Hypofractionated Radiation Therapy Can Clinical Data Further Improve the Therapeutic Ratio?

Efforts of AAPM and Others

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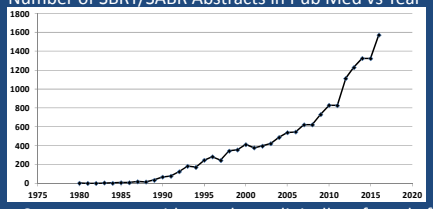
Stereotactic Body Radiotherapy (SBRT) aka Stereotactic Ablative Body Radiotherapy (SABR)

Number of SBRT/SABR Abstracts in Pub Med vs Year



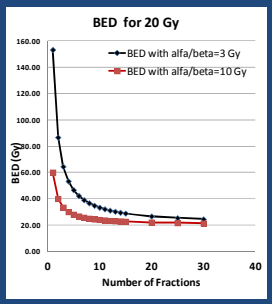
Can we extract guidance about clinically safe and effective dose distributions from critical review of this literature ?

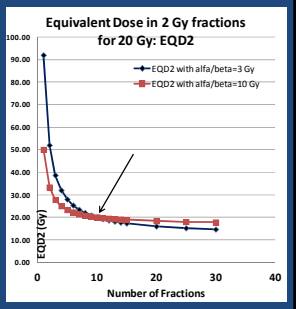
Can it help understand whether different radiobiological principles at work in SBRT vs conventional fractionation?

- High dose per fraction, small number (1-~ 10) of fractions
- Most treatments with MV photons
- Used for small-medium tumors anywhere in body
  - Primaries or mets
- With excellent immobilization and image guidance the results are very favorable
  - local control comparable or superior to conventional fractionation or surgery
  - Applicable to inoperable patients
  - Efficient for patients and probably for bottom line of depts
  - Serious complication rate is low but there have been some unexpected complications along the way
- Why so efficient? How to avoid complication?
- SBRT outcomes need analysis to understand, use better

- Cell killing does not depend on 'absorbed dose' alone
- The simple linear-quadratic (LQ) model is widely used.
- For a total dose D delivered in N fractions:
  - Biologically Effective Dose (BED) = D (1+[D/N]/[α/β])
  - Equivalent Dose in Q Gy per fx (EQDQ)=BED/(1+Q/[α/β])
    - Q is often set to 2 Gy
  - Equivalent Dose in η fx = BED /(1+ D/η]/[α/β])
    - Used to compare hypofractionated schemes
  - α/β is a sometimes-measured radiobiological parameter, often assumed to be low (1-5 Gy) for normal tissue damage, high (~ 10 Gy) for tumor control
- Measurements are tough; doubts about LQ for SBRT
  - There are fancier versions of LQ and there are other models but
  - LQ works approximately, simple to use, nothing better around

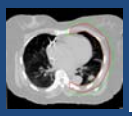
BED and EQD2 for 20 Gy
V20 is a common SBRT metric for lung

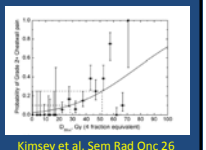




Unexpected Complication of SBRT Chest Wall Pain

- Chest wall pain, occasional rib fracture in lung sbrt
- Rare in conventionally fractionated treatment
- For dosimetry, artificial structure
  - Grade 2=Moderate pain
  - Grade 3=severe pain
  - Grade 4=disabling pain





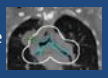
Kimsey et al, Sem Rad Onc 26

- My dept guidelines are:
  - Target coverage is primary (chest wall pain isn't lethal)
  - Try for V_30 Gy ≤ 30 cc.
  - If that compromises coverage, try for V_30 Gy ≤ 70 cc.
  - If that fails, MD counsels patient about potential for CW pain

Unexpected Complication of SBRT
Fatal (Grade 5) Complications in Lung SBRT

- Early days _Grade 5 complications in central lung sbrt with aggressive schedule (20-24 Gy x 3 fx)

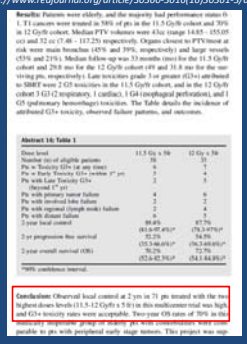
Reported by Timmerman et al, J Clin Onc 2006

