HDR and SBRT: Competitive treatments?

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Disclosures

Non-salaried Consultant for Nucletron.

I have received honoraria for lectures from Varian & Zeiss.

Outline of the presentation

- Definition of SBRT/HDR-IGBT/IORT:
- Potential advantages of BT:
- "New biology" in SBRT, HDR-IGRT & IORT?:
- Lung Model: an example of non competitive treatment with SBRT & HDR-IGBT?:
- Breast Model: an example of competitive treatment with IORT & HDR-IGBT in APBI?:
- Prostate Model: an example of complementary or competitive treatment with EBRT/SBRT & HDR-IGBT?:
- Conclusions:

Stereotactic Ablative Body Radiotherapy (SABR or SBRT): What's in name

The accurate delivery of highly conformal, high-dose radiation therapy to limited-volume targets in the body with:

- High dose per fraction (> 7-10 Gy)
- Single or few fractions (1-5) in 1-1.5 wks
- Highly precise image-guided radiation delivery
- Rapid dose fall-off gradients encompassing target

Loo BW et al.
Practical Radiation Oncology (2011) 1, 38–39

IGBT with HDR: What's in name

The precise delivery of highly conformal, high dose radiation therapy to limited-volume targets in the body with:

- High dose per fraction (> 7-10 Gy)
- Single or few fractions (1-5) in 1-1.5 wks
- Highly precise image-guided radiation delivery
- Rapid dose fall-off gradients encompassing target

But with in IGBT with HDR:

- Lower integral dose.
- Longer clinical experience than SBRT.

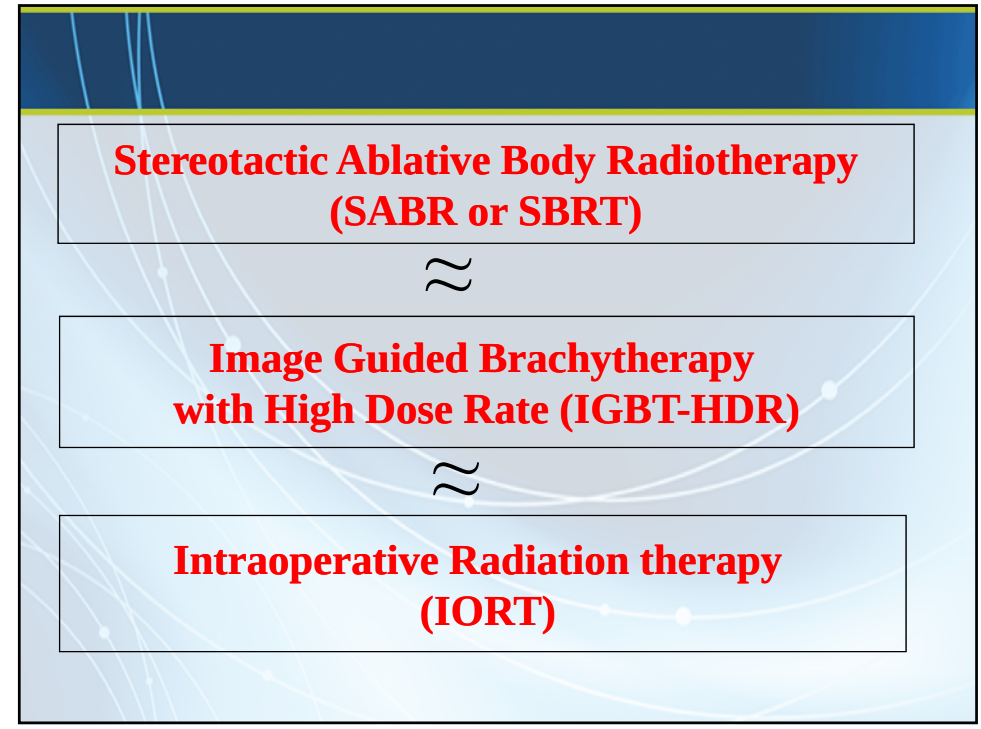
IORT: What's in name

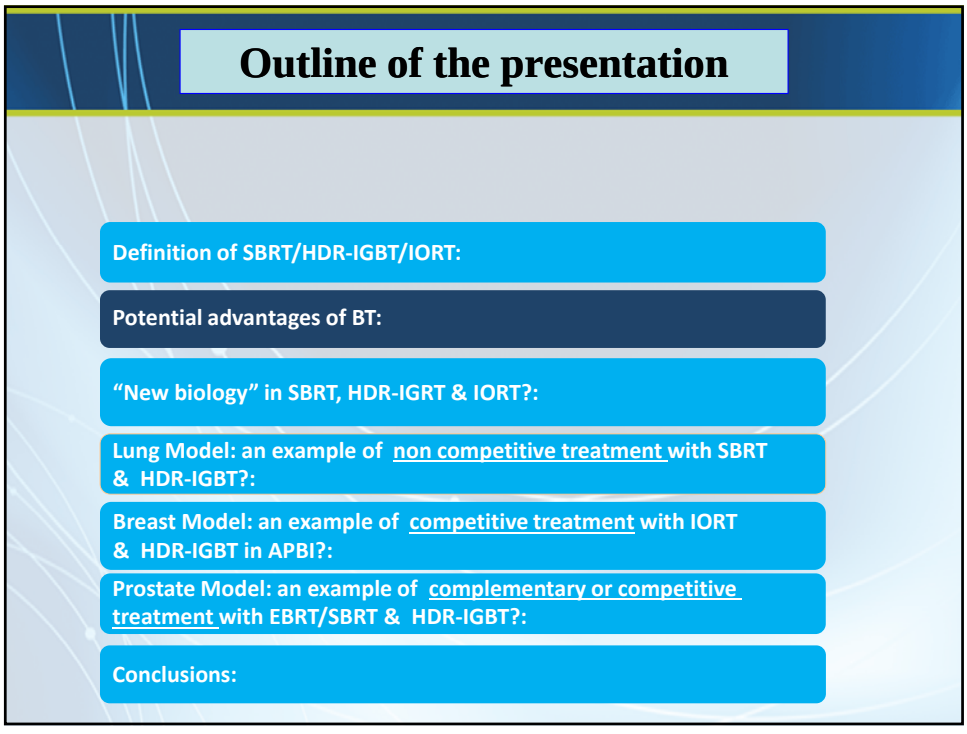
The precise delivery of highly conformal, high dose radiation therapy to limited-volume targets in the body with:

