SBRT – Milano, 24 ottobre 2014

Prospettive della SBRT tra evidenze e rischi

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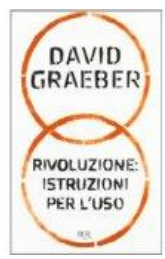
OSPEDALE SAN RAFFAELE

Prologue

…be prepared to (guide) a revolution…?

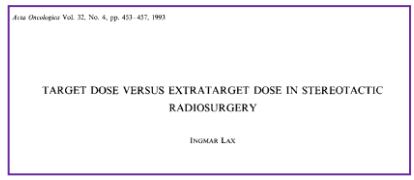


- ***Practical Utopian's Guide to the Coming Collapse***
- DAVID GRAEBER
- **[from *The Baffler* No. 22, 2013]**

…be prepared to (guide) a revolution…?

- ….In the wake of a revolution, ideas that had been considered veritably lunatic fringe quickly become the accepted currency of debate….
- Before the French Revolution, the ideas that change is good, that government policy is the proper way to manage it, and that governments derive their authority from an entity called "the people" were considered the sorts of things one might hear from crackpots and demagogues, or at best a handful of free thinking intellectuals who spend their time debating in cafés. A generation later, even the stuffiest magistrates, priests, and headmasters had to at least pay lip service to these ideas……

back to the origins…



Acta Oncologica Vol. 32, No. 4, pp. 453–457, 1993

TARGET DOSE VERSUS EXTRATARGET DOSE IN STEREOTACTIC RADIOSURGERY

INGMAR LAX

Courtesy: G. Gagliardi, Karolinska

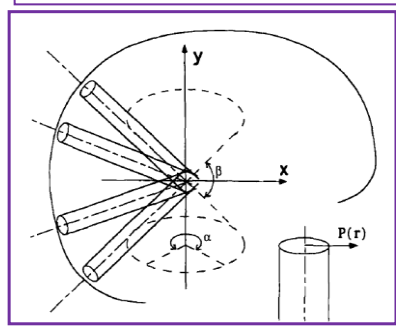


Fig. 1. Irradiation geometry. A continuum of circular beams are distributed in the angular interval α, β. For illustration purposes four discrete beams are shown. The dose profile of the single beam is P(r), cf. Fig. 3 ($\beta = 0$, D(y)). The radius of the target is R.

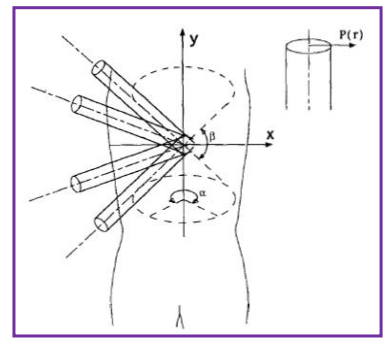
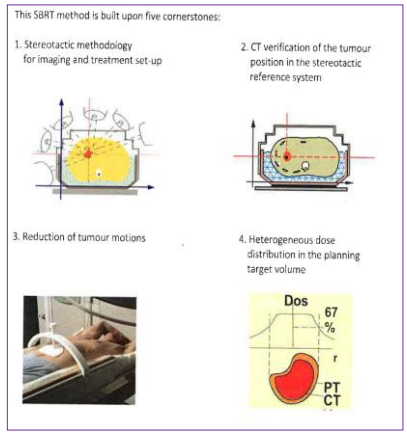


Figure Irradiation geometry. A continuum of circular beams are distributed in the angular interval ***α , β***. The radius of the beams is *R*. The dose profile of the beams is given by ***P(r)***; taken from Lax *et al* and reproduced with permission from *Acta Oncologica*.