No Fly Zone 

"At the time the Indiana report was published, few reports had outlined any toxicity with SABR—as if it were "magic." We shared both the positive and the negative aspects of our experience. The Radiation Therapy Oncology Group 0236 study excluded central tumors and showed considerably less toxicity than the Indiana experience using the same dose and. We await the results of the Radiation Therapy Oncology Group 0813 study, which might shed further light on this issue. For now, we fly, but fly cautiously and continue to search for safer routes of passage." *Timmerman, IJROBP 2015, V 93*

RTOG 0813 (ASTRO ABSTRACT 2016)

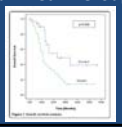
http://www.redjournal.org/article/S0360-3016(16)30361-3/abstract

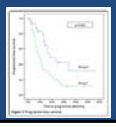


RTOG reached 60 Gy in 5 fractions
Full paper is not out yet

Unexpected Complication
Carotid Blowout Syndrome (CBOS) in SBRT for Recurrent H&N

- CBOS="rupture of the carotid artery and its branches"
- CBOS in 17.8% of 46 H&N patients retreated with SBRT
  - Median Rx 30 Gy/5 fx (Cengiz et al, IJROBP 2011, Vol 81)
- "Bleeding occurred only in patients whose carotid artery walls were circumscribed by the tumor with a degree ≥ 180°"
- CBOS in 11/75 H&N pts re-treated with SBRT (Yazici et al, Rad Onc 2013)
  - CBOS in 7/ 43 patients treated daily (Group I) and 4/32 subsequent patients treated every-other-day (Group II)
    - 1/7 survived in Group I, 2/4 survived in Group II





WGSBRT: Working Group of AAPM's Biological Effects Subcommittee
Approved in 2011: ~ 75 Members - Physicists, MDs, Radiobiologists

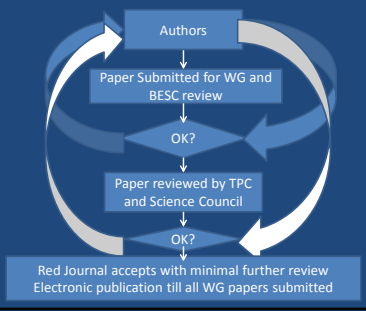
Charge

The radiobiology of hypofractionated treatments may differ considerably from that of standard fractionated treatments, in regards to repair, reoxygenation, dose-rate effects, volume effects, fraction size effects, etc. ***The working group will generate reports, including but not limited to, critically surveying the published data regarding:***

1. **Tumor response**: review of the effect of hypofractionation on local control.
2. **Normal tissue response**: review of the effect of hypofractionation on normal tissue tolerances.
3. **Radiobiology** of hypofractionated treatments.
4. **Clinical rationales** for the diverse prescription schemes in current use (e.g. 20GyX3 versus 24GyX1).
5. **Standards for reporting outcome**, including endpoints, defining/contouring of target and normal structures, dose definitions.

https://www.aapm.org/org/structure/?committee_code=WGSBRT

- Catchy names are important!
- The group adopted the nickname **HyTEC**
  - (Hypofractionation Treatment Effects in the Clinic
- Per agreement: Red Journal, TPC, Science Council



- 8 papers (organ, general) are currently in review
  - Liver TCP
  - Liver NTCP (liver enzymes)
  - SBRT retreatment of H&N cancer
  - Radiation Induced Optic Neuropathy (RION)
  - Radiation Induced Lung Toxicity (RILT)
  - Spine NTCP
  - Immunogenic Effects of SBRT
  - Indirect Cell Death
- WGSBRT annual updates at AAPM and ASTRO since 2014

- There are many reviews by other groups and authors
  - ***Seminars in Radiation Oncology, V 26 Issue 2* (2016)** combines new NTCP data and literature reviews for complications other than those underway by HyTec (Jimm Grimm was the organizer/editor)
  - ***Numerous TCP studies, focused on mechanism***
    - Lung: Liu F, et al (2017) , Radiother Oncol 122; Lung&Brain: Shuryak et al (2015) Radiother Oncol 115
  - ***Lung NTCP lit review*** (Zhao et al (2016) IJROBP 95: 1357-1366
  - ***Liver toxicity*** (Velec et al, IJROBP In Press)

WGSBRT soldiers on despite obstacles

RILT (Radiation Induced Lung Toxicity)
RILT= Radiation pneumonitis or fibrosis

- There are several different grading schemes (RTOG, SWOG, CTCAE) but crudely….
  - Grade 0: No clinical or subclinical effects
  - Grade 1: Radiographic; minimal symptoms
  - Grade 2: Symptomatic but does not interfere with Activities of Daily Life (ADL)
  - Grade 3 : Symptomatic, interferes with ADL, requires medical intervention such as steroids, oxygen
  - Grade 4: Very symptomatic, major intervention
    - Hospitalization
  - Grade 5: Death

