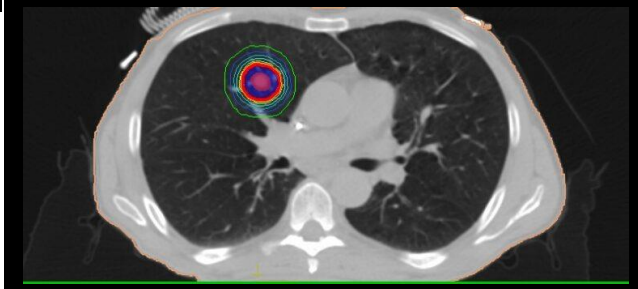

The Physics of Hypofractionation & SRS/SBRT

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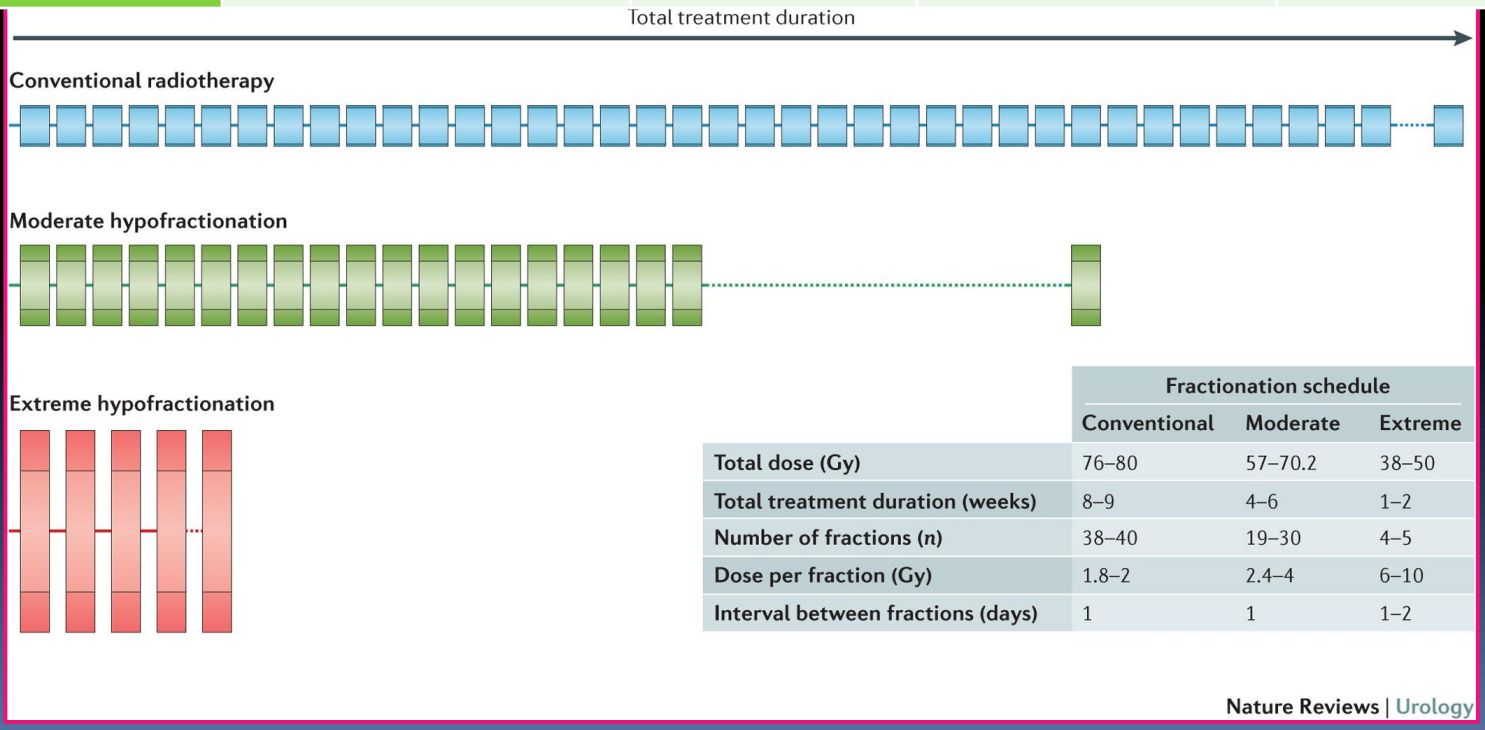
Learning Objectives: Hypofractionation & SRS/SBRT

- ✓ Technical issues
- ✓ Technical reports / Protocols
- ✓ Quality assurance
- ✓ Safety aspects
- ✓ Limitation

Hypo fractionation

Parameter Fractionation	N (No of Fractions)	D (Total Dose)	d (Dose / Fraction)	X (Fraction / week)
CONVENTIONAL	30-35	60-70	180-210	5
HYPO (Moderate)	↓	↓	↑	↓
HYPO (Extreme)	↓↓	↓↓	↑↑	↓↓
HYPER	↑	↑	↓	↑



	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (*n*)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

Nature Reviews | Urology

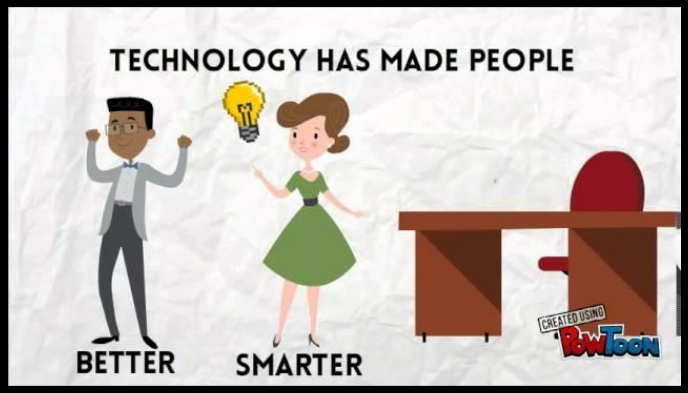
Hypo fractionation : Advantages

Merits	Demerits
Cost reduction	Late Tissue toxicity
Convenience	Cosmesis
Radiobiology	Radiobiology

Hypo fractionation : Overcome limitations

- ✓ Lesser resources
- ✓ Old patients
- ✓ Problems in mobility
- ✓ Complicated set ups
- ✓ Palliations
- ✓ Radiobiological limitations

Hypo fractionation : Modern technical advantages



- ✓ High-energy beams (MeV energy range)
- ✓ Achieving high degree target conformity
- ✓ Sparing normal tissues
- ✓ Maintaining precession in delivery

Hypo fractionation : Professionals

- ✓ Radiation Oncologist
- ✓ Radiological Physicist
- ✓ Mould room Technologist
- ✓ Imaging Technologist
- ✓ Dosimetrist
- ✓ Therapy Technologist

