27th ICRO-AROI 2017

Is HypoFractionation The Future?

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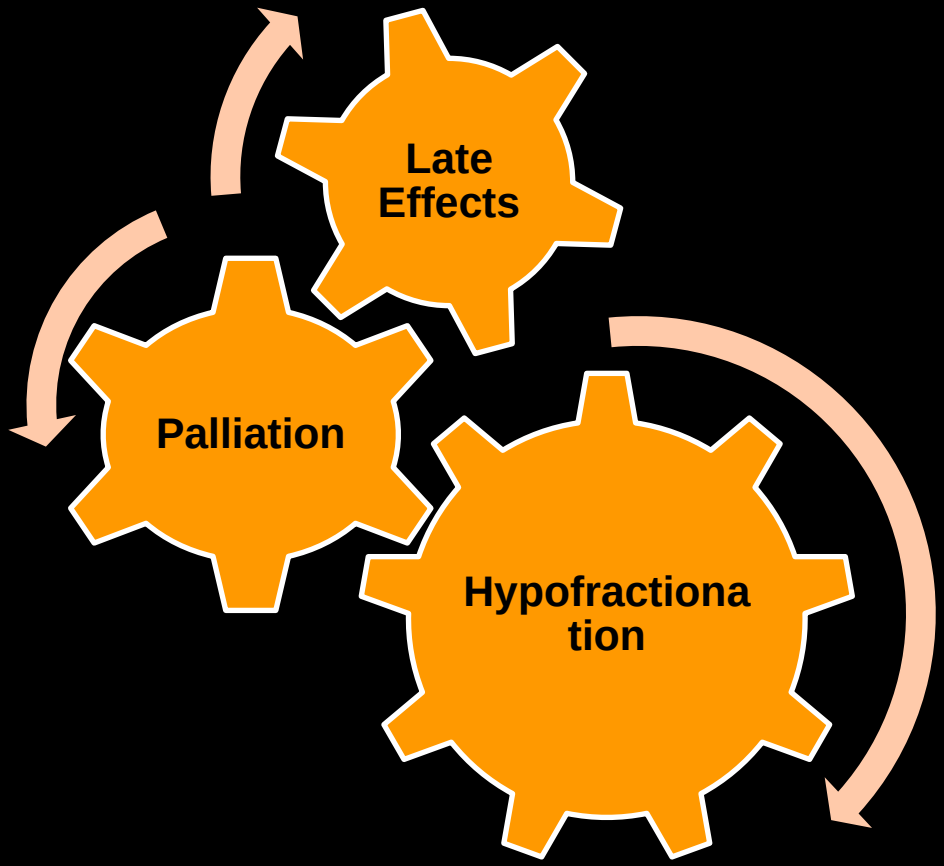
Max Super Speciality Hospital, Mohali

Traditional Mindset !!



HypoFractionation

- Past
- Present
- Future

HypoFractionation

The Past

Wilhelm Conrad Röntgen: Discovery of X-ray
(November 8 ,1895)

The Past..

July 1896, Victor Despeignes treated first patient of stomach cancer with X rays

- **Two half-hour treatments each day**
- **Patient died after three weeks, tumor shrunk by 50%**
- **First physician to publish a paper on radiotherapy**

The Past..

- By 1903, 2300 patients were irradiated
- Mostly hypofractionation

1906 : Law of Bergonie And Tribondeau

Jean A Bergonie

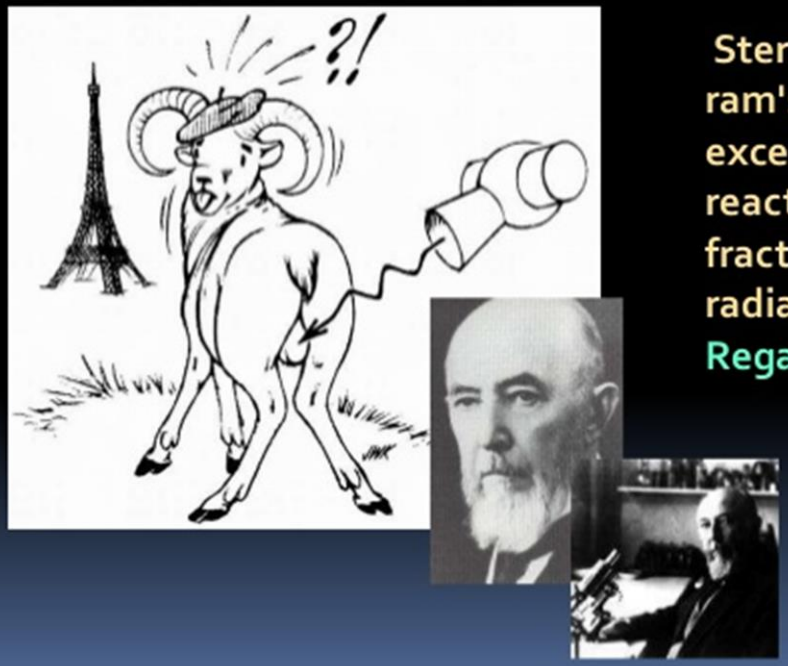
L M Tribondeau

cells tend to be radiosensitive if they have

- **High division rate**
- **Long dividing future**
- **Unspecialized phenotype**

Birth of Fractionation

1911 : Concept of fractionation



Sterilization of ram's testis without excessive skin reactions using fractionated radiation (Claude Regaud)

Regaud C, Coutard H – Pioneers of fractionation

Seitz L, Wintz H.

Unsere Methode der Roentgen-Tiefentheapie und ihre Erfolge. Berlin: Urban und Schwarzenberg, 1920

- **Advocated short course therapy for treatment of cervical cancer**

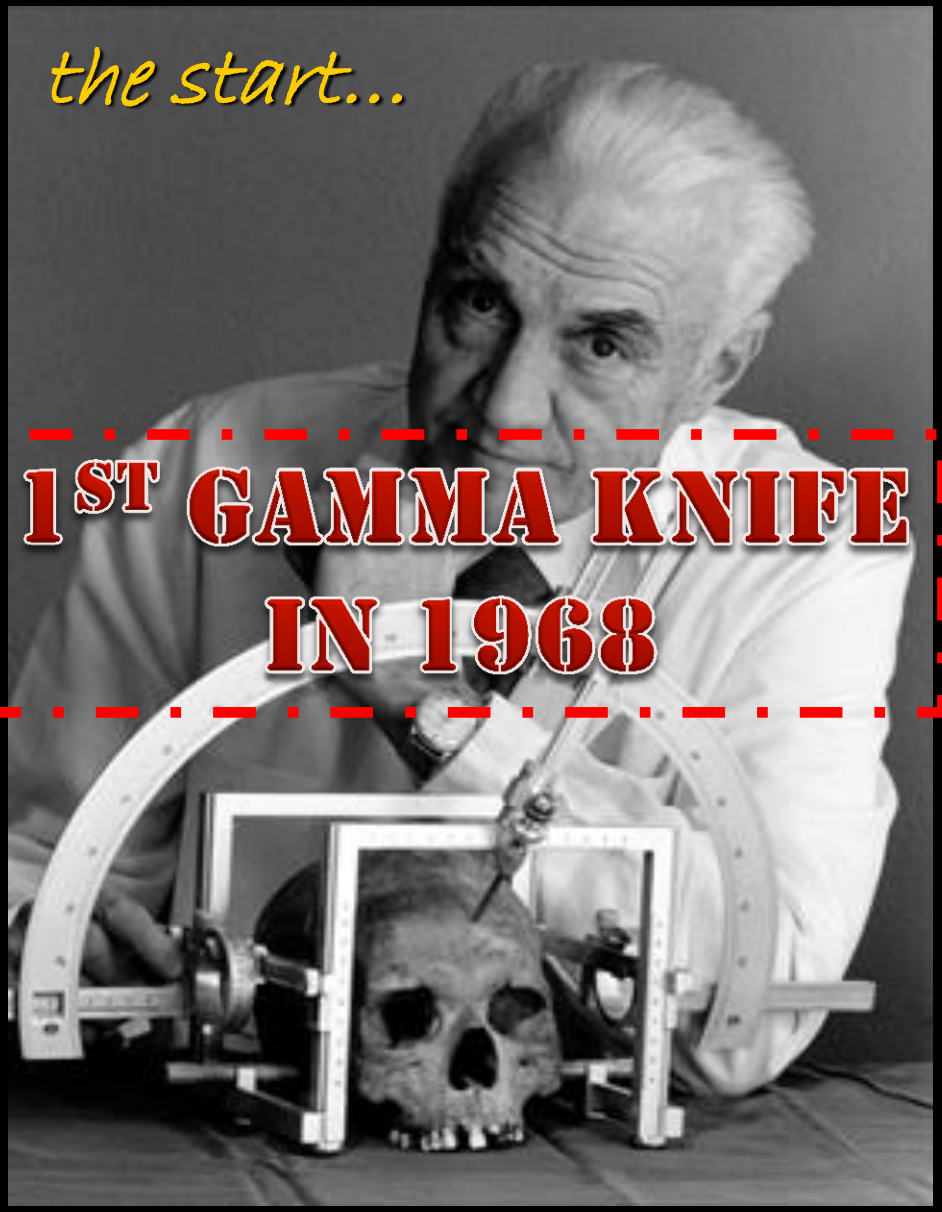
Coutard H.

Roentgen Therapy of Epitheliomas of the tonsillar region, hypopharynx and larynx from 1920 to 1926.

AJR Am J Roentgenol, 1932:28; 313-31

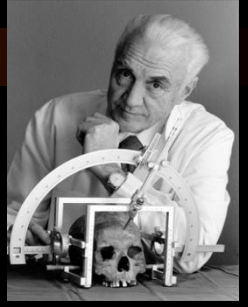
Hypofractionation

The Past: 1950s..