back to the origins…



Acta Oncologica Vol. 33, No. 6, pp. 677–683, 1994

STEREOTACTIC RADIOTHERAPY OF MALIGNANCIES IN THE ABDOMEN

Methodological aspects

INGMAR LAX, HENRIC BLOMGREN, INGEMAR NÄSLUND and RUT SVANSTRÖM

"A method for stereotactic high dose-radiotherapy of malignancies in the abdomen has been developed. A stereotactic frame for the body has been developed and a method for the fixation of the patient in the frame is described".

in Italia……..The polycentric multiple arc complanar technic, or telebrachytherapy. A 4-year experience (an innovative way for the local control of solid neoplasms)

- R. Polico; L. Stea; M. Antonello; M. Princivalli; C. Marchetti; M. Busetto; S. Schiavon; G. Pizzi

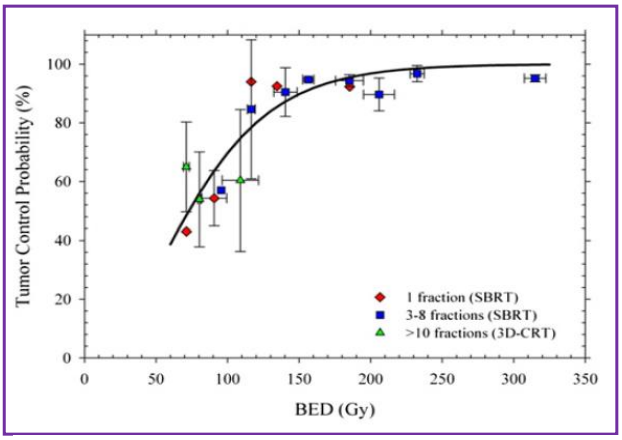
Radiologia Medica. 1995;90(1-2):113-123.

The Lancet Oncology Commission

Delivering affordable cancer care in high-income countries

Sullivan *et al*, Lancet Oncology, 2011

in select settings. SBRT delivery of large doses of radiation causes a greater radiation-induced inflammatory response, increased danger signalling, and more antitumour immunity, leading to an otherwise unpredicted improved clinical response.[169–171] Additionally, the shorter overall treatment time associated with SBRT enhances clinical control by minimising the effect of accelerated tumour repopulation, and it decreases in-patient costs. A recent multicentre cooperative group study of lung SBRT reported 3-year primary tumour control of 97·6%, significantly higher than historical rates of 30–40% achieved with conventional radiotherapy approaches.[172]



1) No indications that CFRT and SBRT produce different tumor probabilities when adjusted for BED
2) no difference in TC with single/multifraction SBRT
3**) higher TCP explained by higher tumour BEDs**

Tumor control probability (TCP) as a function of biological effective dose (BED) for stage I non-small cell lung cancer.

Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer

J. Martin Brown, PhD,* David J. Brenner, PhD,† and David J. Carlson, PhD‡

Int J Radiation Oncol Biol Phys, Vol. 85, No. 5, pp. 1159–1160, 2013

Why does SBRT work?
(i.e. why is it safe to deliver such huge fraction sizes?....the parallel organ case...lungs, liver....)

-'Parallel' normal tissues respond according to ≈ mean dose in the tissue/organ

-The mean dose is much lower than the tumour dose. Therefore the radiobiological effect is much less than is indicated by $BED_{\alpha/\beta=3}$

-Furthermore the more conformal is the treatment the lower is the mean dose (relative to the tumour dose)

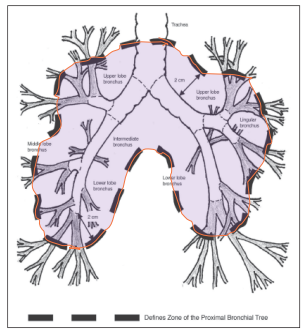
STEREOTACTIC BODY RADIATION THERAPY FOR EARLY-STAGE NON–SMALL-CELL LUNG CARCINOMA: FOUR-YEAR RESULTS OF A PROSPECTIVE PHASE II STUDY