Grade 2+

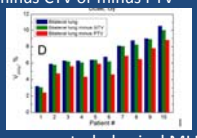
Grade 3+

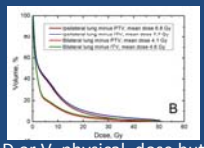
Zhao et al, "Simple Factors Associated with radiation-induced lung toxicity after stereotactic body radiation therapy of the thorax: A pooled analysis of 88 studies" (IJROBP 95, 2016)

- Search criteria
  - Before 12/14, English, lung SBRT (primary or met), no other lung RT, detailed RILT data given
  - Started with 329 studies
  - 88 studies (7752 patients) met all search criteria
  - 77 reported RP, 25 reported fibrosis
  - 65 reported Rx BED10, 14 reported MLD, 19 reported V20
- Most RILT was radiation pneumonitis: Overall Average RILT
  - 9.1 % G2+(95% CI 7.15-11.4%); 1.8% G3+ (1.3-2.5%)
- Significant factors
  - Older age (G2+), Largest tumor dimension (G2+, 3+)
- Not significant
  - Gender, Rx BED10, Histology, tumor location, GTV, PTV, Smoking status, Mean Lung Dose (MLD), V20

The WGSBRT lung subgroup further analyzed studies that reported dosimetric correlations with symptomatic RILT

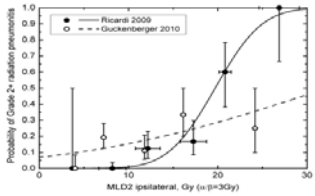
- Different studies used different grading systems
  - most were CTCAE, older papers used SWOG, RTOG)
- Studies defined the 'lung' structure differently
  - Ipsilateral lung, Bilateral lungs, bilateral lungs minus GTV or minus ITV or minus CTV or minus PTV



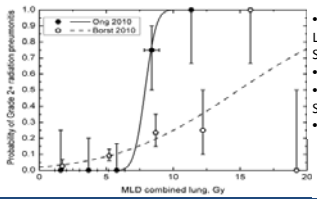


- Most papers reported physical MLD or V_physical_dose but a few reported Mean EQD2 or V_EQD2
- A strong non-dosimetric factor that contra-indicates SBRT emerged: Interstitial Lung Disease (ILD)

Mean Lung Dose



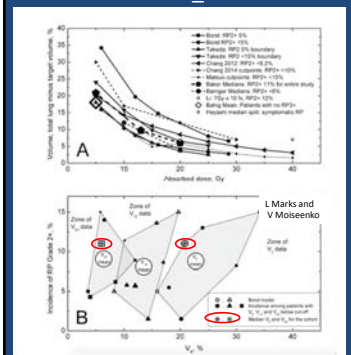
- Both use ipsilateral lung NOT CTV
- ~ equal # patients (59 and 60)
- Both use LQ corrected DVHs and calculate mean EQD2
- **Different RP definitions**
- Ricardi: RP=symptoms worsening from baseline: RTOG scoring
- Guckenberger: RP=any symptom (including radiological): gave steroids for any symptom: SWOG scoring



- Ong is a small study **(18 pts)**: Lung=combined lungs NOT PTV Scoring is CTCAE 4
- Borst has **128** pts
- Lung= combined lungs NOT GTV Scoring is CTC2 or SWOG
- Physical doses used by both

Curves generated from data in papers by V Moiseenko; Error bars are 1 SD

V20 and other V_Doses



Qualitative: lower V_x corresponds to lower RP2+

HYTECH DRAFT GUIDELINES

- For SBRT in 3-5 fractions, RILT risk is limited if bilateral MLD< 8 Gy and V20 <10-15%
- More data needed for new fractionations : **10 Gy x 7, 7.5 Gy x 8, 4 Gy x 15**
- More thorough and organized data from peer-reviewed publications is urgently needed

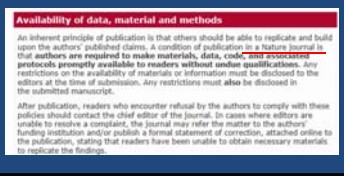
- *"Typically, papers on the dose-volume dependence of complications are not written to maximize their utility for either clinical application or subsequent meta-analysis"*
  (QUANTEC, IJROBP 76, 2010)