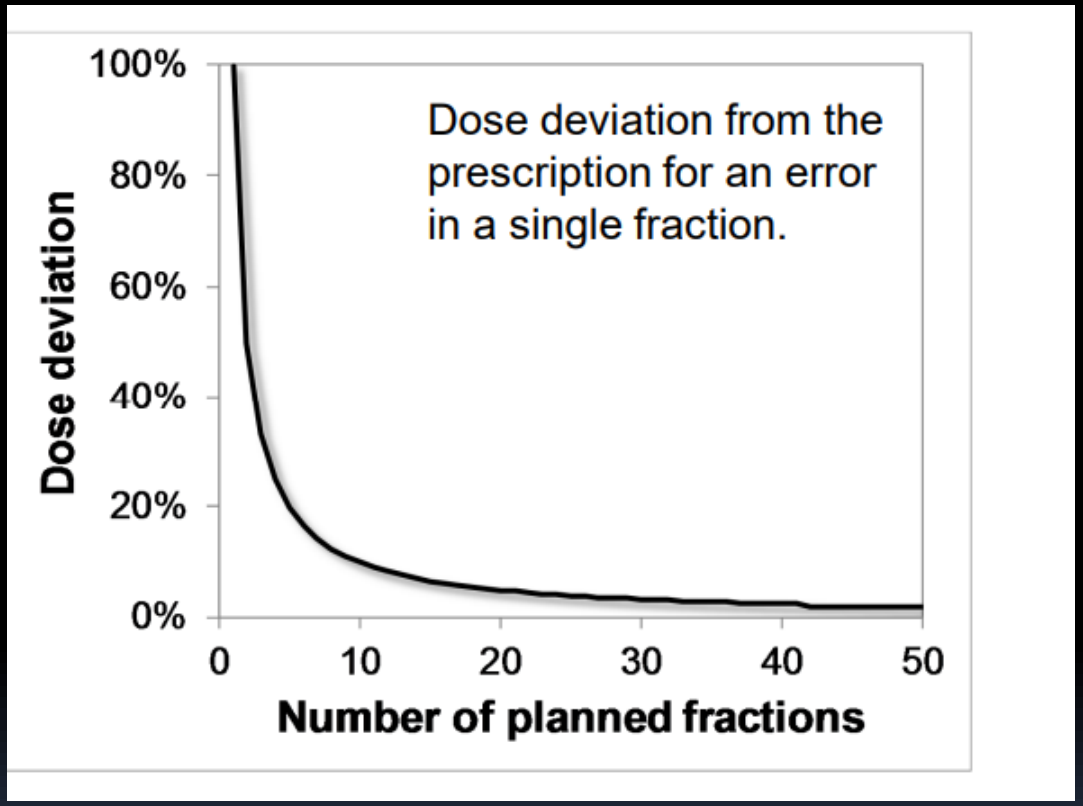
Hypo fractionation : Patients selection

- ✓ Justified treatment
- ✓ Cooperative
- ✓ Can tolerate prolonged treatment
- ✓ Unavoidable patients issues
- ✓ Non emergency cases

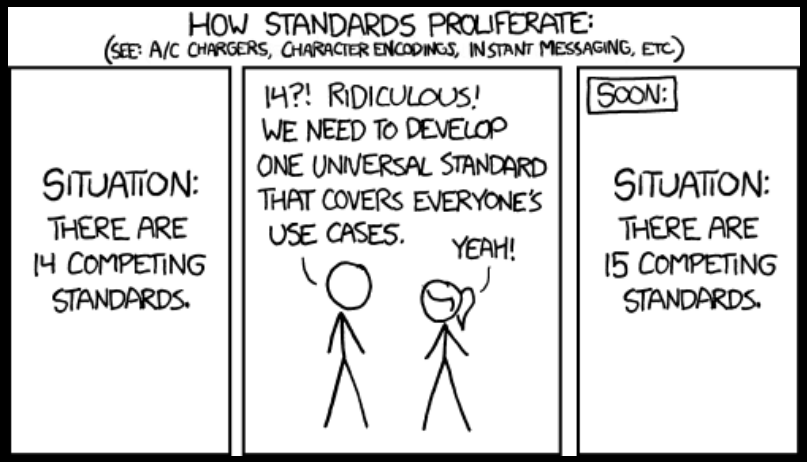
Hypo fractionation : Equipment

- ✓ High degree patient setup and immobilization devices.
- ✓ 3D,4D Imaging equipment.
- ✓ High performing Treatment planning software and hardware.
- ✓ Compatible treatment verification /QA equipment.
- ✓ High Precision radiation delivery equipment.

Hypo fractionation : Challenges

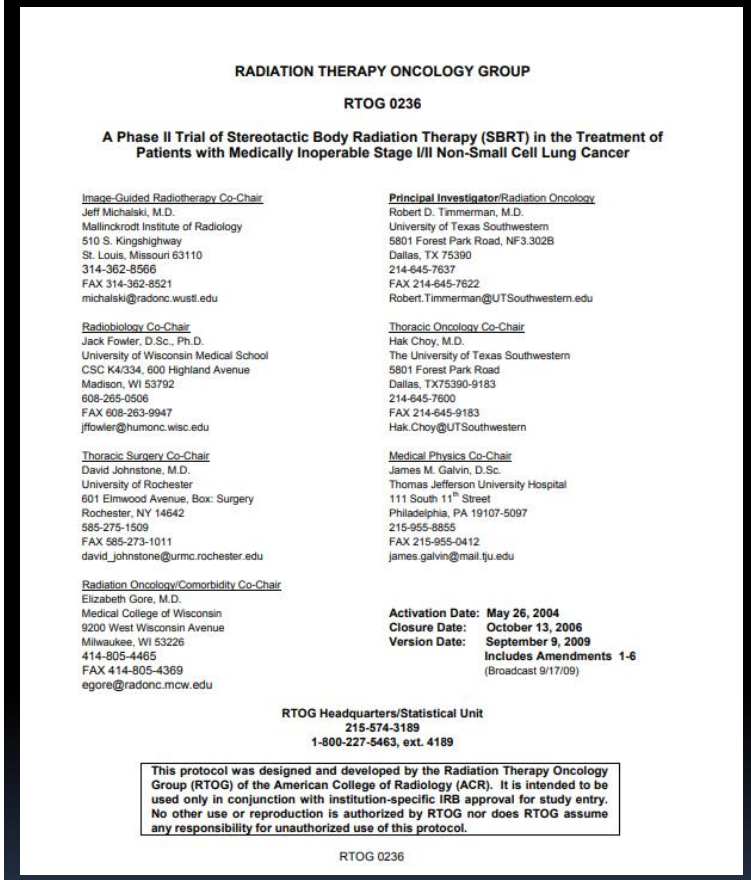


Hypo fractionation : Standards / Protocols



- ✓ Timmerman Sheet (RTOG 0236) : 2004
- ✓ AAPM TG-101 :2010
- ✓ NRG/RTOG protocols (RTOG 0915) : 2015
- ✓ HyTEC : 2020

Hypo fractionation : Timmerman Sheet (RTOG 0236)



RADIATION THERAPY ONCOLOGY GROUP

RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

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Version Date: September 9, 2009
Includes Amendments 1-6
(Broadcast 9/17/09)

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2004

Objective: Determine if radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable treatment outcome in patients with medically inoperable early stage non-small cell lung cancer .

Patients: T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer.

Hypo fractionation : Timmerman Sheet (RTOG 0236) Contd..

Stereotactic Targeting and Treatment:

- ✓ Targeting, planning, and directing Radiation beams
- ✓ Along any trajectory in 3-D space
- ✓ Toward a target of known 3-D coordinates

Dose Fractionation :

- ✓ 20 Gy per fraction
- ✓ At the edge of the PTV.
- ✓ 3 fractions over 8-14 days for a total of 60 Gy.

Note: Intensity Modulated RT (IMRT) Is Not Allowed

Hypo fractionation : Timmerman Sheet (RTOG 0236) Contd..

