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

解读（上）

杨瑞杰, 副研究员

硕士研究生导师

北京大学第三医院

报告背景与概述

- Received 1 Dec 2009; published 14 July 2010
- 24 well recognized experts from 19 institutes
- Medical physicist, radiation oncologist, therapist

Practical guideline

- General information and recommendation
- Not inflexible rules/requirements
- Not legal standard/litigation

SBRT: The report of AAPM Task Group 101

- 概念与特点
- 历史与原理
- 适应症
- 模拟定位成像与治疗计划
- 患者定位、固定、靶区定位和治疗实施
- 特殊剂量学考虑
- 临床实施
- 展望

SBRT 概念与特点

Stereotactic body radiation therapy (SBRT):
An emerging radiotherapy procedure that is highly effective in controlling early stage primary and oligometastatic cancers at locations throughout the abdominopelvic and thoracic cavities, and at spinal and paraspinal sites.

Major features

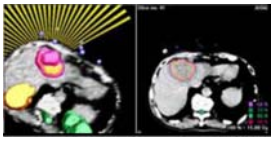
- Delivery of large doses in a few fractions
- High biological effective dose (BED)
- High conformalty of high doses to the target
- Rapid fall-off doses away from the target

SBRT 概念与特点

- The practice of SBRT therefore requires a high level of confidence in the accuracy of the entire treatment delivery process.
- *In SBRT, confidence in this accuracy is accomplished by the integration of modern imaging, simulation, treatment planning,* image guidance *and delivery technologies into all phases of the treatment process; from treatment simulation and planning, and continuing throughout beam delivery.*

SBRT 概念与特点

- Increased number of beams, non-coplanar beam
- Small or no beam margins for penumbra
- Inhomogeneous dose distributions (dose-painting)



SBRT 特点

TABLE I. Comparison of typical characteristics of 3D/IMRT radiotherapy and SBRT.

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

II. 历史与原理

- 4000 publications spanning several decades (SRS)
- 生物学优势
  - Few fractions
  - Large fraction dose
  - Short treatment time
- 临床结果: lung, liver, paraspinal
- 成本效益

SBRT治疗转移性肿瘤的理由

- 失败模式：系统治疗与局部治疗结合
- 疾病自然史：局限性转移
  - Oligometastases is the intermediate stage before meta-
- Norton-Simon假说:
  - Low burden, exponential growth, plateau
- 细胞杀伤与免疫调节
- 姑息治疗:
  - Tumor abuts/overlaps a previously irradiated region

III. 适应症

- The majority of patients: lung, liver, and spinal tumors
- Boost in addition to regional nodal irradiation
- Most investigators: well-circumscribed tumors
- The need to keep the volume of normal tissue receiving high doses kept to a minimum requirements that only well-defined targets can be considered for SBRT
- Maximum cross sectional diameter up to 5 cm, some centers 7 cm
- Careful evaluation of normal tissue function/ dose Distribution
  - Pulmonary function
  - Volume of normal liver that is irradiated
  - Tumors proximal to mainstem bronchi, trachea, esophagus, gastric wall, bowel, blood vessels, or spinal cord

III. 适应症

Recommendation:

- SBRT is still developing
- Follow established guideline
- Clinical trials (IRB): develop new guidelines
  - Regimens departing substantially from published experiences
  - Apply SBRT for indications not previously reported

IV. 模拟定位成像与治疗计划

- 模拟定位成像
- 肿瘤运动数据采集、定量与呼吸运动管理
- 成像伪影
- 治疗计划
  - 剂量不均匀性、剂量梯度与跌落、射束几何学
  - 射束选择与射束几何学
  - 剂量计算矩阵分辨率
  - 基于生物效应的治疗计划
  - 正常组织耐受性
- 治疗计划报告

IV.A. 模拟定位成像

- 成像方式: CT, MRI, PET/CT
- 扫描范围：射野边缘外5-10 cm, 15 cm(非共面)
- 扫描层厚: 1-3 mm

IV.B. 肿瘤运动数据采集、定量与呼吸运动管理

- 肿瘤和器官运动原因: 呼吸,心跳,蠕动,充盈,排空
- 呼吸运动复杂性: 平面成像局限性
- 呼气末和吸气末成像高估PTV大小
- 自由呼吸快速螺旋CT不能描述肿瘤实际位置
- 多层CT也不能代表平均位置
- 基于人群数据确定Margin的问题
- AAPM TG 76