Prof. Lars Leksell

the development…



1951	Concept of Radiosurgery by Prof Leksell
1968	1st Gamma Knife in Stockholm, Sweden
1988	Linac-based Radiosurgery, Univ of Florida
1997	3mm Micro MLC M3 by BrainLab
2006	Frameless Radiosurgery by BrainLab

- Leksell L. The stereotaxic method and radiosurgery of brain.
  Acta Chir Scand ***1951***

- Blomgren H et al. Stereotactic high dose fraction radiotherapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients.
  Acta Oncol ***1995***

- Uematsu M et al. Focal, high dose and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience.
  Cancer ***1998***

HypoFractionation

The Redux..

Pretty well established

- **Brain**
  - Metastases
  - Benign lesions
  - AVM, Trigeminal Neuralgia
- **T1-T2 Lung Primaries**
- **Prostate:** Moderate Hypofractionation
- **Breast**
  - Hypo fractionation
  - Accelerated fractionation

HypoFractionation

Pretty well established

- **Oligo mets**
  - **Lung**
  - **Liver**
  - **Spine metastasis**

HypoFractionation

Being explored

- Prostate
  - Extreme HypoFractionation in Low risk Prostate
- Pancreas

HypoFractionation in CNS

Clinical Uses of Radiosurgery

- **Malignant**
  - Brain metastases
  - Primary brain tumors (Reirradiation)
- **Benign**
  - Arteriovenous malformations (AVM)
  - Acoustic Neuroma
  - Meningiomas
  - Trigeminal Neuralgia

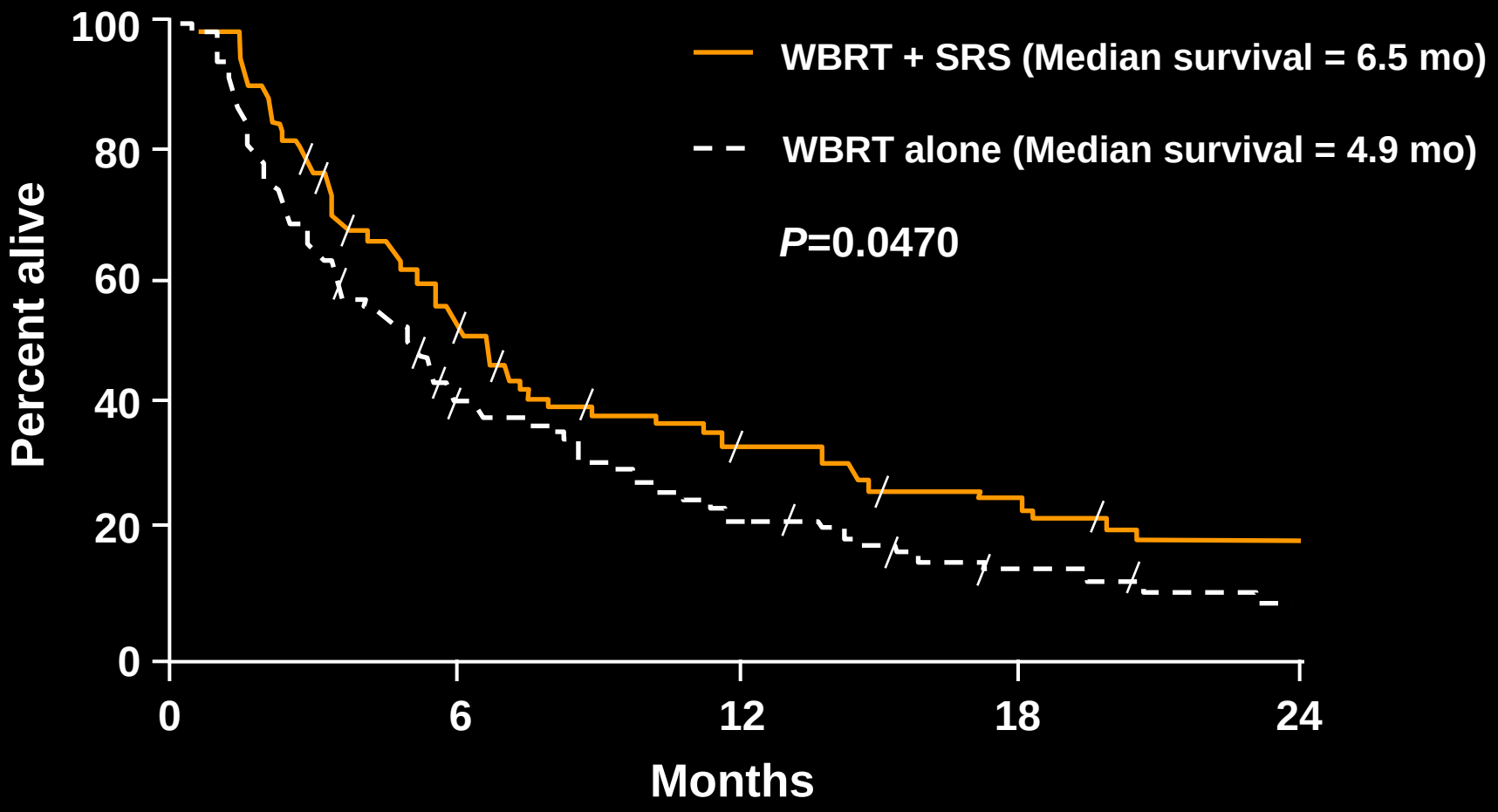
Rationale for Radiosurgery

If surgery works, so should radiosurgery

- Spherical/pseudospherical
- Generally non-infiltrative
- Most <4 cm
- Grey-White location (“non-eloquent”)
- Improved local control = better survival
- Need higher doses for local control