Physical Factors : Photon energies 4-10 MV

Minimum Field Aperture : 3.5 cm(Electronic disequilibrium)

Patient Positioning :

- ✓ Comfortable, Reproducible
- ✓ Stereotactic frames (surround ~ three sides)
- ✓ Reference ~ stereotactic coordinate system

Image Acquisition :

- ✓ Computed Tomography (CT) (Scan sep < 3mm)
- ✓ Simultaneous view of patient anatomy and fiducial system

Target :

- ✓ GTV ~ Pulmonary windows
- ✓ GTV and CTV are identical (No Margin)

Hypo fractionation : Timmerman Sheet (RTOG 0236) Contd..

- ✓ Coplanar / non-coplanar beam arrangements.
- ✓ Static beams or arcs
- ✓ Preferably: Non opposing , 7- 10 beams, ~ Equal weighting.
- ✓ BEV: Field aperture approximate PTV (No additional margin).
- ✓ PTV ~ 60-90% line (rather than 95-100%).
- ✓ Hotspots within the target.
- ✓ Normalization : Defined point (~ ISO) ~ center of mass of PTV.
- ✓ No correction for tissue heterogeneity (unit density)

Hypo fractionation : Timmerman Sheet (RTOG 0236) Contd..

Target

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to the PTV		Ratio of 50% Prescription Isodose Volume to the PTV, $R_{50\%}$		Maximum Dose 2 cm from PTV in any Direction, D_{2cm} (Gy)		Percent of Lung receiving 20 Gy total or more, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	none	minor	none	Minor	none	minor	none	minor
2.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15
2.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15
3.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15
3.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15
4.0	<1.2	1.2-1.4	<3.8	3.8-4.0	<30.4	30.4-32.4	<10	10-15
4.5	<1.2	1.2-1.4	<3.7	3.7-3.9	<32.7	32.7-34.7	<10	10-15
5.0	<1.2	1.2-1.4	<3.6	3.6-3.8	<35.1	35.1-37.1	<10	10-15
5.5	<1.2	1.2-1.4	<3.5	3.5-3.7	<37.4	37.4-41.7	<10	10-15
6.0	<1.2	1.2-1.4	<3.3	3.3-3.5	<39.7	39.7-41.7	<10	10-15
6.5	<1.2	1.2-1.4	<3.1	3.1-3.3	<42.0	42.0-44.0	<10	10-15
7.0	<1.2	1.2-1.4	<2.9	2.9-3.1	<44.3	44.3-46.3	<10	10-15

OAR

Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)

Hypo fractionation : Timmerman Sheet (RTOG 0236) Contd..

- ✓ 59 patients ,55 were evaluable
- ✓ 44 patients : T1 and 11 patients : T2
- ✓ Median follow-up of 4.0 years
- ✓ The 5-year primary tumor failure rate was 7%.
- ✓ The 5-year involved lobe (local) failure rate was 20%.
- ✓ The 5-year local-regional failure rate was 38%.
- ✓ The 5-year disseminated failure rate was 31%.
- ✓ The 5 years were DFS~26% and OS~40%
- ✓ The median overall survival was 4 years
- ✓ Toxicity grade 3 ~15 and grade 4 ~ 2

Hypo fractionation : AAPM TASK GROUP REPORT- 101

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

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2010

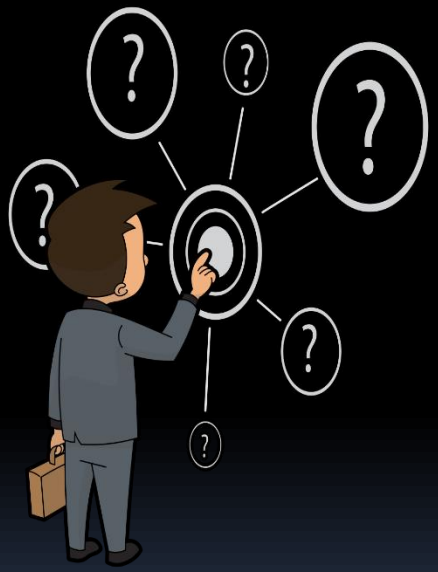
- Practice guideline (SBRT)
- Medical physicists, clinicians, and therapists
- Includes a review of the literature
- Information for establishing a SBRT Program
- ✓ Protocols
- ✓ Equipment
- ✓ Resources
- ✓ QA procedures
- ✓ Prescribing, reporting, and recording.

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Comparisons

Characteristic	3D/IMRT	SBRT
Dose/fraction	1.8–3 Gy	6–30 Gy
No. of fractions	10–30	1–5
Target definition	CTV/PTV (gross disease+clinical extension): Tumor may not have a sharp boundary.	GTV/CTV/ITV/PTV (well-defined tumors: GTV=CTV)
Margin	Centimeters	Millimeters
Physics/dosimetry monitoring	Indirect	Direct
Required setup accuracy	TG40, TG142	TG40, TG142
Primary imaging modalities used for treatment planning	CT	Multimodality: CT/MR/PET-CT
Redundancy in geometric verification	No	Yes
Maintenance of high spatial targeting accuracy for the entire treatment	Moderately enforced (moderate patient position control and monitoring)	Strictly enforced (sufficient immobilization and high frequency position monitoring through integrated image guidance)
Need for respiratory motion management	Moderate—Must be at least considered	Highest
Staff training	Highest	Highest+special SBRT training
Technology implementation	Highest	Highest
Radiobiological understanding	Moderately well understood	Poorly understood
Interaction with systemic therapies	Yes	Yes

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..



Patients Selection

- Site : Brain, lung, liver, and spinal tumors.
- SBRT as a boost.
- Preferably : Cross-sectional diameter ~ 5 cm (max)
- SBRT is still developing

Recommendations :

- ✓ Unpublished indications
- ✓ Formal prospective clinical trial

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Patient Immobilization

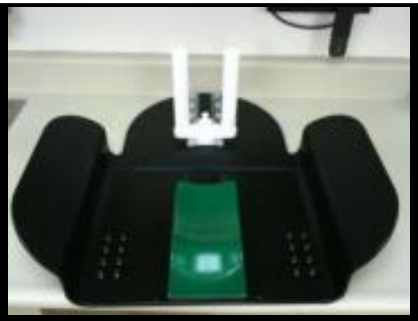
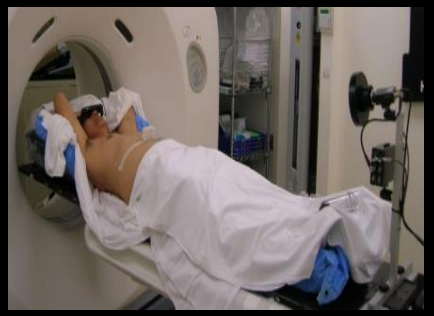
- ➢ High degree immobilization
- ➢ Patient comfort issues
- ✓ Longer treatment setup time
- ✓ Longer irradiation time
- ➢ Treatment setup related issue
- ✓ Multiple radiation portal entry/exit
- ✓ Patient position – Neck , Hand position etc.