- The same is true of the much more recent SBRT literature
  - Rx doses reported but **dose distribution data is seldom reported** (e.g. mean dose, D_volume)
  - For studies with a wide range of Rx's, **outcomes often lumped together without consideration of fractionation effects**
  - Important **risk structures defined differently** in different reports (spinal cord, canal, thecal sac?)
  - **Different definitions** of 'local control' and specific complications used
  - **Unreported denominators**
    - Dose-volume data for those with complications but not those without

- Reporting standards must improve if future patients are to optimally benefit from today's clinical experience

Going Forward In General

- HyTec encounters the same problems as QUANTEC
  - Conventionally published information is not enough
  - Journals could require DVHs vs outcomes, treatment and treatment planning details as supplementary information
  - Outcomes should be consistently graded
- Maximizing information sharing through peer-reviewed publication would not be impossible
  - It is done by some high-ranked scientific journals


Availability of data, material and methods

An inherent principle of publication is that others should be able to replicate and build upon the authors' published claims. A condition of publication in a Nature Journal is that **authors are required to make materials, data, code, and associated protocols promptly available to readers without undue qualifications.** Any restrictions on the availability of materials or information must be disclosed to the editors at the time of submission. Any restrictions must **also** be disclosed in the submitted manuscript.

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- Due to time limitations, this material won't be in the talk but might be of interest _ Ellen Yorke

Radiation-induced Optic Nerve/chiasm Neuropathy
RION

- Cranial SRS (1 fx) and fSRS (multiple fx) used for decades
  - Leksell Gamma Knife _ 1968
- Radiation injury to optic structures can cause symptomatic vision loss
  - Patients at risk often have good expected survival
- Several grading systems
  - RTOG, LENT SOMA, CTCAE Vns 3 and 4
- Crudely
  - Grade 0 None
  - Grade 1 Asymptomatic; detected only by exam
  - Grade 2 'Mild' symptoms (depends on grading system)
  - Grade 3 Worse vision limitation
  - Grade 4 Blindness
- Test frequency and type of test varies with study

HyTec Review
Lead author Dr Michael Milano, MD

- PubMed search for papers (1990-2015)
  - Report dose to optic nerves, chiasm at least in patients with RION
    - Sufficient dose detail to estimate optic structure doses
  - Tx in 1-5 fx
    - If prior RT, the 1-5 fx group had to be separately analyzed
  - No eye or optic nerve tumors
    - Had to distinguish tumor progression effects from RION
  - No case reports (larger studies only)
- 34 studies (1578 patients)
- Year of treatment surrogate for technology
  - MRI for accurate contouring, small grid calculation)
  - All patients treated before 1997 vs some or all after 1997

Results

- Because optic structures small (nerves 1-3.5 mm diameter) Dmax usually reported and was used throughout HyTec report
- Treatment era significant factor
  - Treat ≥ 1997, no prior RT crude RION rate <1%
  - <1997 crude rate 3.6%*
- Treatment method (gamma or cyberknife, linac) not significant
- Prior RT a significant risk factor
  - Tx ≥ 1997 crude rate with prior RT is 7/61, without 9/1224
  - Denominators probably reflect sensible caution!
  - Of note: events with prior RT were at SRS Dmax<9 Gy

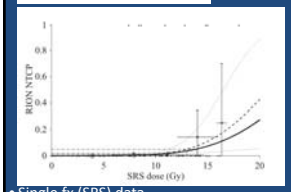
Mathematical Model

- Probit model

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-u^2}{2}} du$$

$$t = \frac{D - TD50}{m \cdot TD50}, \quad m = \frac{1}{\gamma_{50}\sqrt{2\pi}}$$

- LQ model corrected doses to accommodate data from 1-5 fx
- α/β= 1.6 Gy (also adopted in Quantec)
- $EQD2_{1.6}$ =157.3 Gy, γ_{50} =1.31 (m~0.3)



- Single fx (SRS) data
- Probit model, after 1997, no prior RT
- Two types of fits (dashed, solid)

Recommended for NTCP< 1%,

	1 fx	3 fx	5 fx
HyTec D_{max}	< 10 Gy	< 20 Gy	< 25 Gy
TG 101 $D_{0.035\ cc}$	< 10 Gy	< 17.4 Gy	< 25 Gy
Sem Rad Onc 2016, Hiniker D_{max}	< 10 Gy	< 20 Gy	< 25 Gy

- Pts with previous RT at ~ 10x risk
- Consider conventional fx!

WGSBRT Members (2014)

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Although this is an AAPM Working Group, the members include
Physicists,
Radiation Oncologists,
Neurosurgeons,
Radiobiologists,
Biomathematicians