IV.B. 肿瘤运动数据采集、定量与呼吸运动管理

运动肿瘤成像方法

- Slow CT
- breath-hold
- gating
- 4DCT (MIP, MinIP)

IV.C. 成像伪影

- 运动伪影
  - 患者固定，呼吸训练
  - 4D technique
- 金属伪影
  - CT value to electron density conversion table
  - AAPM TG 65

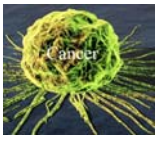
- Recommendation: If target and radiosensitive critical structures cannot be localized on a sectional imaging modality with sufficient accuracy because of motion and/or metal artifacts, SBRT should not be pursued as a treatment option.

治疗计划

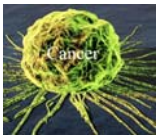
- （剂量处方和靶区定义）
- 剂量不均匀性、剂量梯度与跌落
- 布野原则
- 剂量计算矩阵分辨率
- 基于生物效应的治疗计划
- 正常组织耐受性

剂量处方和靶区定义

- 剂量处方：基本特点和原则
  - GTV及其紧临近区域高分次剂量，靶区内热点可以接受
  - 最小化靶区外正常组织高剂量区：靶区外剂量跌落快



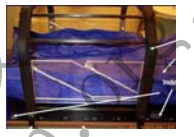
靶区定义



- ICRU 50, 62
- CTV经常在GTV基础上不外放
  - Especially for metastatic lung, liver, and paraspinal
  - GTV外小范围显微外侵，临床报道局部控制率非常高
  - 这些区域不是复发来源，可能已经接受较高剂量照射
- IM 大小取决于呼吸控制措施（imaging, planning, delivery）
- SM plus IM 0.5 cm axial planes, 1.0 cm superior/inferior (suppressed respiratory motion)
- Isotropic expansion of CTV with 4D imaging (some institutes)
- 2-3 mm margin surrounding the enhancing tumor for primary diseases (some clinicians)

靶区定义: 确定外放边界

- 目前很难基于临床结果确定
- 要考虑具体计划的剂量梯度
- 高分次剂量
- 摆位和定位技术
- 文献数据
- 系统研究：收集和分析临床数据



剂量不均匀性、剂量梯度与跌落

- SBRT剂量处方通常按较低的等剂量线（比如80%）处方
- 靶区外考虑射束半影外放边界很小或不外放
- 有利于靶区外剂量跌落和正常组织保护
- 问题是靶区内剂量不均匀（靶区内没有功能正常组织可以接受）
- 而且有利于肿瘤控制（中心乏氧区）
  - 乏氧区时空变化
- SBRT临床研究支持：给予尽可能高的安全剂量

剂量梯度与跌落

- 射野数目
- 射线能量: 高能半影宽,次级电子,低密度组织小野更明显
- 肺: 6 MV穿透力和半影的较好折中
- 限束装置分辨率(MLC 叶片宽度): 窄好,适形度好
- 放射源大小, 次级电子影响，叶片宽度的效应
- 病变小于3 cm, 3mm leaf width, else 5 mm

布野原则

- Avoidance of sensitive organs, mechanical constraints
- Short beam paths for most beams
- More beams: better conformity, sharp dose fall-off
- Plateau of beam number: dose distribution and delivery time
- Restricting the entrance dose of individual beam <30% of total dose
- Avoiding beam overlap (skin reaction)
- 胸腹部病变：5-8 个静态适形射野（共面或非共面）
- 椎体病变：
  - 9-11后野和后斜野（18-20度等间隔）
  - 靶区和脊髓间梯度12%/mm
  - 90% 处方剂量包绕靶区