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Patient Immobilization : Body

WITH FRAME	WITHOUT FRAME



Stereotactic body frames :

- ✓ Physical immobilization
- ✓ Initial approximation target localization

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Patient Immobilization : Accuracy (Body)

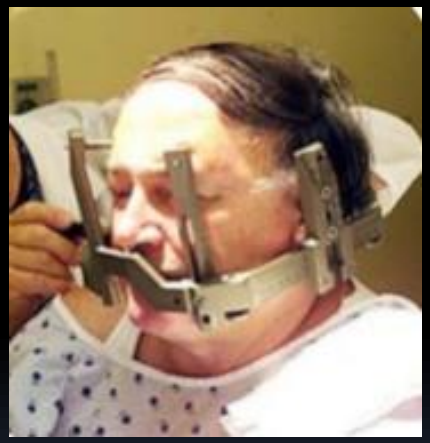
Author, year	Site	Immobilization/repositioning	Reported accuracy
Lax, 1994[a]	Abdomen	Wood frame/stereotactic coordinates on box to skin marks	3.7 mm Lat, 5.7 mm Long
Hamilton, 1995[b]	Spine	Screw fixation of spinous processes to box	2 mm
Murphy, 1997[c]	Spine	Frameless/implanted fiducial markers with real-time imaging and tracking	1.6 mm radial
Lohr, 1999[d]	Spine	Body cast with stereotactic coordinates	≤3.6 mm mean vector
Yenice, 2003[e]	Spine	Custom stereotactic frame and in-room CT guidance	1.5 mm system accuracy, 2–3 mm positioning accuracy
Chang, 2004[f]	Spine	MI™ BodyFix with stereotactic frame/linac/CT on rails with 6D robotic couch	1 mm system accuracy
Tokuuye, 1997	Liver	Prone position jaw and arm straps	5 mm
Nakagawa, 2000[g]	Thoracic	MVCT on linac	Not reported
Wulf, 2000[h]	Lung, liver	Elekta™ body frame	3.3mm lat,4.4 mm long
Fuss, 2004[i]	Lung, liver	MI™ BodyFix	Bony anatomy translation 0.4, 0.1, 1,6 mm (mean X,Y,Z); tumor translation before image guidance 2.9, 2.5, 3.2 mm (mean X,Y,Z)
Herfarth, 2001[j]	Liver	Leibinger body frame	1.8–4.4 mm
Nagata, 2002[k]	Lung	Elekta™ body frame	2 mm
Fukumoto, 2002[l]	Lung	Elekta™ body frame	Not reported
Hara, 2002[m]	Lung	Custom bed transferred to treatment unit after confirmatory scan	2 mm
Hof, 2003[n]	Lung	Leibinger body frame	1.8–4 mm
Timmerman, 2003[o]	Lung	Elekta™ body frame	Approx. 5 mm
Wang, 2006[p]	Lung	Medical Intelligence body frame stereotactic coordinates/CT on rails	0.3 ± 1.8 mm AP, -1.8 ± 3.2 mm Lat, 1.5 ± 3.7 mm SI

Accuracy ~ 2-3 mm

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

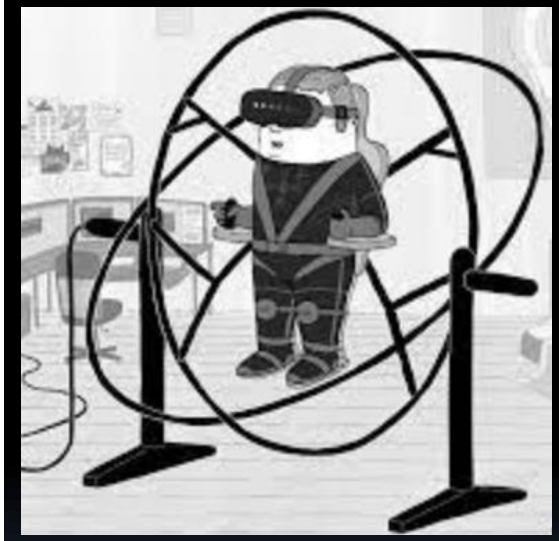
Patient Immobilization : Head

WITH FRAME	WITHOUT FRAME



Accuracy ~ 1-2 mm

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..



Simulation Imaging : Static targets (General)

SBRT demands

- ✓ Precise delineation of patient anatomy
- ✓ Targets segmentation for planning
- ✓ Clear visualization for localization (treatment delivery)

CT or 4DCT (3D anatomical data sets)

- ✓ Visualizations
- ✓ Dose calculation

MRI /PET (3D anatomical / functional data sets)

- ✓ Assist in target segmentation
- ✓ Visualization

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

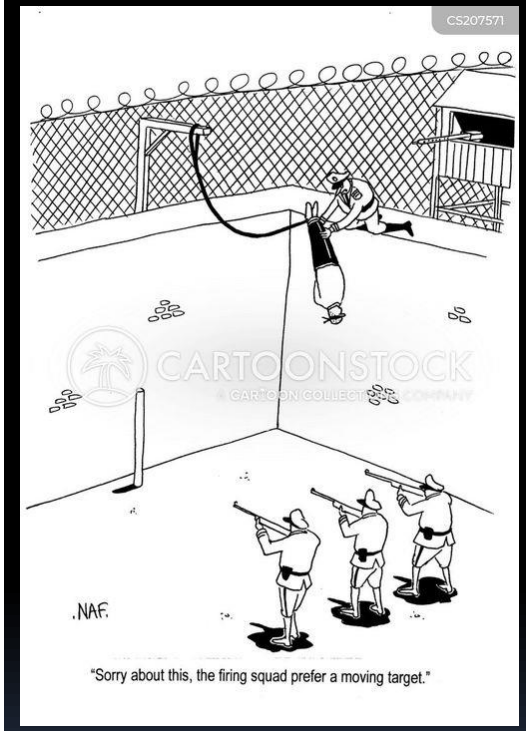
Simulation Imaging : Static targets (General)

Recommendation:

- ✓ Patient in the treatment position.
- ✓ Cover the target and all organs at risk
- ✓ Extend
  - ~ 5–10 cm superior / inferior beyond the VOI (Coplanar)
  - ~ 15 cm superior / inferior beyond the VOI (Non coplanar)
- ✓ Slice thickness of 1–3 mm

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Simulation Imaging : Moving Targets



Tumour motion : sources

- ✓ Respiration
- ✓ Cardiac function
- ✓ Peristaltic activity
- ✓ Organ filling and emptying

Tumour motion : management strategies

- ✓ Slow CT
- ✓ Breath-hold techniques
- ✓ Gated approaches
- ✓ 4DCT (max-intensity projection/min intensity projection)
- ✓ Respiration-correlated PET-CT

Recommendation:

- ✓ If Simulation / localization without sufficient accuracy (motion and/or metal artifacts)
- ✓ SBRT should not be pursued as a treatment option

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Treatment planning : Conditions

Target:

- ✓ A small volume (gross tumor +close vicinity)
- ✓ Very high dose per fraction
- ✓ Hotspots within the target ~ often acceptable

Normal tissue:

- ✓ High dose should be minimized
- ✓ Sharp dose fall off outside the target.

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Treatment planning : strategies

Segmentation:

- ✓ ICRU 50 and 62 :GTV, CTV, PTV, and OAR
- ✓ GTV and CTV ~ Often identical
- ✓ CTV size : Tumor motion ~ Added margin : ITV

Dose heterogeneity

- ✓ Dose prescriptions : Low isodoses (~ 80%)
- ✓ Small/ no margins - Penumbra at the target edge
- ✓ Dose heterogeneity acceptable

Dose fall off

- ✓ Energy up to 6 MV
- ✓ Multiple non overlapping beams
- ✓ Resolution of beam shaping device (finer MLC~ 5 mm)

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Treatment planning : strategies

Beam selection and beam geometry:

- ✓ Avoidance of sensitive organs.
- ✓ Mechanical constraints.
- ✓ Short beam paths for most beams.
- ✓ Multiple beam / Arc (Entrance dose < 30% of total dose)
- ✓ Isotopic dose gradient is desirable.