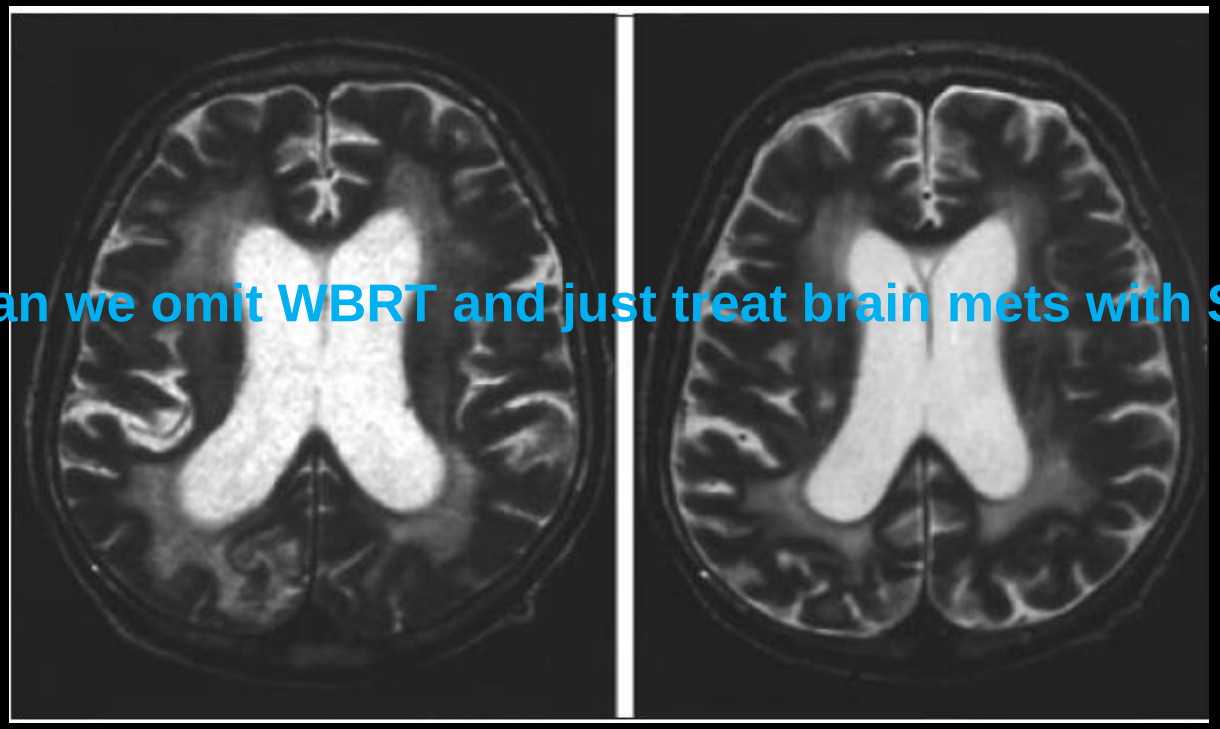
Phase III RTOG 9508 Single Mets

Adding Radiosurgery to WBRT improves survival for single mets



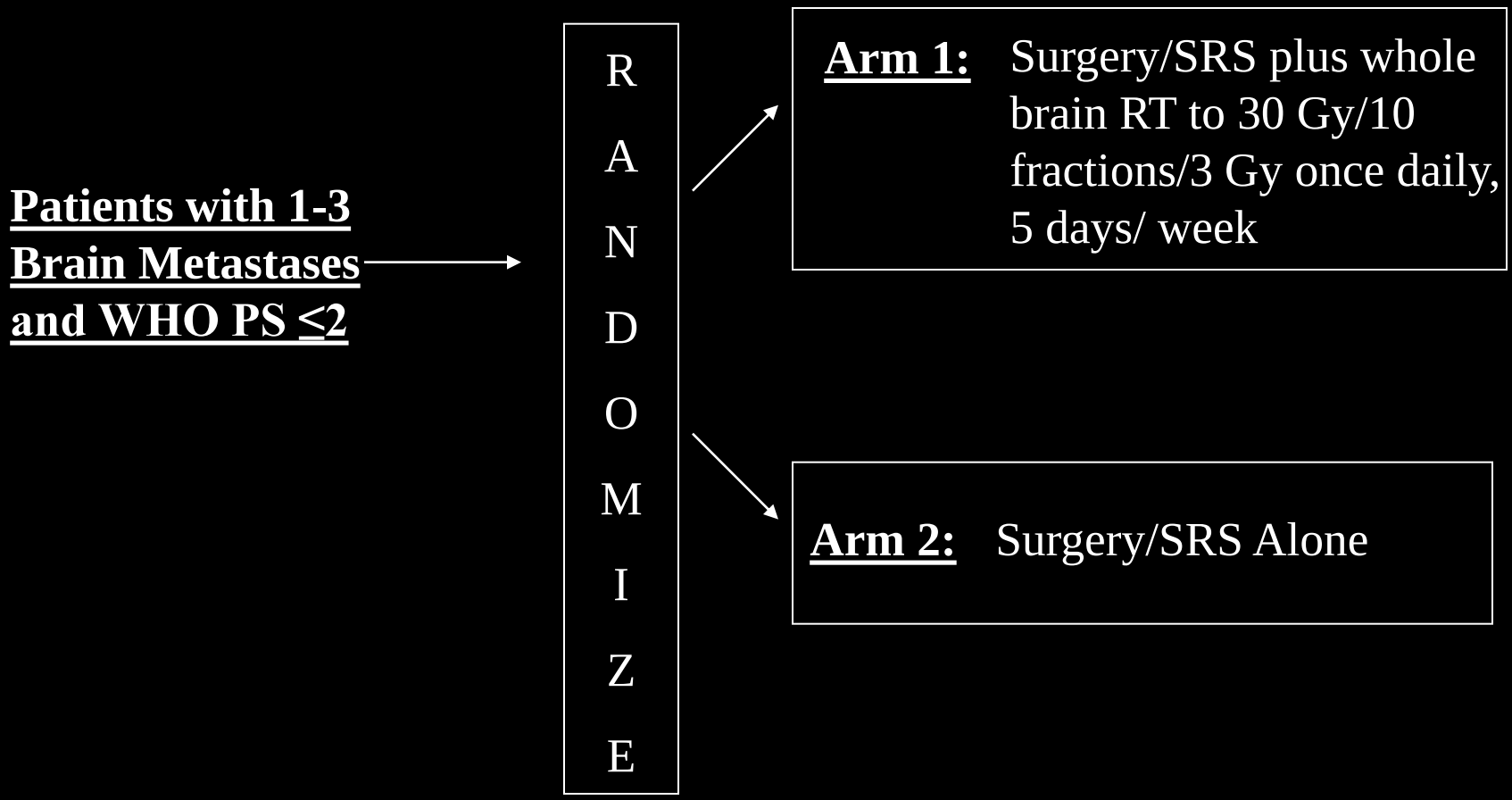
Andrews et al, Lancet, 2004

WBRT vs Radiosurgery?



Can we omit WBRT and just treat brain mets with SRS?

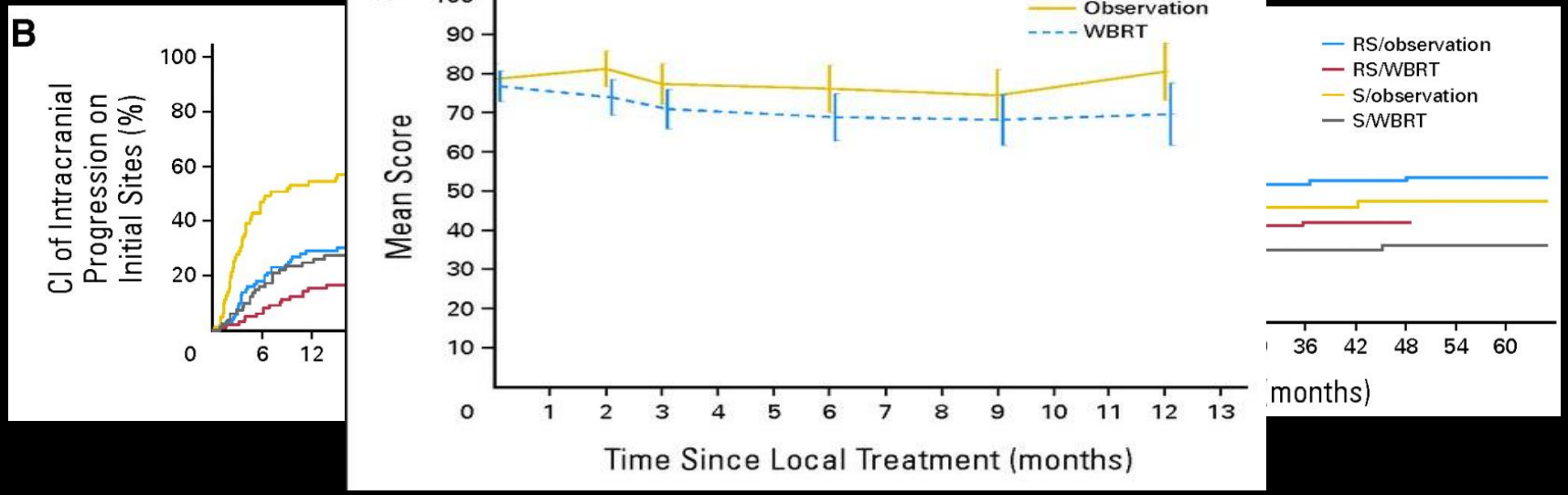
EORTC 22952-26001



Kocher et al, J Clin Oncol, 2011

EORTC 22952-26001

Relapse At T



d Brain Sites

- No Overall Survival Difference
- WBRT a/w greater decline in patient-reported cognitive functioning
- SRS/Surgery alone a/w high intracranial relapse rates→reduced with WBRT

Kocher et al, J Clin Oncol, 2011

Hypo Fractionation in Elderly GBM Patients

Table 3 Studies comparing standard and hypofractionated radiotherapy in elderly patients with GBM

Author Year	Age	*N*	OS (month) Std-RT	OS (month) Hypo-RT	Hazard ratio (95% CI)	*P*
Roa 2004[35]	≥60 years	100	5.1	5.6	0.89 (0.59–1.36)	0.57
Malmström 2012[23]	60–70 years	198	7.6	8.8	1.06 (0.73–1.54)	0.77
	>70 years	81	5.2	7.0	0.59 (0.37–0.93)	0.02
Minniti 2015[38]	≥65 years	329	12.0	12.5		0.500
	propensity matched analysis	90			0.93 (0.66–1.31)	0.70
Guedes de Castro* 2017[37]	≥65 years	61	6.2	6.8	NA	0.936
	≥65 years, KPS 50–70	40	6.7	7.5		0.904
	≥65 years, KPS >80	21	8.0	8.0		0.890

- **No survival difference**
- **Less neurotoxicity, steroid use and hospitalization with HF**

Spine Mets - Why Radiosurgery?

Advantages of SBRT

- Fewer fractions, more convenient, shorter break from chemotherapy
- Higher effective doses should be more effective and durable
- Less normal tissue irradiated
- Technically straight forward (accurate localization, no motion, etc.)
- Ability to retreat

But ……

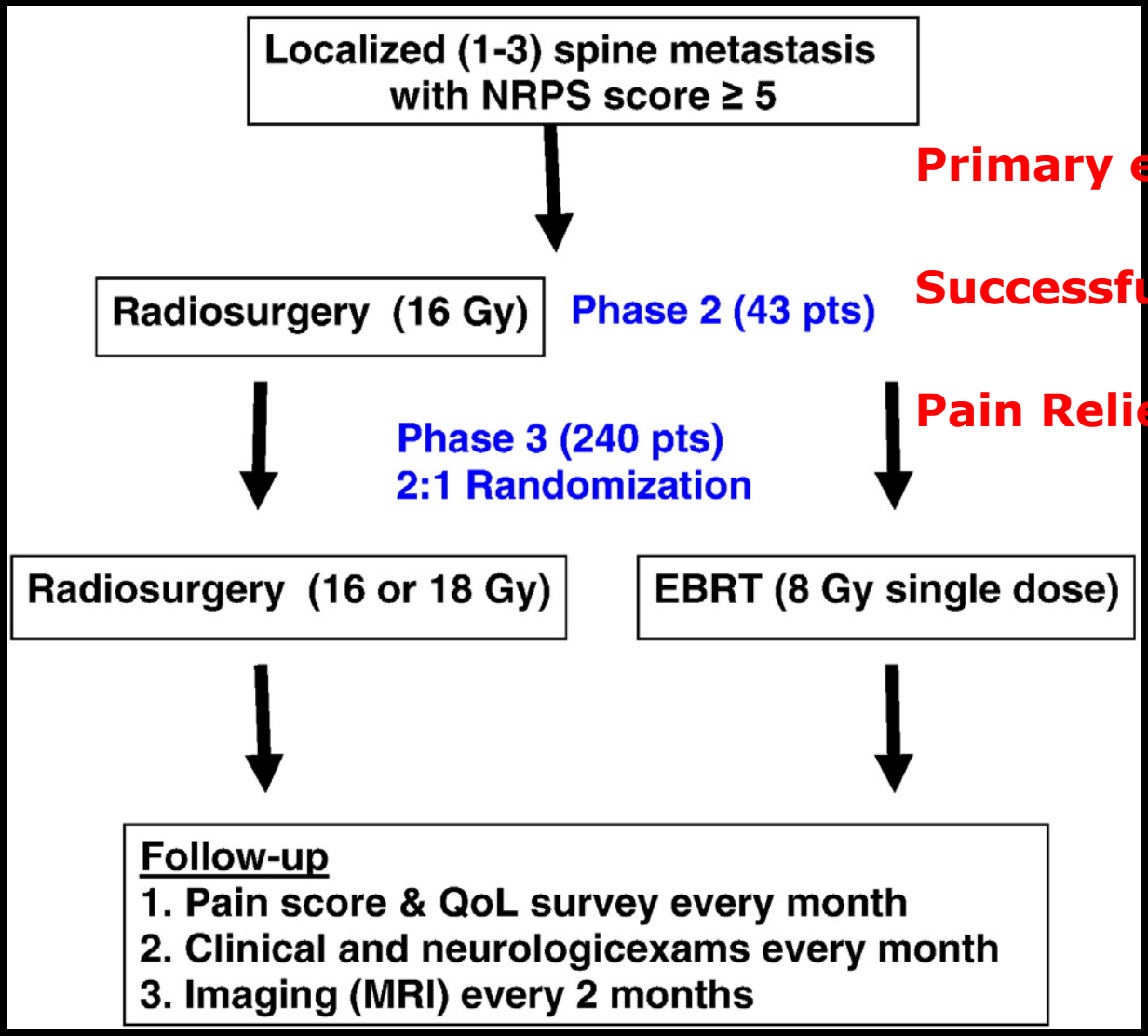
- Little margin for error, paucity of data on cord tolerance to single fraction
- Other potential complications include: mucositis, laryngitis, esophageal stricture, and compression fracture