ACHILLES J. FAKIRIS, M.D.,* RONALD C. MCGARRY, M.D., PH.D.,† CONSTANTIN T. YIANNOUTSOS, PH.D.,‡ LECH PAPIEZ, PH.D.,§ MARK WILLIAMS, M.D.,‖ MARK A. HENDERSON, M.D.,* AND ROBERT TIMMERMAN, M.D.§

*Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN; †Department of Radiation Medicine, University of Kentucky, Lexington, KY; ‡Division of Biostatistics, Indiana University School of Medicine, Indianapolis, IN; §Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX; and ‖Division of Pulmonology, Indiana University School of Medicine, Indianapolis, IN

Purpose: The 50-month results of a prospective Phase II trial of stereotactic body radiation therapy (SBRT) in medically inoperable patients are reported.
Methods and Materials: A total of 70 medically inoperable patients had clinically staged T1 (34 patients) or T2 (36 patients) (≤7 cm), N0, M0, biopsy-confirmed non–small-cell lung carcinoma (NSCLC) and received SBRT as per our previously published reports. The SBRT treatment dose of 60-66 Gy was prescribed to the 80% isodose volume in three fractions.
Results: Median follow-up was 50.2 months (range, 1.4–64.8 months). Kaplan-Meier local control at 3 years was 88.1%. Regional (nodal) and distant recurrence occurred in 6 (8.6%) and 9 (12.9%) patients, respectively. Median survival (MS) was 32.4 months and 3-year overall survival (OS) was 42.7% (95% confidence interval [95% CI], 31.1–54.3%). Cancer-specific survival at 3 years was 81.7% (95% CI, 70.0–93.4%). For patients with T1 tumors, MS was 38.7 months (95% CI, 25.3–50.2) and for T2 tumors MS was 24.5 months (95% CI, 18.5–37.4) ($p = 0.194$). Tumor volume (≤5 cc, 5–10 cc, 10–20 cc, >20 cc) did not significantly impact survival: MS was 36.9 months (95% CI, 18.1–42.9), 34.0 (95% CI, 16.9–57.1), 32.8 (95% CI, 21.3–57.8), and 21.4 months (95% CI, 17.8–41.6), respectively ($p = 0.712$). There was no significant survival difference between patients with peripheral vs. central tumors (MS 33.2 vs. 24.4 months, $p = 0.697$). Grade 3 to 5 toxicity occurred in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 patients (27.3%) with central tumors (Fisher's exact test, $p = 0.088$).
Conclusion: Based on our study results, use of SBRT results in high rates of local control in medically inoperable patients with Stage I NSCLC.