Calculation grid size :

- ✓ Extremely high-dose gradients near the boundary.
- ✓ Isotropic grid size of 2 mm or finer.

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Treatment planning : Normal tissue dose tolerance

		One fraction		Three fractions		Five fractions		
Serial tissue	Max critical volume above threshold	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	Threshold dose (Gy)	Max point dose (Gy)[a]	End point (≥Grade3)
Optic pathway	<0.2 cc	8	10	15.3 (5.1 Gy/fx)	17.4 (5.8 Gy/fx)	23 (4.6 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			9		17.1 (5.7 Gy/fx)		25 (5 Gy/fx)	Hearing loss
Brainstem (not medulla)	<0.5 cc	10	15	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)	23 (4.6 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord and medulla	<0.35 cc	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2 cc	7		12.3 (4.1 Gy/fx)		14.5 (2.9 Gy/fx)		
Spinal cord subvolume (5–6 mm above and below level treated per Ryu)	<10% of subvolume	10	14	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equina	<5 cc	14	16	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral plexus	<5 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Brachial plexus	<3 cc	14	17.5	20.4 (6.8 Gy/fx)	24 (8 Gy/fx)	27 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy
Heart/pericardium	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10 cc	31	37	39 (13 Gy/fx)	45 (15 Gy/fx)	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and large bronchus[b]	<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis/fistula
Bronchus-smaller airways	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)	21 (4.2 Gy/fx)	33 (6.6 Gy/fx)	Stenosis with atelectasis
Rib	<1 cc	22	30	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35 (7 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
	<30 cc			30.0 (10.0 Gy/fx)				
Skin	<10 cc	23	26	30 (10 Gy/fx)	33 (11 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration
Stomach	<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum[b]	<5 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
	<10 cc	9		11.4 (3.8 Gy/fx)		12.5 (2.5 Gy/fx)		
Jejunum/ileum[b]	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/ obstruction
Colon[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula
Rectum[b]	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/fistula
Bladder wall	<15 cc	11.4	18.4	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/fistula
Penile bulb	<3 cc	14	34	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10 cc	14		21.9 (7.3 Gy/fx)		30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6	18.6 (6.2 Gy/fx)			23 (4.6 Gy/fx)		Malignant hypertension

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Treatment planning : Reporting

SBRT treatment plans contains

- ✓ Large numbers of beams
- ✓ Unconventional dose fractionations
- ✓ Delivery frequencies
- ✓ Comprehensive image guidance data

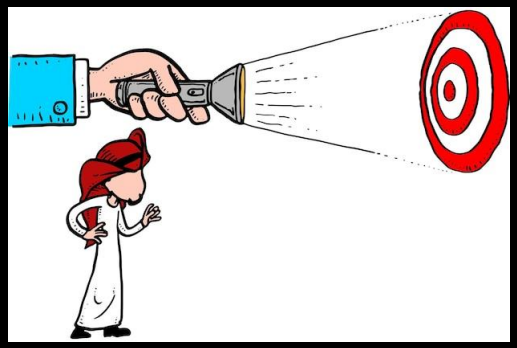
Plan Report

- ✓ Prescription dose
- ✓ ICRU ref point dose or dose/volume
- ✓ Number of treatment fractions
- ✓ Total treatment delivery period
- ✓ Target coverage
- ✓ Plan conformity
- ✓ Dose falloff outside the target
- ✓ Heterogeneity index
- ✓ Notable high / low dose outside PTV
- ✓ Dose to organs at risk

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Target / Tumour localisation

- ✓ Image guidance provides the finest level of localization.
- ✓ Traditional approach ~ 2D MV EPID, Implanted fiducial : Spinal site (2 mm)
- ✓ Volumetric image guidance:
- ✓ KV / MV CBCT
- ✓ Dual or multiple KV Imaging



Target / tumour tracking

- ✓ Monitoring is desirable to track tumour motion
- ✓ Stereoscopic infrared cameras
- ✓ Video photogrammetry
- ✓ Electromagnetic field tracking (Calypso)
- ✓ Surface Guided Radiotherapy

Respiratory gating

- ✓ RPM Gating By Varian Medical System
- ✓ ABC (automatic Breathing Control) By Elekta Medical System)

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Special Dosimetry considerations

Problems with small fields and beamlets (< 10 mm) :

- ✓ Loss of lateral electronic equilibrium
- ✓ Volume averaging,
- ✓ Detector-interface artifacts
- ✓ Collimator effects
- ✓ Detector position-orientation effects

Recommendations:

- ✓ Dosimeter with a spatial resolution ~ 1 mm
- ✓ Stereotactic detectors
- ✓ Maximum inner dia of a detector < half the FWHM of the smallest beam

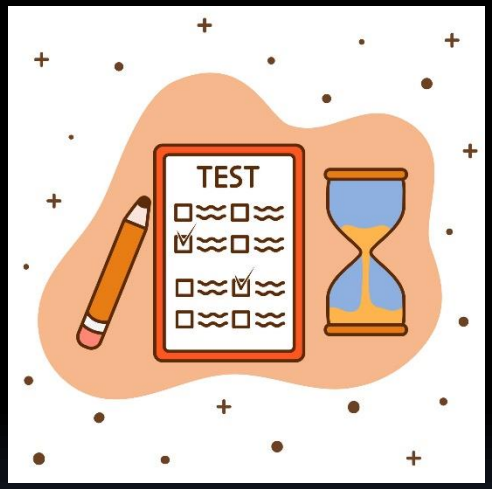
Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Quality assurance: Overview

- ✓ Acceptance
- ✓ Commissioning
- ✓ Quality assurance
- ✓ Patient specific

Source	Purpose	Proposed test	Reported achievable tolerance	Proposed frequency
Ryu *et al.*, 2001[a]	End-to-end localization accuracy	Stereo x ray/DRR fusion	1.0 to 1.2 mm root mean square	Initial commissioning and annually thereafter
Ryu *et al.*, 2001[a]	Intrafraction targeting variability	Stereo x ray/DRR fusion	0.2 mm average, 1.5 mm maximum	Daily (during treatment)
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using stereo x ray/DRR fusion)	0.41 ± 0.92 mm	Initial commissioning and annually thereafter
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using implanted fiducials)	0.28 ± 0.36 mm	Initial commissioning and annually thereafter
Yu *et al.*, 2004[c]	End-to-end localization accuracy	Dosimetric assessment of hidden target (using implanted fiducials)	0.68 ± 0.29 mm	Initial commissioning and annually thereafter
Sharpe *et al.*, 2006[d]	CBCT mechanical stability	Constancy comparison to MV imaging isocenter (using hidden targets)	0.50 ± 0.5 mm	Baseline at commissioning and monthly thereafter
Galvin *et al.*, 2008[e]	Overall positioning accuracy, including image registration (frame-based systems)	Winston–Lutz test modified to make use of the in-room imaging systems	≤2 mm for multiple couch angles	Initial commissioning and monthly thereafter
Palta *et al.*, 2008[f]	MLC accuracy	Light field, radiographic film, or EPID	<0.5 mm (especially for IMRT delivery)	Annually
Solberg *et al.*, 2008[g]	End-to-end localization accuracy	Hidden target in anthropomorphic phantom	1.10 ± 0.42 mm	Initial commissioning and annually thereafter
Jiang *et al.*, 2008[h]	Respiratory motion tracking and gating in 4D CT	Phantoms with cyclical motion	N/A	N/A
Bissonnette *et al.*, 2008[i]	CBCT geometric accuracy	Portal image vs CBCT image isocenter coincidence	±2 mm	daily