Pain Relief

Rationale for RS:

- **More efficient pain relief in higher percentage of patients**
- **Longer duration of pain relief**
- **More rapid onset of pain relief**
- **Lower incidence of re-treatments**

RTOG 0631 –Phase II/III study of image-guided radiosurgery/ SBRT for localized spine metastases



Primary endpoint:

Successful delivery of SBRT (II)

Pain Relief at 3 months (III)

Target Volume include gross disease plus:

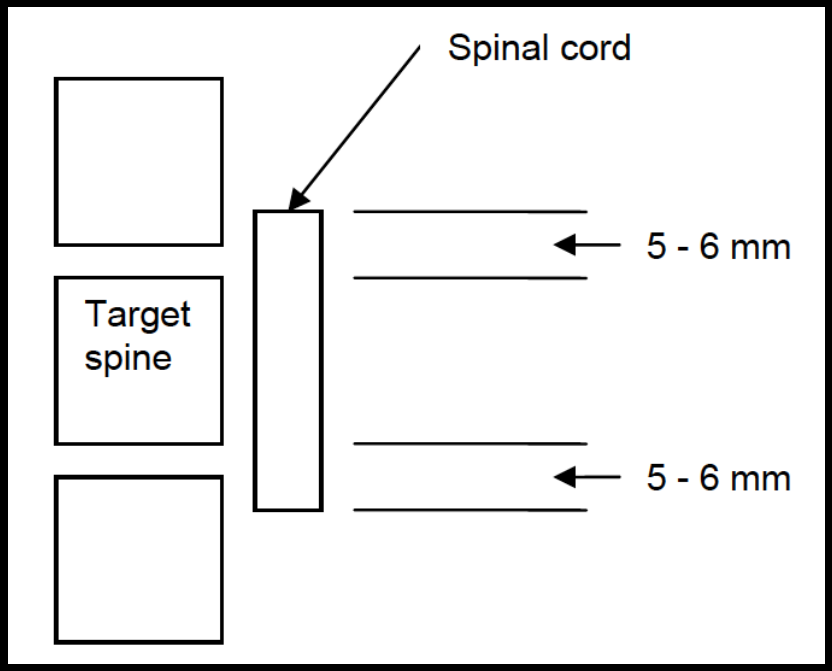
a) vertebral body,
b) lt/rt pedicles if paraspinal or epidural lesion is present

- **Spinal cord delineation requires CT, T1 MR and T2 MR**

- **Two cord volumes are required:**

  a) full cord - from 10 cm above superior extent of target to 10 cm below inferior extent of target

  b) partial cord - from 6 mm above superior extent of target to 6 mm below inferior extent of target



Dose constraints for the partial cord:

- **≤10% receives ≤10 Gy**
- **≤0.35 cc receives ≤10 Gy**
- **≤0.035 cc receives ≤14 Gy**

Cord constraints are absolute. If they cannot be met, treatment cannot be delivered

International Journal of Radiation Oncology biology • physics

www.redjournal.org

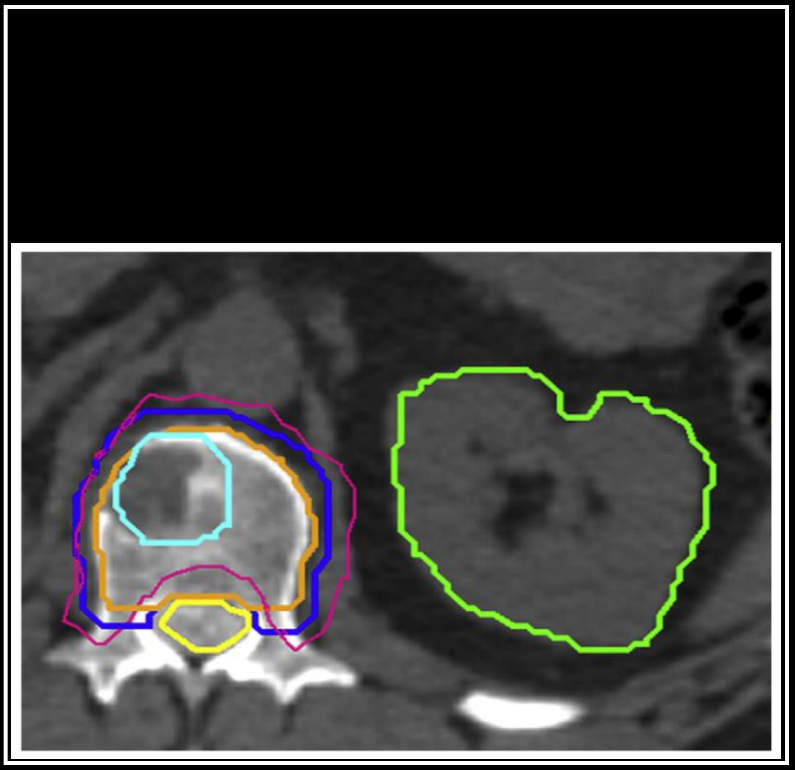
Clinical Investigation: Central Nervous System Tumor

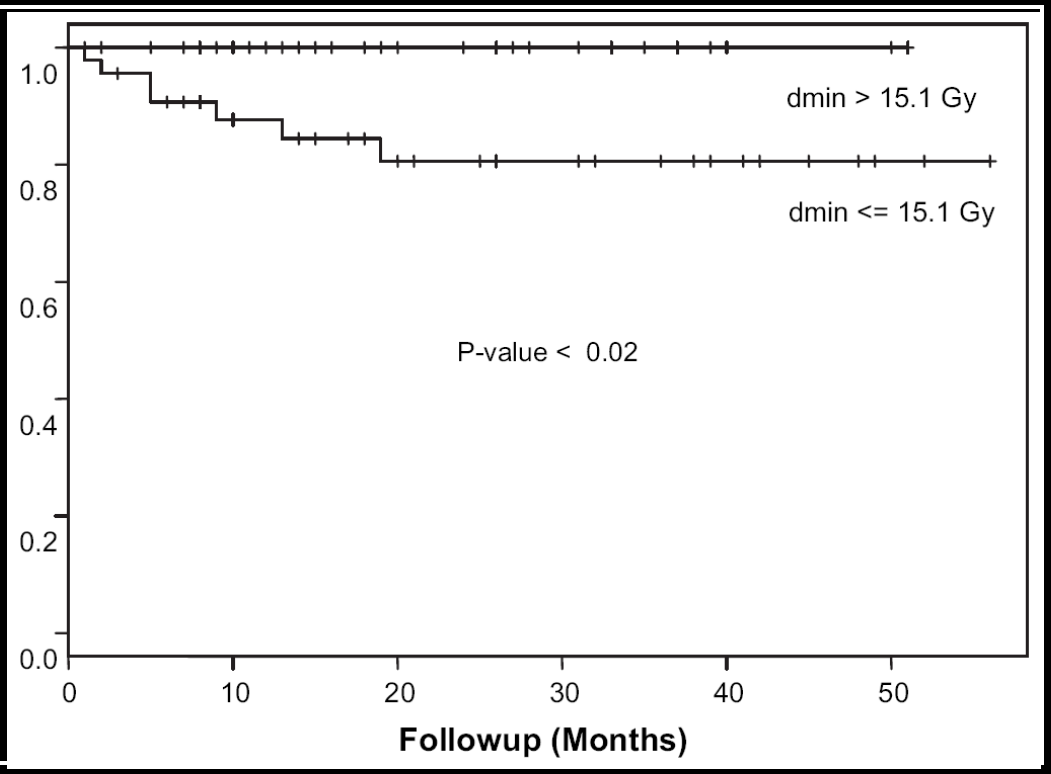
International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

Brett W. Cox, MD,[*,1] Daniel E. Spratt, MD,[*,1] Michael Lovelock, PhD,[†] Mark H. Bilsky, MD,[‡] Eric Lis, MD,[§] Samuel Ryu, MD,[‖] Jason Sheehan, MD,[¶] Peter C. Gerszten, MD, MPH,[**] Eric Chang, MD,[††] Iris Gibbs, MD,[‡‡] Scott Soltys, MD,[‡‡] Arjun Sahgal, MD,[§§] Joe Deasy, PhD,[†] John Flickinger, MD,[‖‖] Mubina Quader, PhD,[‖‖] Stefan Mindea, MD,[¶¶] and Yoshiya Yamada, MD[‡‡]

IJROBP 2012

Dose Response to Spine SRS





Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 4, pp. 1282–1287, 2010

0360-3016/$–see front matter

ELSEVIER

CORRELATION OF LOCAL FAILURE WITH MEASURES OF DOSE INSUFFICIENCY IN THE HIGH-DOSE SINGLE-FRACTION TREATMENT OF BONY METASTASES

D. Michael Lovelock, Ph.D.,* Zhigang Zhang, Ph.D.,† Andrew Jackson, Ph.D.,* Jennifer Keam, M.D.,‡ Justin Bekelman, M.D.,§ Mark Bilsky, M.D.,‖ Eric Lis, M.D.,¶ and Yoshiya Yamada, M.D.‡

Clinical practice of image-guided spine radiosurgery - results from an international research consortium

Matthias Guckenberger[1*], Reinhart A Sweeney[1], John C Flickinger[2,3], Peter C Gerszten[2,4], Ronald Kersh[5,6], Jason Sheeh
Radiation Oncology 2011, **6**:172

