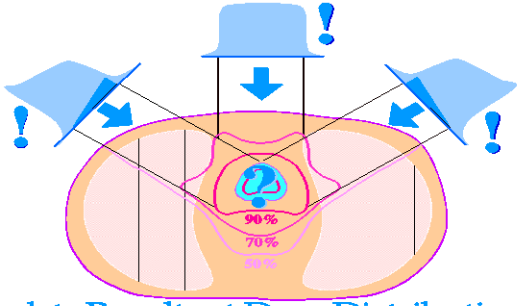
So, it is imperative to determine a number of data that should be provided at least in the form of supplement material by future publications reporting SBRT outcomes.

- Detailed description of the delineation guidelines for the organ(s) under examination.
- Detailed description of the follow-up process, especially regarding the definition of the symptoms.
- The dose volume histograms of the examined structures of the individual patients should be submitted as electronic supplementary data. The submission of the DICOM structure and dose files would be ideal.
- Description of the fractionation scheme applied, including all the treatment breaks.

Treatment Planning Approaches

Forward Calculation:

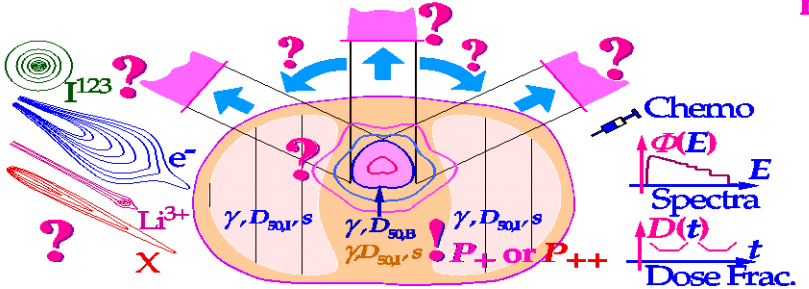
For Classical Beam Angels, Energies and Profiles: !



Calculate Resultant Dose Distribution: ?

Inverse Calculation:

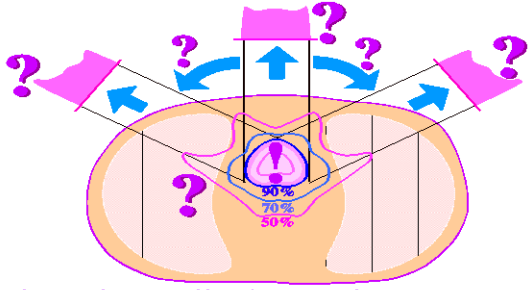
For Known Biological objective functions: !



Calculate Biologically Optimal : Radiation Quality Combination & Dose Fractionation , Beam Angels , Energies and Profiles : ?

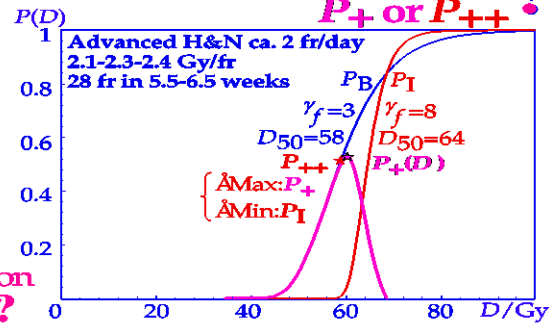
Inverse Calculation:

For Desired Tumor Dose Distribution: !



Calculate Physically Optimal Dose Distribution , Beam Angels , Energies and Profiles:

Biological objective function: !



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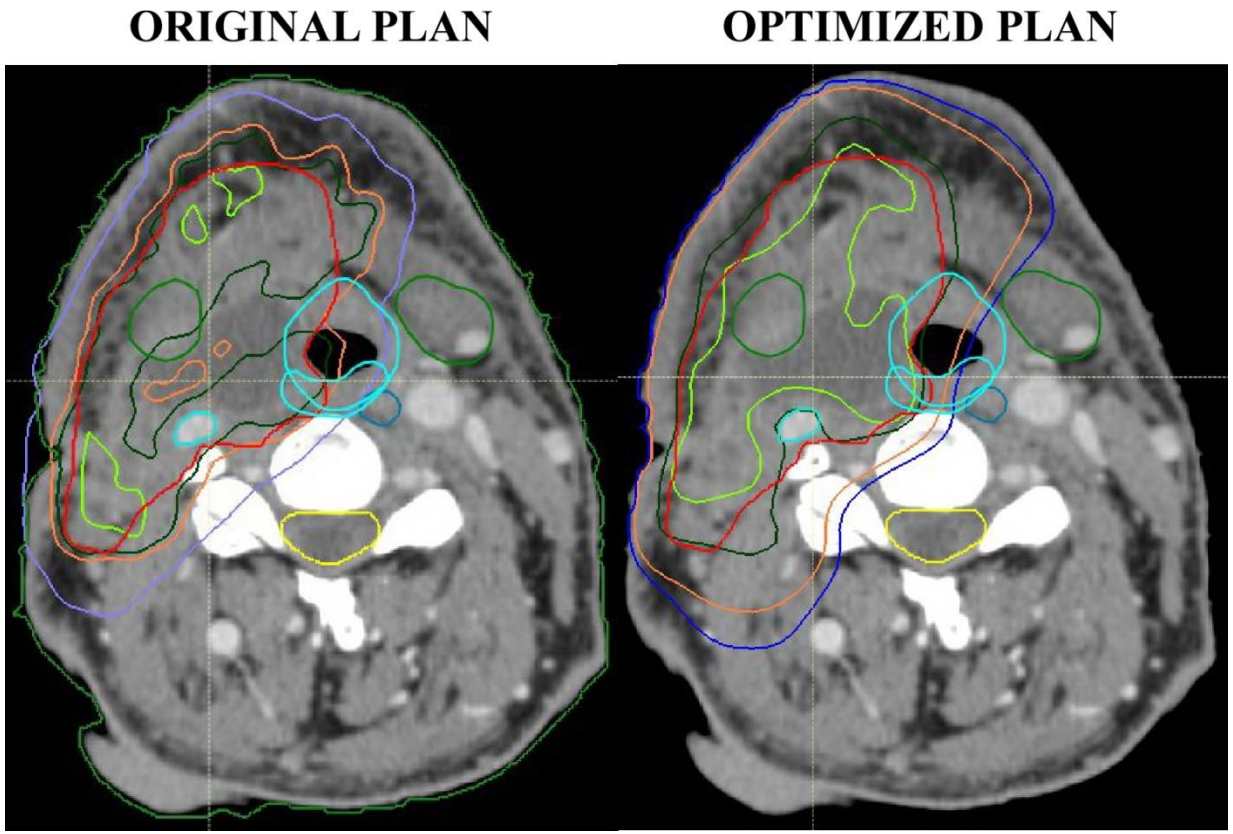
Treatment Planning Optimization

The majority of the patients with carotid blowout had at least 1.8cm of carotid, where the complete circumference received at least 32Gy



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OPTIMIZED PLAN: SOLID **ORIGINAL PLAN: DASHED**