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

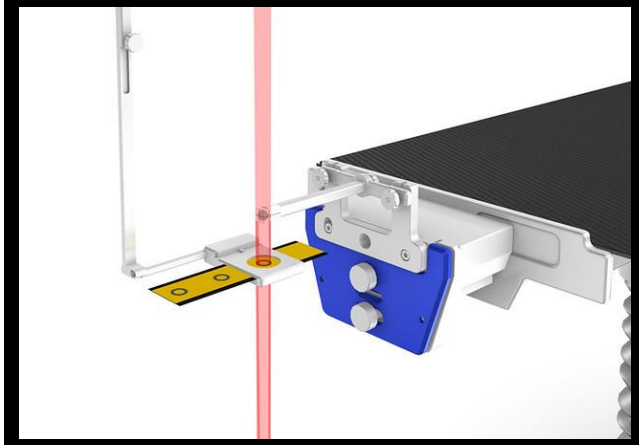


Quality assurance: Tests list

- ✓ Minimizing systematic errors
- ✓ Explore in detail every aspect of the system
- ✓ Periodic and treatment-specific quality assurance
- ✓ Integrity of the simulation imaging data
- ✓ Dose-calculation algorithms
- ✓ Verify the coincidence of radiation and mechanical isocenter
- ✓ MLC leaf sequencing
- ✓ MU calculation algorithms
- ✓ Leaf speed
- ✓ Machine dose rates used for SBRT
- ✓ Accuracy of calibration at these dose rates
- ✓ Delivery precision at small MUs
- ✓ Patient positioning and localization
- ✓ Motion tracking and gating

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Quality assurance: Isocenter checks



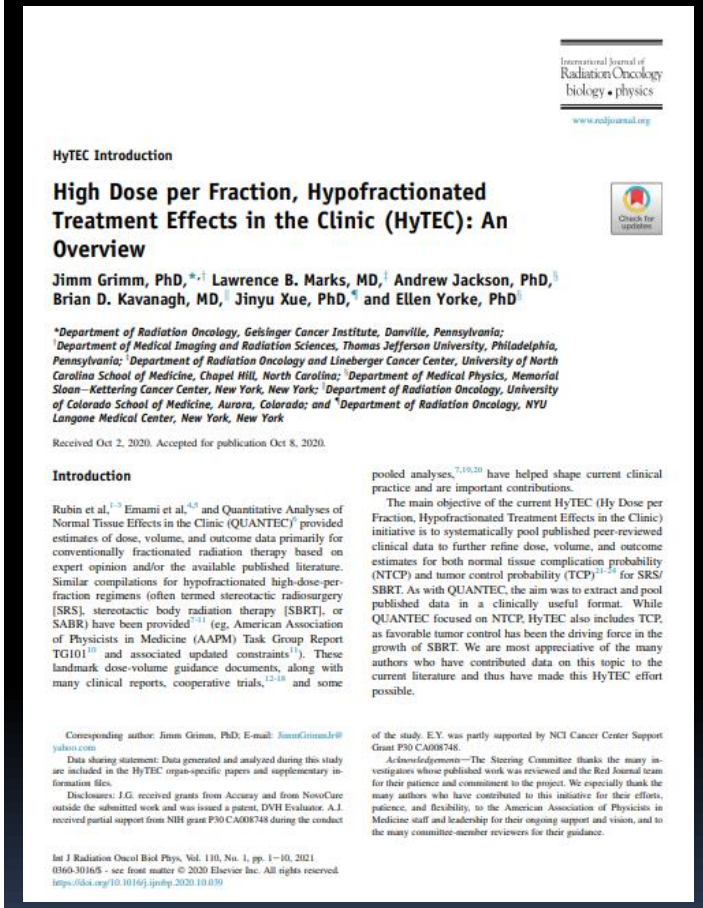
- ✓This technique was introduced by Lutz, Winston
- ✓A small metallic ball (made of steel, titanium or tungsten)
- ✓Represents the isocenter
- ✓Fixed on the treatment table by a locking mechanism.
- ✓The phantom position is adjustable in 3D : micrometer tool.
- ✓ The collimated beam is used to expose
- ✓Radiographic film mounted perpendicular to the beam
- ✓Center of the sphere shadow and the field center matching
- ✓Which must be within ±1 mm for stereotactic treatments)
- ✓Measurements repeated (0°, 90°, 180°, and 270°)
- ✓Alternatively Portal imaging can also used.

Hypo fractionation : AAPM TASK GROUP REPORT- 101 Contd..

Patient Safety

- ✓ Verification of correct patient
- ✓ Correct patient plan
- ✓ Correct isocenter
- ✓ Correct and properly configured immobilization devices
- ✓ Collision with patient or patient accessories
- ✓ Beam interference : arm, elbow, chin or accessories
- ✓ Treatment plan verification
- ✓ Second MU calculation or measurements

Hypo fractionation : HyTEC



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HyTEC Introduction

High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview

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Introduction

Rubin et al,[1-3] Emami et al,[4,5] and Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)[6] provided estimates of dose, volume, and outcome data primarily for conventionally fractionated radiation therapy based on expert opinion and/or the available published literature. Similar compilations for hypofractionated high-dose-per-fraction regimens (often termed stereotactic radiosurgery [SRS], stereotactic body radiation therapy [SBRT], or SABR) have been provided[7-11] (eg, American Association of Physicists in Medicine (AAPM) Task Group Report TG101[10] and associated updated constraints[11]). These landmark dose-volume guidance documents, along with many clinical reports, cooperative trials,[12-18] and some pooled analyses,[7,19,20] have helped shape current clinical practice and are important contributions.

The main objective of the current HyTEC (Hy Dose per Fraction, Hypofractionated Treatment Effects in the Clinic) initiative is to systematically pool published peer-reviewed clinical data to further refine dose, volume, and outcome estimates for both normal tissue complication probability (NTCP) and tumor control probability (TCP)[21-25] for SRS/SBRT. As with QUANTEC, the aim was to extract and pool published data in a clinically useful format. While QUANTEC focused on NTCP, HyTEC also includes TCP, as favorable tumor control has been the driving force in the growth of SBRT. We are most appreciative of the many authors who have contributed data on this topic to the current literature and thus have made this HyTEC effort possible.

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Data sharing statement: Data generated and analyzed during this study are included in the HyTEC organ-specific papers and supplementary information files.

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2020

Objectives:

Systematically pool published peer-reviewed clinical data to further refine dose, volume, and outcome estimates for both normal tissue complication probability (NTCP) and tumor control probability (TCP) for SRS/ SBRT.