	UHW	UPMC	UofT	UVAMC	RSMC
Use of single fraction radiosurgery	No, all patients are treated with either five or ten fractions	Single fraction radiosurgery for 95% of the patients unless very near to spinal cord.	Majority is treated with two or three fractions and specific cases for single fraction	Majority is treated with a single fraction of radiosurgery, occasionally up to 3 fractions	No, majority are treated with three fractions with treatments given one week apart.
Criteria for selection of hypo-fractionated regimes	Selection of fractionation scheme based on life expectancy using the Mizumoto Score		Fractionated protocols in: 1. Epidural disease or large volume and no prior irradiation 2. Prior radiation	Fractionated protocols after prior radiation	If it represents the only site of disease, we use 30 Gy in 3
Schema 1: # fractions and single fraction dose	Good life expectancy: 30 Gy in 10: PTV-elective 48.5 Gy in 10: PTV -macroscopic *	16-24 Gy in 1; Most frequently 17 Gy in 1	20-24 Gy in 1; Most frequently 20 Gy in 1	18 to 24 Gy in 1; Most frequently 20 Gy in 1	24 Gy in 3
Schema 2: # fractions and single fraction dose	Intermediate life expectancy: 20 Gy in 5: PTV-elective 35 Gy in 5: PTV -macroscopic *		24 - 27 Gy in 2-3	24 Gy in 3	30 Gy in 3
Schema 3: # fractions and single fraction dose			30 Gy in 3 (for sarcomas)	18 Gy in 3	

Clinical practice of image-guided spine radiosurgery - results from an international research consortium

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Radiation Oncology 2011, **6**:172

			Tolerance doses Spinal Cord		
	Dosimetric parameter	**Single fraction**	**3 fractions**	**5 fractions**	**10 fractions**
UHW	Dmax to 0.1 cc			23.75 Gy	35 Gy
UPMC	Dmax	11 Gy	18 Gy		
UofT	Dmax	10 Gy	17.5 Gy	22 Gy	
UVAMC	D10	10 Gy	15 Gy	20 Gy	
RSMC	2 cc		18 Gy		
			Tolerance doses Cauda equina		
	Dosimetric parameter	**Single fraction**	**3 fractions**	**5 fractions**	**10 fractions**
UHW	Dmax to 0.1 cc			25 Gy	37.5 Gy
UPMC	Dmax	12 Gy	18 Gy		
UofT	Dmax	12 Gy	18 Gy	23 Gy	
UVAMC	D10	12 Gy	15 Gy	20 Gy	
RSMC	2 cc		24 Gy		

Clinical practice of image-guided spine radiosurgery

	UHW	UPMC	UofT	UVAMC	RSMC
Imaging modality, which is used for GTV definition	MRI and CT	MRI and CT, FDG-PET if available	MRI and CT	CT and MRI	CT, MRI and FDG-PET
Use of an anatomical target volume concept	Anatomical two dose-level target volume concept	Anatomical target volume concept	Anatomical target volume concept	Anatomical target volume concept	Anatomical target volume concept
GTV to PTV safety margin	3 mm	2 mm; 3 mm in the sacrum.	2 mm	2 mm	None
Protocol if PTV overlaps with the. spinal cord	Two dose-level approach; The OAR spinal cord is always in the PTV-elective and is always excluded from the higher dose PTV-macroscopic	PTV within 1 mm to the spinal cord is excluded from the PTV	PTV is limited by the cord or thecal sac for cauda equina	If this occurs, we either operate to resect part of the tumor or fractionate the radiation.	GTV drawn to edge of OAR
Treatment of the vertebra superior and inferior to the metastatic vertebra	No	No	No	No	No
Imaging modality for definition of the spinal cord	Spinal cord in MRI	Spinal cord in MRI	Spinal cord in MRI	Spinal cord in MRI	Spinal canal in CT
Delineation of the spinal cord in cranio-caudal direction	At least 1 level above and below PTV	1 level above and below PTV	At least 1 level above and below PTV	1 level above and below PTV	1 level above and below PTV
Safety margins around the spinal cord in axial directions	1 mm	1 mm	1.5 mm	No	2 mm anterior and 1 mm lateral
Delineation of the cauda equina	Thecal sac	Thecal sac	Thecal sac	Thecal sac	Thecal sac

Pain Relief
Conventional vs. SBRS

	Conventional RT (8 Gy)	SRS (10-25 Gy)
Pain Relief	55-70%	95%
Duration	2.5-5 months	13 months
Onset	3 weeks	14 days
Retreatment	25–30%	0-15%

HypoFractionation in Head & Neck Cancer

Glottic Cancer

Inferior control rates with CFRT, 70Gy/35#

Berwouts D, Head Neck 2016; Eskiizmir G, Oral Oncol 2016

Better control rates with altered fractionation schedules without increase in late effects

Mendenhall WM, IJROBP 2010; Ermis E, Radiat Oncol 2015

Simultaneous Hypo fractionated Accelerated Radiotherapy

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1333–1338, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.04.011

CLINICAL INVESTIGATION **Head and Neck**

MULTI-INSTITUTIONAL TRIAL OF ACCELERATED HYPOFRACTIONATED INTENSITY-MODULATED RADIATION THERAPY FOR EARLY-STAGE OROPHARYNGEAL CANCER (RTOG 00-22)

AVRAHAM EISBRUCH, M.D.,* JONATHAN HARRIS, M.S.,† ADAM S. GARDEN, M.D.,‡

Patients and Methods: Patients with oropharyngeal carcinoma Stage T1–2, N0–1, M0 requiring treatment of the bilateral neck were eligible. Chemotherapy was not permitted. Prescribed planning target volumes (PTVs) doses to primary tumor and involved nodes was 66 Gy at 2.2 Gy/fraction over 6 weeks. Subclinical PTVs received simultaneously 54–60 Gy at 1.8–2.0 Gy/fraction. Participating institutions were preapproved for IMRT, and quality assurance review was performed by the Image-Guided Therapy Center.

HypoFractionation in Breast Cancer

Hypofractionated Breast Irradiation

Clinical Experience

Whelan T, Ontario COG (1993-96)

Yarnold J, RMH/GOC Study (1986-98)

Yarnold J, START Trial A (1998-2002)

Yarnold J, START Trial B (1999-2001)

Long Term Results for Hypofractionated Radiation Therapy in Breast Cancer

Whelan TJ, NEJM 2010; 362(6): 513-20

1234 pts
Post BCS
Node negative
pT< 5cm
No nodal RT
No tumor bed boost

R
A
N
D
O
M
I
Z
E

50Gy/25#/35days

42.5Gy/16#/22days

Primary outcome – local control
Secondary outcome – overall survival, cosmesis

Whelan TJ cont..

Median follow-up 12years

Results –

- **No significant difference in local control, overall survival, excellent or good cosmesis**
- **No difference in cardiac disease related mortality**

Radiotherapy and Oncology 75 (2005) 9-17
www.elsevier.com/locate/radonline

Phase III randomised trial

Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial

John Yarnold[a,*], Anita Ashton[b], Judith Bliss[c], Janis Homewood[c], Caroline Harper[c], Jane Hanson[a], Jo Haviland[c], Søren Bentzen[d], Roger Owen[b]

[a]Academic Radiotherapy Department, The Royal Marsden Hospital, Surrey, UK, [b]Department of Oncology, Gloucestershire Oncology Centre, Cheltenham, UK, [c]Clinical Trials and Statistics Unit, Institute of Cancer Research, Surrey, UK, [d]Human Cancer Biology and Informatics, Gray Cancer Institute, Northwood, UK

Reliable estimate of α/β for late changes in breast appearance

Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial

J Roger Owen, Anita Ashton, Judith M Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Joanne Haviland, Soren M Bentzen, John R Yarnold

The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

The START Trialists' Group*

Lancet Oncol 2008

2236 pts

pT1-3 pN0-1

Nodal RT

Boost 10Gy/5#

5.1yr f/u

End Point
Loco-regional control

RANDOMIZE

50Gy/25#/5wks

41.6Gy/13#/3.2Gy fraction

39Gy/13#/3Gy fraction

Similar control rates

Late effects lower in 39Gy arm

α/β for tumor control 4.6Gy

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

The START Trialists' Group*

Lancet 2008; 371: 1098-107

n=2215
pT1-3a, pN0-1, M0

RANDOMIZE

50Gy/25#, 2Gy/#over 5wks
N=1105

40Gy/15#, 2.67Gy/# over 3wks
N=1110

End points
Locoregional tumor relapse,
Late normal tissue effects
QOL

Median follow-up 6yrs
No difference in locoregional control
Lower rates of late adverse events after 40Gy

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy:
It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT).
Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons.
Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation:
Target definition is the breast tissue in entirety. The whole breast should receive a dose of 45–50.4 Gy in 25–28 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred). All dose schedules are given 5 days per week. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.

Regional Nodal Radiation:
Target delineation is best achieved by the use of CT-based treatment planning. For the paraclavicular and axillary nodes, prescription depth varies based on the patient anatomy. For internal mammary node identification, the internal mammary artery and vein can be used as a surrogate for the nodal location (as the nodes themselves are not usually visible on planning imaging). Based on the post-mastectomy radiation randomized studies and recent trials, radiation therapy of the internal mammary lymph nodes should be strongly considered when delivering regional nodal irradiation. CT treatment planning should be utilized when treating the internal mammary lymph nodal volume to evaluate dose to normal tissues, especially the heart and lung, and dose constraints respected. Dose is 46–50 Gy in 23–25 fractions to the regional nodal fields. All dose schedules are given 5 days per week.

Accelerated Partial Breast Irradiation (APBI):
Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. The NCCN panel accepts the updated 2016 version of the ASTRO APBI guideline, which now defines patients "suitable" for APBI to be one of the following: 1) 50 years or older

HypoFractionation in Lung Cancer

SBRT vs Surgery

Surgery Versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer: Who's Down for the Count?