IV.D 3. 剂量计算矩阵分辨率

IMRT: three studies

- 1% accuracy: 2.5 mm isotropic grid (high dose region of multifield IMRT)
- 5%: 4 mm isotropic grid
- 2.3%, 5.6% difference for 2 mm and 4 mm compared with 1.5 mm

Recommendation

- 2 mm for IMRT, especially in high-dose gradient areas
- Isotropic grid size of 2mm or finer, greater than 3 mm is discouraged

基于生物效应的治疗计划

- **BED (Biological effective dose)**
- **NTD (Normalized total dose)**
- **EUD (equivalent uniform dose)**
- **LQ model for Hypofractionation**

基于生物效应的治疗计划

TABLE II. Summary of normalized tissue doses estimated using an α/β-ratio of 10 (late complications) and 3 Gy (early complications) for various SBRT fractionation schemes used in NSCLC

Total physical dose (Gy)	Reference	NTD_{10} (Gy)	Log_{10} cell kill	Estimated 30-mo. local progression-free survival[a]	NTD_3 (Gy)
$30\times2=60^b$ in 6 weeks	Estimated from Martel, 1999;[c] Fowler 2004[d]	65	9.9	17.7%[b] with repopulation	60
$35\times2=70^b$ in 7 weeks	Estimated from Martel, 1999;[c] Fowler 2004[d]	72	10.9	28.4%[b] with repopulation	70
$4\times12=48$	Nagata, 2002[e]	83	12.6	78.9% no repopulation	144
$3\times15=45$	Nyman, 2006[f]	94	14.2	90.8% no repopulation	162
$5\times12=60$	Hodge, 2006[g]	110	16.7	97.1% no repopulation	180
$3\times20=60$	McGarry, 2005;[h] Timmerman 2003[i]	150	22.7	>99% no repopulation	276
$3\times22=66$	McGarry, 2005;[h] Timmerman 2003[i]	176	26.7	>99% no repopulation	330

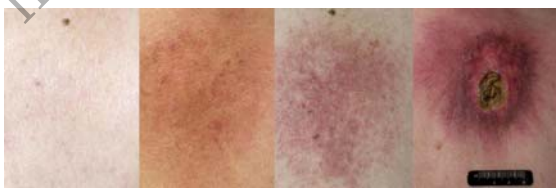
[a]Progression-free survival at 30 months has been estimated using the following dose response model: $LPF_{30\ m}=1/1+(NTD_{50}^{30}/NTD_{30})^{\gamma_{50}}$ using the following parameter values: $NTD_{50}^{30}=84$ Gy; $\gamma_{50}=1.5$ (cf. Ref. 143) when repopulation is included and $NTD_{50}^{30}=70$ Gy; $\gamma_{50}=1.94$ (cf. Ref. 120) when repopulation is not included.
[b]The progression-free survival of patients with NSCLC at 30 months was estimated from Martel *et al.* (Ref. 143) for the schedules marked with "b" and from Fowler *et al.* (Ref. 120) when rapid repopulation can be neglected.

正常组织剂量耐受性

- Hypofractionation different from conventional fractionation
- Unusual complications (fortunately rare) are clinically observed
- LQ model applicability is questioned
- Sharp gradients make HFX more susceptible to setup errors
- Most uncertainties are systematic for single or few - fraction treatments
- Meticulous QA is standard of care

正常组织剂量耐受性

- **大分割不同于常规分割**
- **不成熟：容积效应较强器官的中剂量水平数据**
- **新临床试验或复制其它单位经验：分次/总剂量、间隔时间、总时间**
- **再程治疗要考虑以前剂量**



正常组织剂量耐受性－Table III

- **University of Texas Southwestern, University of Virginia**
- **Indiana University lung SBRT, Karolinska Hospital, Stanford University**
- **Mostly unvalidated, toxicity observation and theory, educated guessing**
- **Sparseness of long-term follow-up**
- **Recommendation:**
  - **Published literature**
  - **Institutional guidelines and prospective trials**

正常组织剂量耐受性－Table III

TABLE III. Summary of suggested dose constraints for various critical organs. Note that for serial tissues, the volume-dose constraints are given in terms of the critical maximum tissue volume that should receive a dose equal or greater than the indicated threshold dose for the given number of fractions used. For parallel tissues, the volume-dose constraints are based on a critical minimum volume of tissue that should receive a dose equal to or less than the indicated threshold dose for the given number of fractions used.