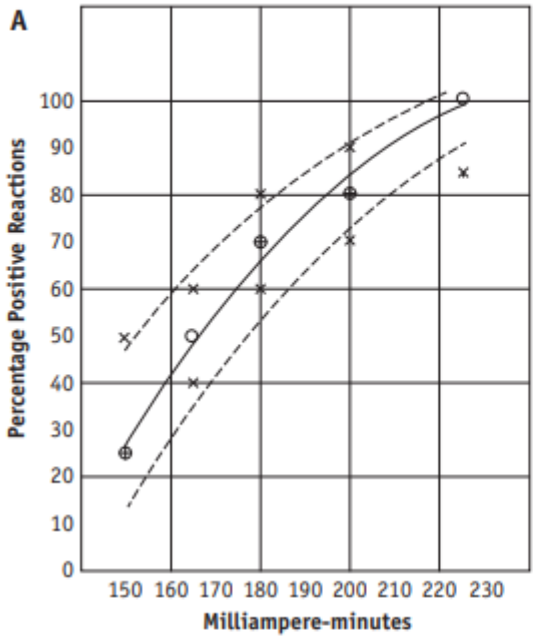
- ✓ QUANTEC focused on NTCP : Conventional
- ✓ HyTEC includes TCP as well : SRS/SBRT/SABR

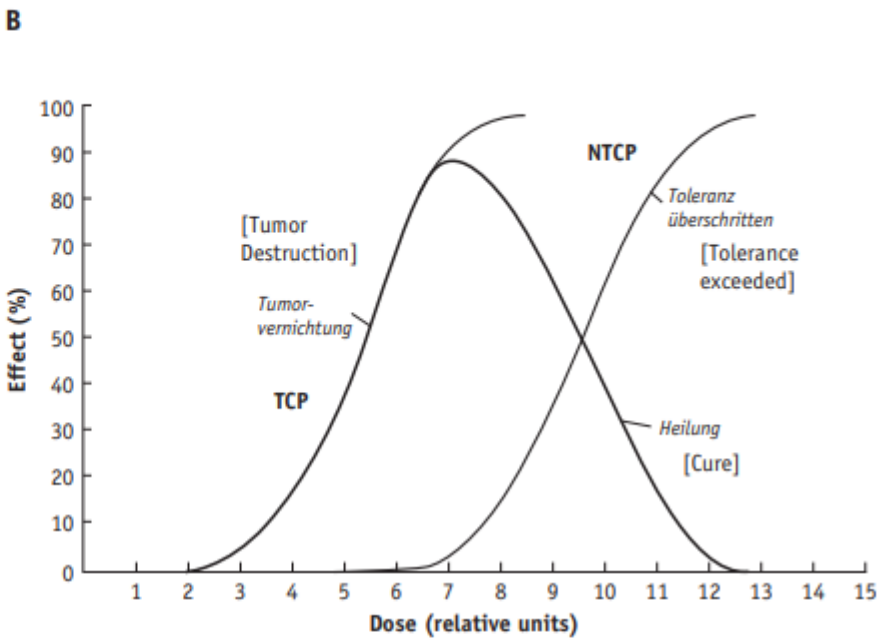
Hypo fractionation : HyTEC Project and group

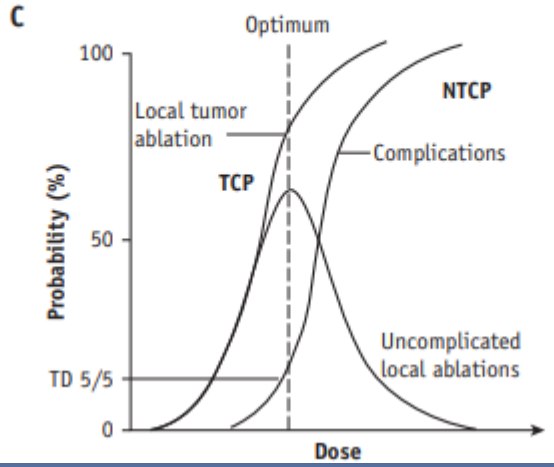
Established within the Biological Effects Sub-Committee (BESC) of AAPM as the Working Group on Biological Effects of Hypo fractionated Radiotherapy / SBRT (WGSBRT).

- ✓ Physicians
- ✓ Clinical physicists
- ✓ Radiobiologists
- ✓ Biostatisticians
- ✓ Bio-mathematicians

Hypo fractionation : HyTEC (Historical context)







Hypo fractionation : HyTEC

Comparison : Emami etal , QUANTEC, HyTEC

Characteristic	Emami et al.	QUANTEC	HyTEC
Scope	26 normal tissues/organs	16 normal organs	7 normal organ papers; NTCP 9 disease site papers; TCP
3D data available	Minimal	More/moderate (studies span ≈ 18-year interval)	Moderate but rapidly increasing
Format dose, volume, and outcome data	Uniform levels of risk (eg, TD 5/5, 50/5); uniform irradiation of 1/3, 2/3, 3/3's of an organ	Nonuniform levels of risk across organs; range of dose-volume metrics	Nonuniform levels of risk across organs; range of dose-volume metrics

Abbreviations: 3D = 3-dimensional; HyTEC = Hy Dose per Fraction, Hypofractionated Treatment Effects in the Clinic; NTCP = normal tissue complication probability; QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic; TCP = tumor control probability; TD 5/5 and TD 50/5 = tolerance dose resulting in a 5% and 50% risk of toxicity at 5 years, respectively.

Hypo fractionation : HyTEC Report

- ✓ Articles addressing TCP and NTCP
- ✓ Six anatomic sites:

1. Cranial
2. Head and neck
3. Thoracic
4. Abdominal
5. Pelvic
6. Spinal

- ✓ Nine articles for TCP
- ✓ Seven articles for NTCP

Hypo fractionation : HyTEC Report : NTCP

Table 2 Summary of NTCP[a] estimates after SRS/SBRT from the HyTEC reports[*]

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)[*]	Notes
Brain; for metastasis	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 5$ cm^3	10%	From Table 3 and Figs. 4 and 5 in paper. Consistent with QUANTEC. Prior whole brain RT appears to not markedly increase risks in most reports (with the exception of brain stem).[†] However, repeat SRS/fSRS to the same area has been associated with markedly increased risks.
		1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	15%	
		1	Symptomatic necrosis	$V_{12Gy} \leq 15$ cm^3	20%	
		3	Edema or necrosis	$V_{20Gy} \leq 20$ cm^3	$\leq$ 10%	
		3	Edema or necrosis	$V_{20Gy} \leq 30$ cm^3	$\leq$ 20%	
		5	Edema or necrosis	$V_{24Gy} \leq 20$ cm^3	$\leq$ 10%	
		5	Edema or necrosis	$V_{24Gy} \leq 30$ cm^3	$\leq$ 20%	
Brain; SRS for arteriovenous malformation	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 10$ cm^3	$\leq$ 10%	From Figure 2 in paper
Optic pathway	Optic nerves and chiasm	1	Neuropathy	$D_{max} < 10$-12 Gy	< 1%	From Table 3 in paper. Consistent with QUANTEC. Prior RT exposure of the optic pathway (either whole brain RT or SRS/fSRS) appears to markedly increase risks.
		3	Neuropathy	$D_{max} < 20$ Gy	< 1%	
		5	Neuropathy	$D_{max} < 25$ Gy	< 1%	
Carotid artery (re-treatment)	Each carotid artery	5	Grade 3-5 bleeding	$D_{max} < 20$-30 Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*[‡]
	Each carotid artery	5	Grade 3-5 bleeding	$D_{0.5cc} < 20$ Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*[‡]
Lungs	Combined lungs minus target[§]	3-5	Grade $\geq$ 2 toxicity[§]	Mean dose $\leq$ 8 Gy; $V_{20Gy} < 10$-15%	10-15%	Preexisting interstitial lung disease appears to increase toxicity risk
Liver; SBRT for primary lesions	Liver minus GTVs[‖]	3	Grade $\geq$ 3 liver enzyme change	Mean dose $\leq$ 13 Gy	<20%	For patients with intact liver function. Various clinical factors (eg, underlying liver impairment per the Child Pugh score, platelet count) can reduce liver tolerance.[#] Consistent with QUANTEC (that broadly considered radiation induced liver injury; this includes liver enzyme changes).
	Liver minus GTVs[‖]	6	Grade $\geq$3 liver enzyme change	Mean dose $\leq$ 18 Gy	<20%	
Liver; SBRT for metastases	Liver minus GTVs[‖]	3	Grade $\geq$3 liver enzyme change	Mean dose $\leq$ 15 Gy	<20%	
	Liver minus GTVs[‖]	6	Grade $\geq$3 liver enzyme change	Mean dose $\leq$ 20 Gy	<20%	