Robert D. Timmerman, *Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX*

- **Safer – fewer complications than resection**
- **Less invasive – better comfort, faster RTW**
- **Faster – three 1-2 hour treatment sessions**
- **Efficacy – better than standard RT; surgery?**
- **Less expensive – more cost-effective?**

Tumour Control Rates : Various Studies

From RTOG 0618

Author	Treatment	Primary Tumor Control
North America/Europe		
Timmerman, 2006	20-22 Gy X 3	95% (2+ years)
Bauman, 2006	15 Gy X 3	80% (3 years)
Fritz, 2006	30 Gy X 1	80% (3 years)
Nyman, 2006	15 Gy X 3	80% (crude)
Zimmermann, 2005	12.5 Gy X 3	87% (3 years)
Timmerman, 2003	18-24 Gy X 3	90% (2 years)
Asia		
Xia, 2006	5 Gy X 10	95% (3 years)
Hara, 2006	30-34 Gy X 1	80% (3 years)
Onimaru, 2003	6 Gy X 8	70% (3 years)
Nagata, 2005	12 Gy X 4	94% (3 years)
Onimaru, 2003	7.5 Gy X 8	100% (3 years)

Phase III Data

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

Lancet Oncol 2015; 16: 630–37

Published Online May 14, 2015 http://dx.doi.org/10.1016/S1470-2045(15)70168-3

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on August 31, 2015

See Comment page 597

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Summary

Background The standard of care for operable, stage I, non-small-cell lung cancer (NSCLC) is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but two independent, randomised, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) closed early due to slow accrual. We aimed to assess overall survival for SABR versus surgery by pooling data from these trials.

Methods Eligible patients in the STARS and ROSEL studies were those with clinical T1–2a (<4 cm), N0M0, operable NSCLC. Patients were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling. We did a pooled analysis in the intention-to-treat population using overall survival as the primary endpoint. Both trials are registered with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986).

Findings 58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery). Median follow-up was 40·2 months (IQR 23·0–47·3) for the SABR group and 35·4 months (18·9–40·7) for the surgery group. Six patients in the surgery group died compared with one patient in the SABR group. Estimated overall survival at 3 years was 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0·14 [95% CI 0·017–1·190], log-rank p=0·037). Recurrence-free survival at 3 years was 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI 0·21–2·29], log-rank p=0·54). In the surgery group, one patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) patients in the SABR group had grade 3 treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or cough, and one [3%] fatigue and rib fracture). No patients given SABR had grade 4 events or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [15%] patients), and lung infections (two [7%]).

Interpretation SABR could be an option for treating operable stage I NSCLC. Because of the small patient sample size and short follow-up, additional randomised studies comparing SABR with surgery in operable patients are warranted.

PRINCIPLES OF RADIATION THERAPY (1 of 10)

Early-Stage NSCLC (Stage I, selected node negative Stage IIA)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.[6-11]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.[12-13]
- A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.[14] This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives.[15-17]
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC* in this section).

Summary

- **SBRT is the *de facto* standard for patients with medically *in*operable stage I NSCLC**
- **SBRT should become *a* standard for all patients with stage I NSCLC**
  - **Equivalent cancer-specific outcomes in controlled comparisons with surgery**
  - **No risk of operative mortality**
  - **Low risk of overall toxicity**
  - **Cheaper?**

HypoFractionation in Liver Tumors

SBRT in Liver Tumors

HCC is 5th most common malignancy worldwide

50% of colorectal cancers develop liver metastases, 15-25% operable

Scope -
Liver Metastasis: Oligometastatic disease, minimal extra-hepatic disease

HCC: Bridge to transplant, combination with Sorafenib or TACE
or recurrent tumors

Results of Conventional RT in HCC

Series	Total Dose, Dose per Fraction	1-Year LC (%)	1-Year OS (%)
Ben-Josef et al[16]	40-90 Gy in 1.5 Gy twice daily	81	57
Mornex et al[18]	36-66 Gy in 2-Gy fx	78	NA
Liu et al[22]	40-60 Gy	61	61
Liang, et al[21]	38-68 Gy in mostly 4- to 6-Gy fx	69 at 3 mo	65
Kim et al[49]	44-54 Gy in 2- to 3-Gy fx	54 CR+PR	43
Oh et al[50]		63 CR+PR	72
Seong et al[20]	25-60 Gy in mostly 1.8- to 5-Gy fx	NA	45
Seo et al[30]	61 Gy in 1.8-Gy fx in 85% of patients	Median TTP 4 mo	35

1 YEAR LC = 54-81%; 1 YEAR OS = 35-72%

RESULTS OF SBRT IN HCC

Table 2 Stereotactic Body Radiotherapy for Hepatocellular Carcinoma

Series	Pts	CP Class A (%)	Tumor Size (Diameter or Volume)	Total Dose/Number of Fractions	1-Year LC (%)	1-Year OS (%)
Mendez-Romero et al[26]	8	75	0.5-7.2 cm	37.5 Gy/3 for <4 cm 25 Gy/5 or 30 Gy/3 for ≥4 cm	75 (All failures 25 Gy)	75
Tse et al[27]	31	100	9-1913 cc	24-54 Gy/6	65	48
Cardenes et al[28]	17 (25 tumors)	35	2-6 cm	36-48 Gy/3 for CPA 36-42 Gy/3 or 40 Gy/5 for CPB	100	75
Goyal et al[51]	6	NA	5-22 cm 106-1268 cc	24-45 Gy/1-3	100	67
Seo et al[30]	38	89	11-464 cc	33-57 Gy/3-4	79	68
Kwon et al[29]	42	90	3-81.8 cc	30-39 Gy/3	72	93
Louis et al[31]	25	88	1.8-10 cm	45 Gy/3	95	79
Stenmark et al[52]	31	69	0.2-222.4 cc	Mostly 50 Gy/5 or 60 Gy/3	88	81

1 YEAR LC = 72-100%; 1 YEAR OS = 67-93%

SBRT LIVER – TOXICITIES

		INCIDENCE
1.	Radiation Induced Liver Disease (RILD)	1-2 %
2.	Soft tissue toxicity – Chest wall / Abdominal wall	0-1%
3.	Duodenal ulcer	1-2%
4.	Transient Rise in Liver Enzymes	

HypoFractionation in Prostate Cancer

Hypofractionated Radiotherapy

Randomized trials evaluating moderately hypofractionated radiotherapy for prostate cancer

Study	Study period	Eligibility	*N*	Total dose/dose per fx/# of fx	Median f/u, mo	5 y bDFS	≥Grade 2 late toxicity	
							GI	GU
Fox Chase [57]	2002–2006	High risk* (34%)	152	76 Gy/2 Gy/38	68	85%	18%	22%
		Low–intermediate risk (66%)	151	70.2/2.7 Gy/26		81%	23%	13%
Regina Elena [58,59]	2003–2007	High risk	85	80 Gy/2 Gy/40	70	79%	17%	16%
			83	62 Gy/3.1 Gy/20		85%	14%	11%
RTOG 0415 [60]	2006–2009	Low risk	547	73.8 Gy/1.8 Gy/41	71	76% (7 y)	3% (≥Gr 3)	5% (≥Gr 3)
			554	70 Gy/2.5 Gy/28		82% (7 y)	5% (≥Gr 3)	6% (≥Gr 3)
Dutch HYPRO [61]	2007–2010	Intermediate or high risk	410	78 Gy/2 Gy/39	60	77%	NR	NR
			410	64.6 Gy/3.4 Gy/19		80%		
CHHiP [62]	2002–2011	Low (15%), intermediate (73%), or high (12%) risk	1,065	74 Gy/2 Gy/37	62	88%	1%	No difference
			1,074	60 Gy/3 Gy/20		91%	2%	
			1,077	57 Gy/3 Gy/19		86%	2%	

bDFS = biochemical disease-free survival; f/u = follow-up; fx = fraction; NR = not reported.

*High-risk defined as PSA > 20, Gleason score 8–10; ≥ cT3, or Gleason score 7 ≥ 4 biopsy cores.

Moon DH et al, Urol Oncol 2017

SBRT

Extreme Hypofractionation

Select studies evaluating stereotactic body radiation therapy for prostate cancer

Study	Study period	Eligibility	*N*	Total dose/ # of fx (delivery technique)	Median f/u, mo	bDFS	≥Grade 2 late toxicity	
							GI	GU
Madsen et al. [65] (phase I/II)	2000–2004	Low risk	40	35.5 Gy/5 (3DCRT)	41	90% (4 y)	8%	20%
Loblaw et al. [66] (phase I/II)	2006–2008	Low risk	84	35 Gy/5 (IMRT)	55	98% (5 y)	8%	5%
King et al. [67] (phase I/II)	2003–2009	Low risk	67	36.25 Gy/5 (CyberKnife)	32	94% (4 y)	2%	9%
McBride et al. [68] (phase I)	2006–2008	Low risk	45	36.25–37.5/5 (CyberKnife)	44	97.7% (3 y)	12%	20%
Bolzicco et al. [69] (phase I/II)	2006	All groups	100	35 Gy/5 (CyberKnife)	36	94.4% (3 y)	1%	4%
Katz and Kang [70,71] (retrospective)	2006–2010	Low risk	324	35–36.25 Gy/5 (CyberKnife)	72	96% (7 y)	4%	11%
		Intermediate risk	153			89%		
Chen et al. [72] (retrospective)	2008–2010	All groups	100	35–36.25 Gy/5 (CyberKnife)	28	99% (2 y)	1%	31%
Oliai et al. [73] (retrospective)	2007–2010	Low risk	36	35–37.5 Gy/5 (CyberKnife)	31	100% (3 y)	9%	32%
		Intermediate risk	22			95%		
		High risk	12			77%		
Lukka et al. [76] (phase II)	NR	Low risk	119	36.25 Gy/5	20	NR	≥Grade 3 acute GI/GU: 1.7% (5 fx) vs. 2.8% (12 fx) ≥Grade 3 late GI/GU: 0.8% (5 fx) vs. 1.7% (12 fx)	
			121	51.6 Gy/12 (CyberKnife or IMRT)				

bDFS = biochemical disease-free survival; fx = fraction; NR = not reported.

Fractionation Schemes

- **Moderate Hypofractionation**
  - 51Gy to 72Gy Total dose
  - 2.5Gy to 3.64Gy Dose/Fraction
  - 14-30 fractions over 19-45 days

- **Extreme Hypofractionation**
  - 33.5Gy to 50Gy Total dose
  - 6.7Gy to 10Gy Dose/Fraction
  - 4-5 fractions over 4-29 days

Washington University

70Gy/28fxn/2.5Gy

36.25Gy/5fxn/7.25Gy

Clemente et al, IJROBP 2014

- Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.

Cost-Effective RT!!