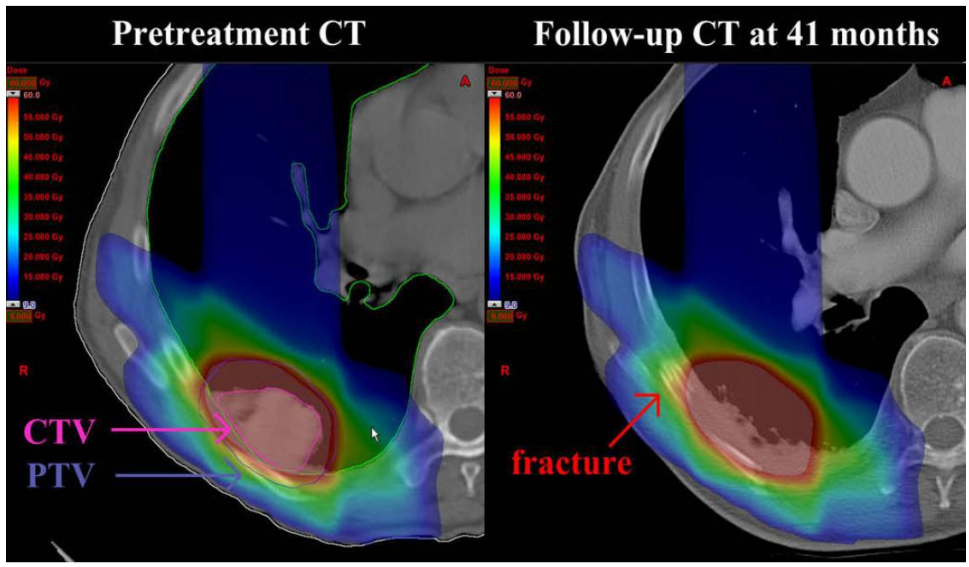
'Risk-adapted' SABR for central lesions



- RTOG-defined central "no-fly zone"
- EU data suggests "fly-with-care zone" [Haasbeek CJ, 2011; Nuyttens J, 2012]

- **Risk adapted approach** Use of daily fractions of 7.5 Gy or less, instead of 10-20 Gy per fraction [Haasbeek CJ, 2011; Nuyttens J, 2011]

Courtesy: S. Senan



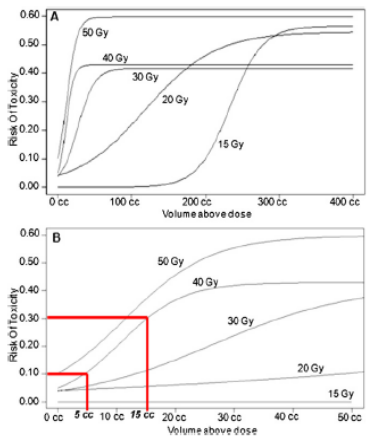
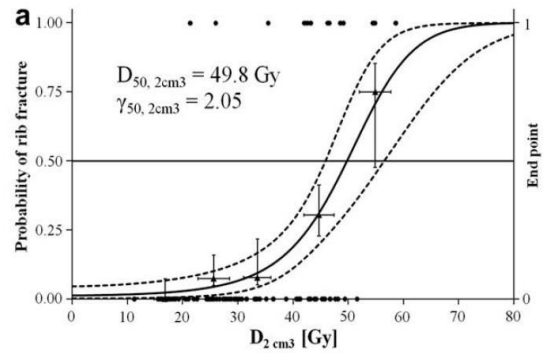


Fig. 2. Volume–risk analysis based on median effective dose–response model for development of any severity chest wall (CW) toxicity at designated dose levels: (a) risk for 0 to 400 cc and (b) 0 to 50 cc of CW receiving particular dose.

Andolino et al 2011



Petterson et al 2009

Extending the original SBRT concept…Why ?

- Practical/economical reasons
- Low α/β (or maybe low…) tumours (prostate, breast ?..... rationale for large dose/fraction in the LQ model)
- New biology of large fraction sizes (?)
- High precision RT (IGRT, ART, 4D……) may drastically reduce the overlap between PTV and OAR

- High precision RT (IGRT, ART, 4DRT…) may drastically reduce the overlap between PTV and OAR
- …but, reducing the number of fractions dramatically increases the impact of geometric uncertainties…

$$r \leftrightarrow \pi r^2 \leftrightarrow \frac{4}{3}\pi r^3$$

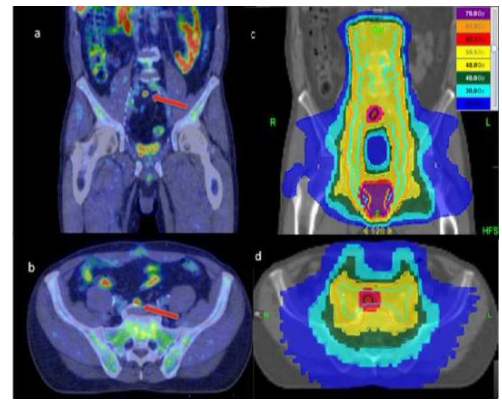
Courtesy: D. Verellen

Extending the original SBRT concept… few highly crucial warnings !!!!