(*continued on next page*)

Table 2 (*continued*)

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)[*]	Notes
Liver; SBRT for metastases	Liver minus GTVs[‖]	3-6	Liver dysfunction and grade 3-5 general GI toxicity[¶]	$\geq$700 cm^3 receives $\leq$ 15-17 Gy[#]	<13%	Critical volume limit, spare 700 cm^3[#,**]
Bladder	Bladder (as a solid organ)[††]	4-5	Late grade $\geq$2 urinary toxicity	$V_{Prescription\ Dose} < 5$-10 cm^3	<20%	In context of prostate SBRT. All reviewed prescription doses were 35-40 Gy in 4-5 fractions. See Pelvic NTCP paper, Table 4, for additional constraints. Many of the reviewed studies treated every-other-day in hopes of reducing toxicity.
Rectum	Rectum (as a solid organ)[††]	4-5	Late grade $\geq$3 bowel toxicity	$D_{max} < 35$-38 Gy	<3%	
Urethra	Prostatic urethra	4-5	Late grade $\geq$2 urinary toxicity	$D_{max} < 38$-42 Gy	<20%	
Spinal cord	Spinal cord, canal, or thecal sac[‡‡]	1	Myelopathy	$D_{max} < 12.4$-14 Gy	1-5%	These data are for patients without prior RT (from Table 3 in paper). Information for the setting of re-irradiation are in Table 4 of the paper. Consistent with QUANTEC.
		2		$D_{max} < 17$-19.3 Gy	1-5%	
		3		$D_{max} < 20.3$-23.1 Gy	1-5%	
		4		$D_{max} < 23$-26.2 Gy	1-5%	
		5		$D_{max} < 25.3$-28.8 Gy	1-5%	

Hypo fractionation : HyTEC Report : TCP

Table 3 Summary of TCP estimates from the HyTEC reports[*]

Tumor site/type	Volume segmented, margin	Number of fractions	Endpoint[†]	Dose (Gy), or dose-volume parameters[‡]	Rate (%)[†]	Notes
Brain metastases	GTV + 0-2 mm margin[§]	1	2-year local control,	≤2 cm, 18-24 Gy	80%-95%	1-year local control ≈ ≥85%-90%
		1	by lesion size	2-3 cm, 18 Gy	66%	1-year local control ≈ 75%
		1		>3 cm, 15 Gy	47%	1-year local control ≈ 70%
		3		2-3 cm, 24-30 Gy	65%-84%	1-year local control ≈ 80%
		3		>3 cm, 21-27 Gy	53%-69%	1-year local control ≈ 75%
		5		2-3 cm, 30-35 Gy	75%-85%	1-year local control ≈ 80%
		5		>3 cm, 25-30 Gy	59%-69%	1-year local control ≈ 75%
Vestibular Schwannoma	GTV+ 0-2 mm margin[‖]	1	3-5 year local control	≥12 Gy	≥91%	Variable PTV margins used. Most available data are with a single fraction.
		3		18 Gy	≥91%	
		5		25 Gy	>91%	
Head & neck; retreatment	GTV + 0-6 mm margin	5	2-year local control	45 Gy	50%	Majority of newer studies used 2-6 mm margin
Lung; T1-2 lesions[¶]	ITV or IGTV + 3-8 mm	3	1-5 year local control	33 Gy	<50%	Based on minimal data
		3	1-5 year local control	45-54 Gy	≥75%	In most studies
		3	1-5 year local control	≥60 Gy	≥80%-85%	In most studies
		4	1-5 year local control	42-48 Gy	≥70%	In most studies
		4	1-5 year local control	>52 Gy	≥80%-85%	In most studies
		5	1-3 year local control	≥ 50 Gy	≥ ≈ 80%	In all studies
Liver; primary tumor	Variable	3-5	2-year local control	BED_{10} = 60-72 Gy[#]	90%	No clear dose response relationship within the range of reported schedules (including 11-18 Gy x 3; 12 Gy x 4; 8-10 Gy x 5). Authors recommend 8-10 Gy x 5 as a conservative approach.
Liver metastases	Variable	1-5	2-year local control	BED_{10} > 100 Gy[#]	≥90%	Estimated based on BED_{10} >112, including 15-25 Gy x 3
		1-5		BED_{10} < 100 Gy[#]	65%-76%	Estimated based on BED_{10} ranging from 60-84 Gy, including 24-26 Gy x 1; 10-12.5 Gy x 3; 10 Gy x 4
Adrenal	Mixed[**]	Median 5[††]	1-year local control	Prescription BED_{10} > 116.4 Gy	>95%	Model-based estimate. Clinical examples of fractionation schedules providing BEDs in this range include 15 Gy x 3 = 45 Gy (BED_{10} = 112.5) and 11 Gy x 5 = 55 Gy (BED_{10} = 115.5 Gy). Respiratory motion control in all studies.

(*continued on next page*)

Table 3 (*continued*)

Tumor site/type	Volume segmented, margin	Number of fractions	Endpoint[†]	Dose (Gy), or dose-volume parameters[‡]	Rate (%)[†]	Notes
Pancreas	GTV + 2-5 mm	1	1-year local control	20-25 Gy	79%-88%	Rates shown are without surgery (reported local control rates are higher in patients with surgery pre- or post-SBRT)
		3		30-36 Gy	79%-86%	
		5		33 Gy	77%	
Prostate, low-intermediate risk	Varied: prostate + 0-5 mm PTV margin	5	5-year freedom from biochemical relapse	36.1 Gy[††]	95%	
Prostate, high risk		5		38.7 Gy[††]	95%	Caution is needed in interpreting these data because few such patients are included in the published literature and these are likely highly selected patients.
Spine[‡‡]	CTV + 0-2 mm	1	2-year local control	18 Gy	82%	Much uncertainty exists in interpreting the data from the literature and in the creation of these resultant model based estimates.
		1		20 Gy	90%	
		1		22 Gy	94%	
		1		24 Gy	96%	
		2		24 Gy	82%	
		3		27 Gy	78%	
		3		30 Gy	85%	

Hypo fractionation : Limitations

- ✓ More resource intensive : special equipment
- ✓ Higher man-hour for planning and QA time
- ✓ Higher complicated process : Potential for error
- ✓ High degree immobilization : uncomfortable ,invasive
- ✓ Longer treatment execution time
- ✓ Limited randomized data.


THANK YOU
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