Advances in Radiation Oncology (2017) 2, 249–258

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ROI Value of RT Publication Award Winner

Long-term economic value of hypofractionated prostate radiation: Secondary analysis of a randomized trial

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Abstract

Purpose: Moderately hypofractionated intensity modulated radiation therapy (HIMRT) for prostate cancer shortens the treatment course while providing outcomes comparable with those of conventional intensity modulated radiation therapy (CIMRT). To determine the long-term economic value of HIMRT, including the costs of managing long-term radiation toxicities, a cost minimization analysis compared CIMRT with dose-escalated HIMRT using patient-level data from a randomized trial.

Methods and materials: Men with localized prostate cancer were randomized to CIMRT (75.6 Gy in 42 fractions over 8.4 weeks) or HIMRT (72 Gy in 30 fractions over 6 weeks). A decision tree modeled trial probabilities of maximum late bowel and urinary toxicities using patient-level data with a median follow-up of 6 years. Costs were estimated from the healthcare perspective using the 2014 national reimbursement rates for services received. Patient-level institutional costs, adjusted to 2014 dollars, verified reimbursements. A sensitivity analysis assessed model uncertainty.

Results: The cost for HIMRT and toxicity management was $22,957, saving $7,000 compared with CIMRT ($30,241). CIMRT was the common factor among the 5 most influential scenarios that contributed to total costs. Toxicity represented a small part (<10%) of the average total cost for patients with either grade 2-3 bowel toxicity or grade 2-3 urinary toxicity. However, toxicity management reached up to 26% of the total cost for patients with both high-grade bowel and urinary toxicities. There was no threshold at which CIMRT became the less costly regimen. Institutional costs confirmed the economic value of HIMRT ($6,000 in savings).

Conclusions: HIMRT is more cost-efficient than CIMRT for treating prostate cancer, even when taking into account the costs related to late radiation toxicities. HIMRT enhances the value of prostate radiation when compared with CIMRT.

J Natl Cancer Inst. 2017 Nov 1;109(11). doi: 10.1093/jnci/djx068.

Cost-effectiveness Analysis Comparing Conventional, Hypofractionated, and Intraoperative Radiotherapy for Early-Stage Breast Cancer.

Deshmukh AA[1], Shirvani SM[1], Lal L[1], Swint JM[1], Cantor SB[1], Smith BD[1], Likhacheva A[1].

Author information

Abstract

BACKGROUND: Early-stage breast cancer is among the most prevalent and costly malignancies treated in the American health care system. Adjuvant radiotherapy after lumpectomy represents a substantial portion of breast cancer expenditures. The relative value of novel radiotherapeutic approaches such as intraoperative radiotherapy (IORT) and hypofractionated whole breast irradiation (HF-WBI) compared with conventionally fractionated whole breast irradiation (CF-WBI) is unknown. Therefore, we used prospectively collected outcomes from randomized clinical trials (RCTs) to compare the cost-effectiveness of these approaches.

METHODS: We constructed a decision-analytic model that followed women who were treated with lumpectomy for early-stage breast cancer. Recurrence, mortality, complication rates, and utilities (five-year radiation-associated quality of life scores), were extracted from RCTs. Costs were based on Medicare reimbursement rates. Cost-effectiveness from societal and health care sector perspectives was estimated considering two scenarios-the first assumes that radiation-associated disutility persists five years after treatment, and the second assumes that disutility discontinues. Lifetime outcomes were summarized using incremental cost-effectiveness ratios (ICERs). Deterministic and probabilistic sensitivity analyses evaluated the robustness of the results.

RESULTS: HF-WBI dominated CF-WBI (ie, resulted in higher quality-adjusted life-years [QALYs] and lower cost) in all scenarios. HF-WBI also had a greater likelihood of cost-effectiveness compared with IORT; under a societal perspective that assumes that radiation-associated disutility persists, HF-WBI results in an ICER of $17 024 per QALY compared with IORT with a probability of cost-effectiveness of 80% at the $100 000 per QALY willingness-to-pay threshold. If radiation-associated disutility is assumed to discontinue, the ICER is lower ($11 461/QALY), resulting in an even higher (83%) probability of relative cost-effectiveness. The ICER was most sensitive to the probability of metastasis and treatment cost.

CONCLUSIONS: For women with early-stage breast cancer requiring adjuvant radiotherapy, HF-WBI is cost-effective compared with CF-WBI and IORT.

Potential Perils..

- Patient selection
- Accurate delineation of target and OAR
- Lack of understanding of tolerance to hypo fractionation
- Heterogeneity of planning algorithms
- QA/QC

Why No Pencil Beam Algorithms?

Stereotactic body radiation therapy: The report of AAPM Task Group 101

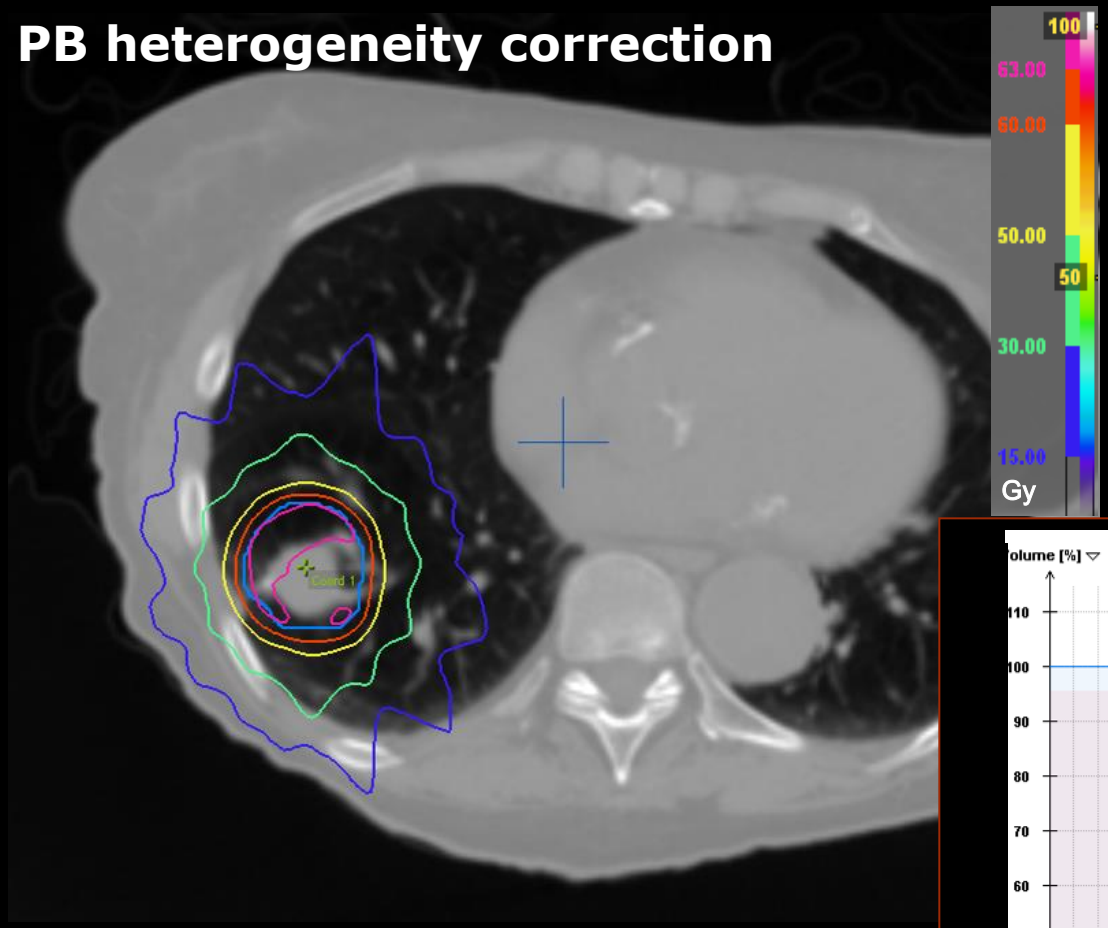
VI.B. Problems associated with small-field heterogeneity calculations

Head-and-neck and lung tumors are often situated at air-tissue interfaces. The effects of transient electronic disequilibrium and increased lateral electron range in air will result in an important reduction in the central axis dose beyond the cavity and potentially an underdosage of the tumor.[231–233]

Recommendation: Algorithms that account for 3D scatter integration such as convolution/superposition have been found (including by the RPC study) to perform adequately in most clinical situations, including (in many cases) circumstances where there is a loss of electronic equilibrium such as the lung tissue interface or tumor margin in low-density medium. Calculation algorithms accounting for better photon and electron transport such as Monte Carlo would be ideal for the most demanding circumstances, such as a small lesion entirely surrounded by a low-density medium. However, at the time of this publication, Monte Carlo calculations are not yet widely available in the clinic. Pencil-beam algorithms accounting for only 1D scatter corrections are not recommended for accurate estimate of the dose in such tumors and in general for any lung tumors.[237] For site-specific recommendations, the clinical user should refer to Report 85 of Task Group 65.[236]

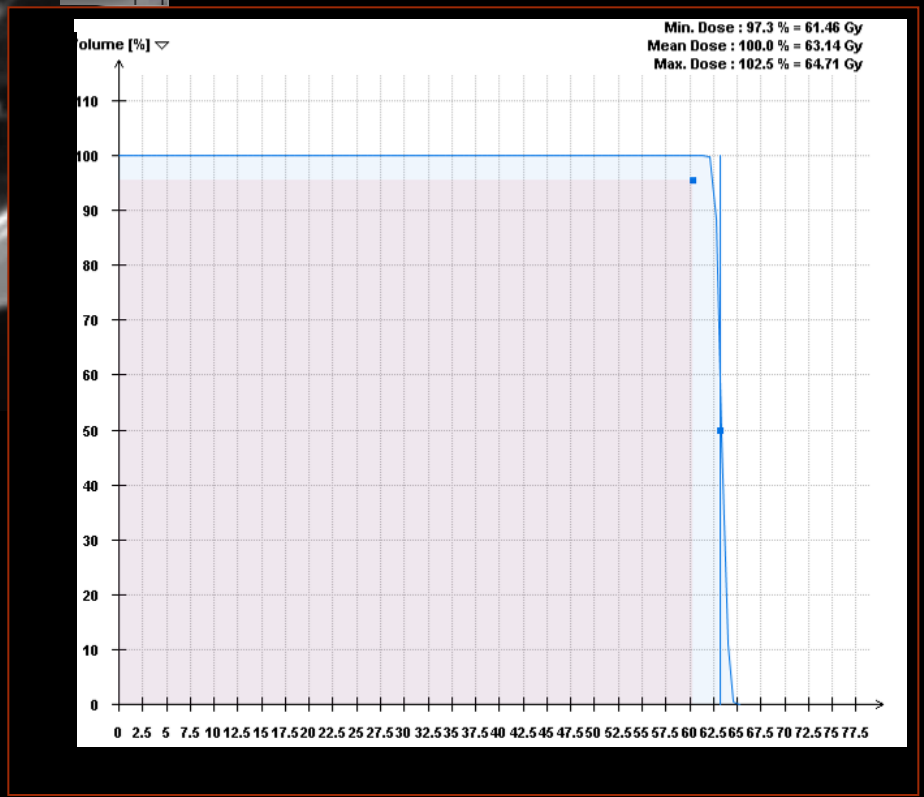
What happens if you use pencil beam?