- 1) A surgical-like approach may compete with surgery but may also “castrate” RT (that differently from surgery may permit to prophylatically treat large volumes !!!!!!!!)
- 2) What about late toxicity….? Fractionation has been an incredibly efficient tool to safely deliver high doses….SBRT does not exploit the sub-lethal damage repair of fractionated RT (…what about re-oxigenation ?)
- 3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

1) A surgical-like approach may compete with surgery but may also “castrate” RT (that differently from surgery may permit to prophylatically treat large volumes !!!!!!!!)

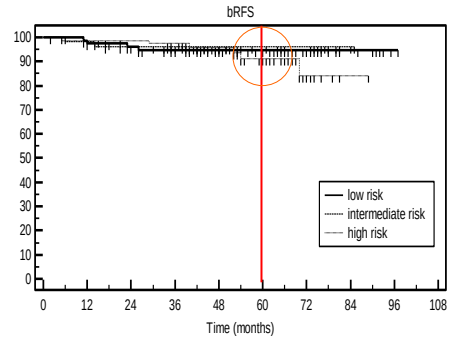
- Treating T, M, N+ only ??
- Repeating SBRT vs large fields + boost to positive volumes
- Speed of relapse outside the treated region/risk of M *vs* life expectancy….



Picchio, Fodor et al. 2013

1) A surgical-like approach may compete with surgery but may also "castrate" RT (that differently from surgery may permit to prophylatically treat large volumes !!!!!!!!)

- The prostate case: growing evidence that "volume" is as important as "dose" for intermediate-high risk patients
- Pelvic node RT (WPRT) is a low-toxicity treatment in the IMRT era (!)
- SBRT (maybe) for low-risk only ?



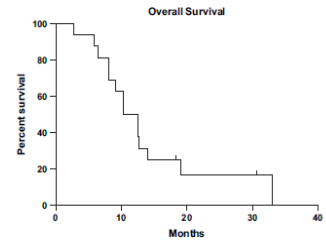
211 patients, median f-up: 5years; WPRT for all intermediate/high risk pts. 71.4/74.2 Gy to the prostate and 51.8Gy to nodes (28 fractions, SIB), Phase I_II trial with Tomotherapy (unpublished data)

2) What about late toxicity….? Fractionation has been an incredibly efficient tool to safely deliver high doses….SBRT does not exploit the sub-lethal damage repair of fractionated RT (…what about re-oxigenation ?)

- To be aware that, in most cases with a well tailored dose distributions delivering relevant doses to OARs, SBRT is detrimental compared to conventionally fractionated RT (LQ-corrected BED/EQD2)
- Ex: extension of SBRT in the abdomen, re-treatments,….

GEMCITABINE CHEMOTHERAPY AND SINGLE-FRACTION STEREOTACTIC BODY RADIOTHERAPY FOR LOCALLY ADVANCED PANCREATIC CANCER

Devin Schellenberg, M.D.,* Karyn A. Goodman, M.D.,† Florence Lee, B.S.,* Stephanie Chang, B.A.,* Timothy Kuo, M.D.,‡ James M. Ford, M.D., Ph.D.,§ George A. Fisher, M.D., Ph.D.,§ Andrew Quon, M.D.,¶ Terry S. Desser, M.D.,¶ Jeffrey Norton, M.D.,‖ Ralph Greco, M.D.,‖ George P. Yang, M.D., Ph.D.,‖ and Albert C. Koong, M.D., Ph.D.*



(CA)19-9 levels either at diagnosis or after Cyberknife SBRT had longer survival (p <0.01). Acute gastrointestinal toxicity was mild, with 2 cases of Grade 2 (13%) and 1 of Grade 3 (6%) toxicity. Late gastrointestinal toxicity was more common, with five ulcers (Grade 2), one duodenal stenosis (Grade 3), and one duodenal perforation (Grade 4). A trend toward increased duodenal volumes radiated was observed in those experiencing late effects

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- Late toxicity often unpredictable
- Reports of unexpected toxicities with hypo/SBRT
- LQ-model is less reliable (unreliable?) for NTCP estimates with (very) high dose-fraction
- Evolution to late damage much more complex than LQ predictions….role of fibrosis, vascularization

- Lack of controlled trials !!!!!

Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology

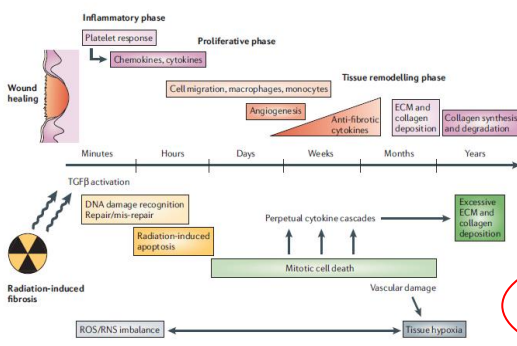
Søren M. Bentzen

Educational review

Pathogenetic mechanisms in radiation fibrosis

John Yarnold[a,*], Marie-Catherine Vozenin Brotons[b,c]

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)



- The classical framework for discussing early and late side effects was the target-cell hypothesis: that the severity of side effects mainly reflected cell depletion as a result of the direct cell killing of a putative target cell leading to subsequent functional deficiency. This was the prevailing biological model until the mid 1990s.
- Recent research in radiobiology and molecular pathology has caused a change of paradigm, particularly in the understanding of late effects: radiation induces a concerted biological response at the cell and tissue level effected by the early activation of cytokine cascades.
- Fibrogenesis and excessive extracellular matrix and collagen deposition has a key role in the development and expression of many types of late effects. This can be seen as a wound-healing response gone wrong.

Box 1 | **The heyday of the target-cell hypothesis**

Box 3 | **Predisposing factors for radiotherapy-related side effects**

- …the intensity of the inflammatory phase may highly impact on the evolution to fibrosis…and depends (also) on the daily dose (!!!)

Bentzen et al. 2006

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- The breast case

EDITORIAL

REPORTS OF UNEXPECTED LATE SIDE EFFECTS OF ACCELERATED PARTIAL BREAST IRRADIATION—RADIOBIOLOGICAL CONSIDERATIONS

SØREN M. BENTZEN, PH.D., D.SC.,* AND JOHN R. YARNOLD, M.D., FRCR.†

*Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI and †Section of Radiotherapy, Institute of Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom

The atrophic/fibrotic radiation response pathway is a major component of many late radiation side effects, and although the pathogenesis is complex (17), there is a clear dose–incidence relationship and a well-characterized fractionation sensitivity of the clinical endpoints that reflect this response pathway (18). Fibrosis is strongly associated with breast appearance and cosmesis, as illustrated by Hepel *et al.* (2), who

The Effect of Dose-Volume Parameters and Interfraction Interval on Cosmetic Outcome and Toxicity After 3-Dimensional Conformal Accelerated Partial Breast Irradiation

Kara Lynne Leonard, MD, MSc,* Jaroslaw T. Hepel, MD,*,† Jessica R. Hiatt, MSc,† Thomas A. Dipetrillo, MD,*,† Lori Lyn Price, MSc,† and David E. Wazer, MD*,†

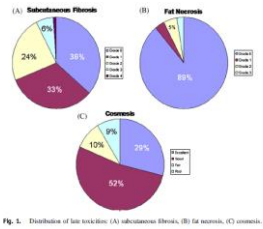


Fig. 1. Distribution of late toxicities: (A) subcutaneous fibrosis, (B) fat necrosis, (C) cosmesis.