		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 <1.2 cc	10 7	14	18 (6 Gy/fx) 12.3 (4.1 Gy/fx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx) 14.5 (2.9 Gy/fx)	30 (6 Gy/fx)	Myelitis
Spinal cord subvolume (5–6 mm above and below level treated per Rys)	<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

IV. E 治疗计划报告

- 特点
  - 多野照射
  - 大分次剂量
  - 影像引导
- 剂量分布的报告
  - Target coverage, dose homogeneity, dose outside of the target
  - Volumes of normal tissue exposed to lower doses
- 示例
  - Prescription dose
  - Conformity and heterogeneity
  - Dose falloff and hotspot outside the target

小 结

- 综合、回顾、共识、推荐
- 具体问题探讨
- 具体推荐

SBRT: Deliver system and image guidance

- Static conformal, IMRT, conformal arc
- Isocentric and non-isocentric, multiple isocenter
- Coplanar, non-coplanar

Prescription for SBRT

Local Control Rate of Early-Stage Non-Small Cell Lung Cancer Treated with SBRT

Investigator	Dose, Prescription	Approximate minimal total dose delivered to PTV (Gy)	SFED (Gy)	BED (Gy)	SED (Gy)
Timmerman, et al. (2006)	20-22 Gy x 3 (60% isodose)	60-66	56.4-62.4	132-147	107-119
Timmerman, et al. (2003)	18-20 Gy x 3 (60% isodose)	54-60	50.4-56.4	118-132	95-107
Nyman, et al. (2006)	15 Gy x 3 (PTV periphery)	45	41.4	96	78
Xia, et al (2006)	5 Gy x 10 (50% isodose)	50	34.3*	78	63
Zimmermann, et al. (2006)	12.5 Gy x 3 (60% isodose)	37.5	33.9	78	63
Wulf, et al. (2005)	12.5 Gy x 3 (65% isodose)	37.5	33.9	78	63
Hara, et al. (2006)	30-34 Gy x 1 (minimal dose to CTV or PTV)	30-34	30-34	68-78	55-63
Fritz, et al. (2006)	30 Gy x 1 (isocenter)	24	24	68	55
Hof, et al. (2003)	19-26 Gy x 1 (isocenter)	15.2-20.8	15.2-20.8	32-46	34-48
Nagata, et al. (2005)	12 Gy x 4 (isocenter)	48 Gy to isocenter	42.6 to isocenter	99 isocenter	80 to isocenter

Abbreviations: SBRT = stereotactic body radiotherapy; PTV = planning target volume; SFED = single fraction equivalent dose; BED = biologically effective dose; SED = standard effective dose; CTV = clinical target volume; CFRT = conventionally fractionated radiotherapy
*Because dose per fraction is smaller than transition dose (D_t), this was calculated using $SFED_{LQ}$.

RTOG 0915

小 结

- 不同实施技术、设备
- 处方方法差异：点、等剂量线、体积处方
- 病变大小位置
- Metrics
- 展望：肿瘤和正常组织生物学效应

小 结

中国问题：

- 适应症：报告中肺、肝、椎体（概念、临床结果）
- 前列腺、乳腺、胰腺、肾脏
- 大病变
- 多分次
- 治疗目的：根治性、姑息性

参考资料

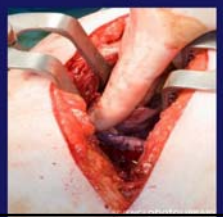
- Guidelines, books
- Clinical trials (RTOG 0618, 0813, 0915)
- Practice

Stereotactic Body Radiation Therapy: Transcending the Conventional to Improve Outcomes

Phase III Randomized study:
Stereotactic Ablative Radiotherapy vs. Surgery (SARS) in operable stage I NSCLC

SABR

Lobectomy



致 谢

中国医学科学院肿瘤医院

戴建荣

徐英杰

SBRT: The report of AAPM Task Group 101

Thank You !