PB heterogeneity correction



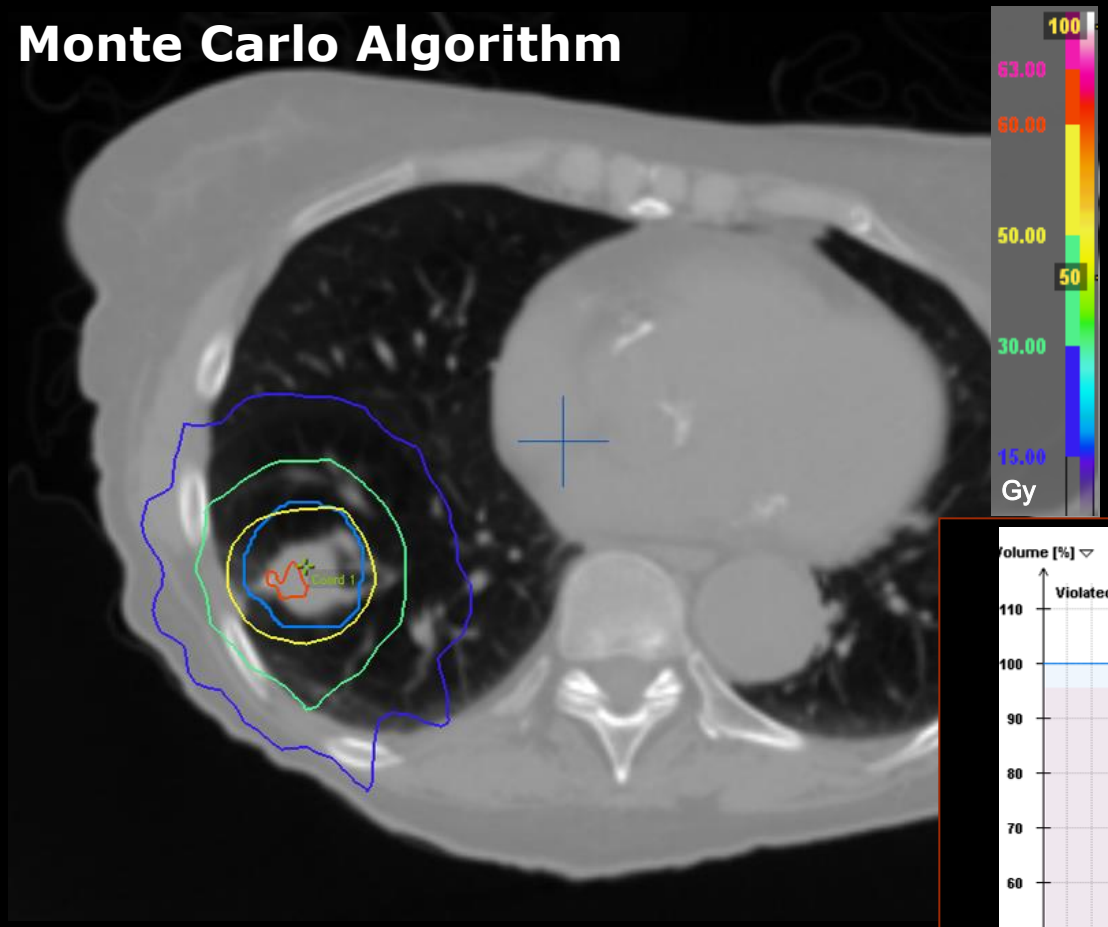
Grossly overestimates dose

Incorrect dose distribution and DVH



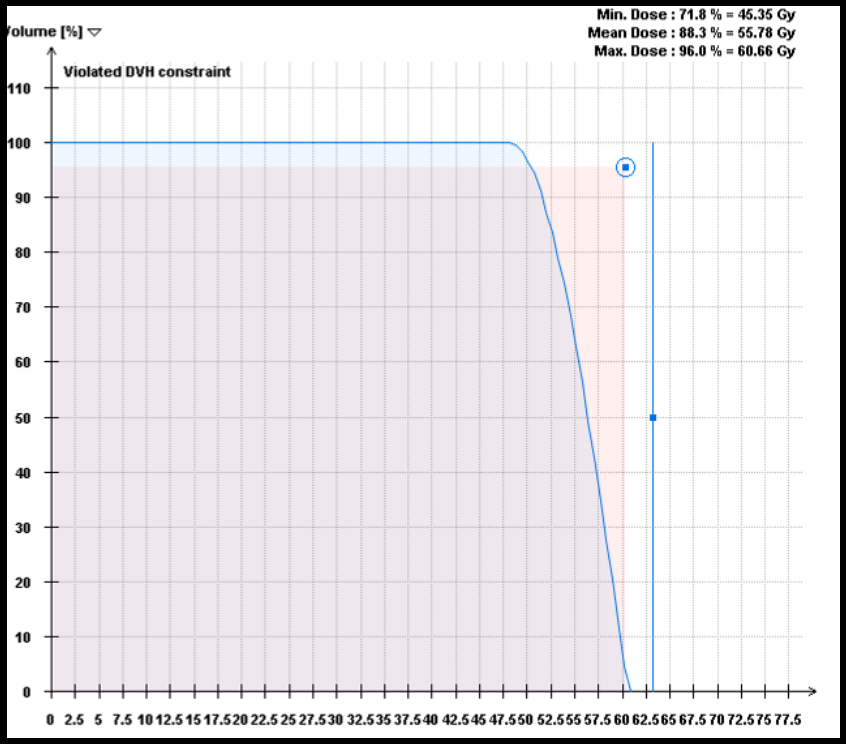
What happens if you use pencil beam?

Monte Carlo Algorithm



Grossly overestimates dose

<u>Actual</u> dose distribution and DVH



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ASTRO

TARGETING CANCER CARE

Five Things Physicians and Patients Should Question

1

Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules.

- Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5–6 weeks, often followed by 1–2 weeks of boost therapy.
- Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (approximately 4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.

10

Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

- Primary analyses of randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors.
- The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small-cell lung cancer.
- Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the highest quality of life without a detriment in overall survival. Patients should discuss these options with their radiation oncologist.

Trials in Progress..

PACE Trial

A trial comparing surgery, conventional radiotherapy and stereotactic radiotherapy for localised prostate cancer

UK FAST Trial

5 fractions of 5.7 and 6Gy vs. 25 fractions of 2Gy

FAST Forward Trial

3 weeks of whole breast irradiation vs. one week course of curative radiation

HYPO-RT-PC Trial

Extreme Hypofractionation vs CFRT in Intermediate Risk Prostate cancer

HypoFractionation

- Patient convenience
- Cost savings

Requirements

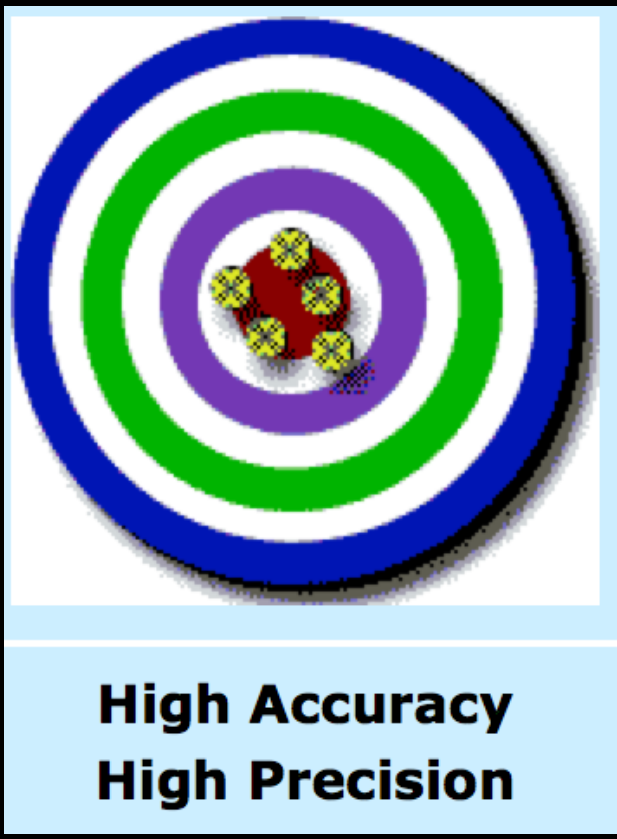
- Same or potentially higher control rates
- Same or lower complications

HypoFractionation

TECHNICAL EXCELLENCE

- Accuracy
- Precision

- **NOT FORGIVING AT ALL**
  - HIGH DOSES
  - SMALL NUMBER OF FRACTIONS



High Accuracy
High Precision

Take Home Points

- Excellent treatment approach for a number of tumors
- Short treatment course
- Acceptable toxicities
- Patient Selection and Expertise

I never think of the FUTURE – it comes soon enough

- Albert Einstein

Is Hypo Fractionation is the future?

Hypo Fractionation is the future