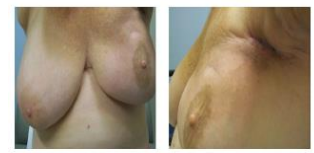
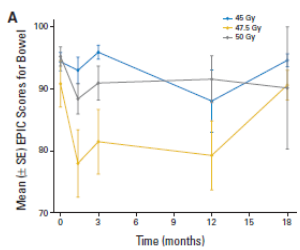


Fig. 2. Patient with grade 3 subcutaneous fibrosis and poor cosmesis at 1 1/2 years of follow-up. Firm induration replaced most of the left breast with associated volume loss, marked axillary scar retraction, and skin hyperpigmentation.

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- The rectum case

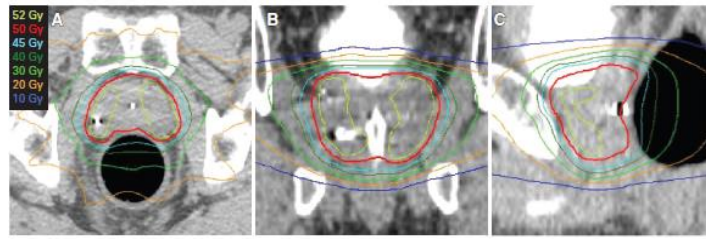


Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

Thomas P. Boike, Yair Lotan, L. Chinsoo Cho, Jeffrey Brindle, Paul DeRose, Xian-Jin Xie, Jingsheng Yan, Ryan Foster, David Pistenmaa, Alida Perkins, Susan Cooley, and Robert Timmerman

Conclusion
Dose escalation to 50 Gy has been completed without DLT. A multicenter phase II trial is underway treating patients to 50 Gy in five fractions to further evaluate this experimental therapy.

Results
Groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in five fractions (45 total patients). The median follow-up is 30 months (range, 3 to 36 months), 18 months (range, 0 to 30 months), and 12 months (range, 3 to 18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all



3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- The rectum case

Rectal volume receiving 50 Gy, cm^3	Clinical sequelae	Location of rectum
4	Diverting colostomy for symptom relief	Anterior rectum
8.66	Rectourethral fistula; diverting colostomy	Anterior 1/8 circumference
1.2	Cauterized and symptoms resolved next day	Posterior rectum, Dieulafoy lesion (AVM)
5.6	Diverting colostomy due to pain, which was reversed after pain resolved	Anterior rectal wall Necrosis and 8 cm ulcer,
4	Rectourethral fistula; diverting colostomy;	Anterior midline rectal wall
3.36	Diverting colostomy	Anterior rectum

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

Results: At the highest dose level, 6.6% of patients treated (6 of 91) developed high-grade rectal toxicity, 5 of whom required colostomy. Grade 3+ delayed rectal toxicity

- 10Gy x 5: 5 colostomy/61 pts !!!!
- Evidence of a threshold effect

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- The bladder case (post-op RT)

Higher-than-expected Severe (Grade 3–4) Late Urinary Toxicity After Postprostatectomy Hypofractionated Radiotherapy: A Single-institution Analysis of 1176 Patients

Cesare Cozzarini[a,], Claudio Fiorino[b], Chiara Deantoni[a], Alberto Briganti[c], Andrei Fodor[a], Mariangela La Macchia[a], Barbara Noris Chiorda[a], Paola Maria Vittoria Rancoita[d], Nazareno Suardi[c], Flavia Zerbetto[a], Riccardo Calandrino[b], Francesco Montorsi[c], Nadia Di Muzio[a]*

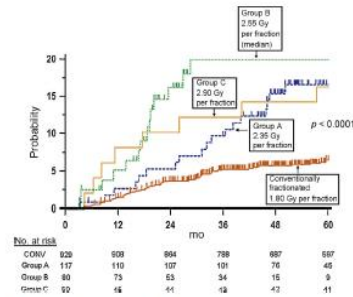


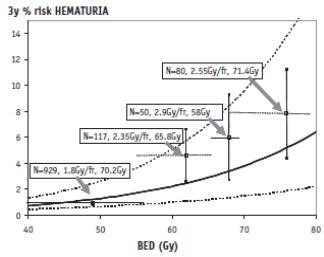
Fig. 2 – Risk of 5-yr severe (Grade ≥3) late urinary sequelae in the conventionally fractionated and hypofractionated cohorts. CONV = conventionally fractionated.

- Unexpected late severe GU tox with moderate HYPO in post-op
- 1176 pts, 929 CONV, 247 HYPO

Cozzarini et al, Eur Urol in press

3) Unexpected toxicities may occur with large dose/fraction…LQ model was extended to normal tissues, but….(!)

- The bladder case (post-op RT)



Physics Contribution

Modelling the Impact of Fractionation on Late Urinary Toxicity After Postprostatectomy Radiation Therapy

Claudio Fiorino, PhD,* Cesare Cozzarini, MD,† Tiziana Rancati, PhD,‡ Alberto Briganti, MD,§ Giovanni Mauro Cattaneo, PhD,* Paola Mangili, PhD,* Nadia Gisella Di Muzio, MD,† and Riccardo Calandrino, PhD*

Intent	FRACT	Dose / fraction (Gy)	Total dose (Gy)	n	EQD2 α/β=5	EQD2 α/β=3	EQD2 α/β=0.4*	% 3-year incidence
SALV	CONV	1.8	73.8	290	71.5	71	67.5	4 ± 1
ADV	CONV	1.8	70.2	639	68	67.5	64	6 ± 1
ADV	HYPO	2.35	65.8	117	69	70.5	75.5	11 ± 3
ADV	HYPO	2.9	58	50	65.5	68	80	14 ± 5
SALV	HYPO	2.55	71.4	80	77	79	88	21 ± 5

Letter to Editor, Eur Urol accepted

- Best-fit with LQ: best α/β values <1
- Introducing a time factor γ (consequential effect ?) fixing $\alpha/\beta=5$
- Best fit values for $\gamma \approx 0.7$-0.8 Gy/day

Conclusions

- After a long “low-profile” period, SBRT is nowdays a well recognized and reputed technique
- Clinically relevant results have been reported especially for lung and liver malignancies
- Appealing of the technique also due to its practical and economical benefits
- Don’t forget the increased risks of missing the target when reducing the number of fractions and/or reducing margins and be cautious for centrally located lung T and in proximity of ribs
- Risks of SBRT outside its “classical” domain (i.e.: “small” target(s) embedded by a “parallel” organ)

Conclusions: Risks of SBRT outside its classical domain

- 1) A surgical-like approach may compete with surgery but may also "castrate" RT…..
- 2) What about late toxicity….? Fractionation has been an incredibly efficient tool to safely deliver high doses….
- 3) Unexpected toxicities may occur with large dose/fraction…LQ model not valid for normal tissues (the fibrotic pathway…)

- Don't put "economy" first !

Need of controlled Phase III trials !!!

Brief Reports and Opinion

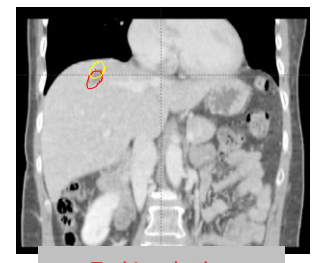
Ego-Based Medicine

Jekwon Yeh, MD,* Arthur Kagan, MD,* and Richard Steckel, MD†

interpretation of the available scientific evidence. Whether the clinical gain versus morbidity associated with a treatment is acceptable is based entirely on the patient. All too often treatments are rendered to patients without their entire understanding of the true benefits and morbidity. A certain morbidity may be considered tolerable to one patient but not to another. The physician's job is to help guide the patient toward a treatment course based on an understanding of the patient's personal values. A patient's choice is ultimately based on their understanding of the pros and cons of a certain treatment. They are in

Ringraziamenti

- GM Cattaneo, C. Cozzarini, N. Di Muzio, P. Passoni
- G. Gagliardi, D. Verellen, S. Senan



--- End Inspiration
--- End Expiration