- High dose per fraction (> 7-10 Gy)
- Single or few fractions (1-5) in 1-1.5 wks
- Highly precise image-guided radiation delivery
- Rapid dose fall-off gradients encompassing target

But with IORT:

- Lower integral dose.
- Local treatment in one single shot (Surgery + RT) .


Stereotactic Ablative Body Radiotherapy (SABR or SBRT)
≈
Image Guided Brachytherapy with High Dose Rate (IGBT-HDR)
≈
Intraoperative Radiation therapy (IORT)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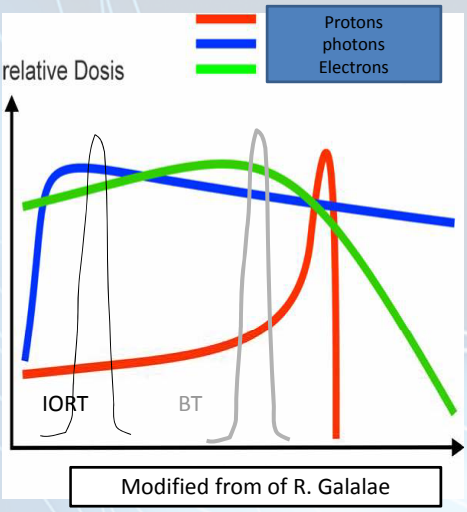
Conclusions:

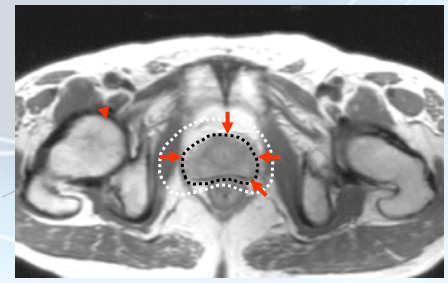
Potential of IORT: Integral dose very low



Modified from of R. Galalae

Potential of IORT: Moving Target: No problem in BT & IORT but remains a problem in EBRT

BT for Prostate: CTV = PTV
No extra margin necessary.
No ITV. Much smaller PTV



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"New Biology" & SBRT

Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2011, Article ID 439752, 7 pages
doi:10.1155/2011/439752

Review Article

The Confluence of Stereotactic Ablative Radiotherapy and Tumor Immunology

Steven Eric Finkelstein,[1] Robert Timmerman,[2] William H. McBride,[3] Dörthe Schaue,[3] Sarah E. Hoffe,[4] Constantine A. Mantz,[1] and George D. Wilson[5]

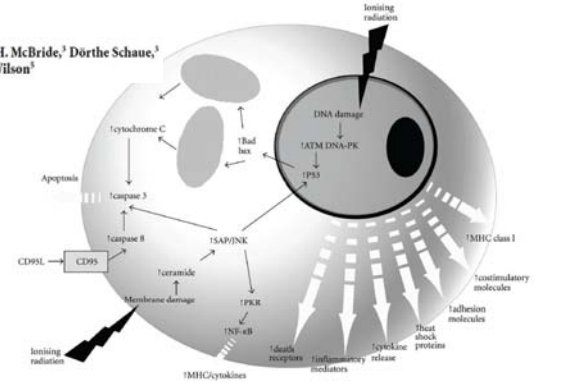

FIGURE 1: *Confluence of SABR and Immunotherapy.* Apoptosis can be initiated by SABR-induced DNA damage and upregulation of the p53 tumor suppressor gene. In addition, apoptosis can be triggered by SABR-induced damage to the cellular lipid membrane, which can induce ceramide formation and activate the SAPK/JNK signaling pathway. Thus, SAPK/JNK can upregulate PKR expression, which can induce MHC and cytokines via NF-κB. SABR can induce cellular expression of MHC Class I, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors.

By courtesy of E. Lartigau.

"New Biology" for SBRT? Ceramide?

...Concurrently with these clinical developments (SBRT), laboratory studies have suggested that at high dose fractions (>8-10 Gy) there may be additional biological processes resulting in enhanced tumor cell killing.

High radiation doses produce Sphingolipid ceramide, is to say sphingomyelinase-dependent rapid vascular collapse that markedly enhances the antitumor effect of radiation...

Garcia-Barros M, Paris F, Cordon-Cardo C, *et al.* Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science, 300 (2003):1155–9
Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. Cancer Cell, 8 (2005):89–91

Corbin KS, et al. (USA)
Extracranial oligometastases: a subset of metastases curable with SBRT
J Clin Oncol. 2013;31(11):1384-90

Brown JM, Brenner DJ, Carlson DJ, (USA)
Dose escalation, not "new biology," can account for the efficacy of SBRTwith NSCLC
Int J Radiat Oncol Biol Phys. 2013;85(5):1159-60

"New Biology" for SBRT? T Cells?

...These antitumor effects were not observed with conventional fractionated radiotherapy or with chemotherapy.
The abscopal or bystander effects of high-dose RT (SBRT/SABR) are consistent with some reports demonstrating Tcells (CD8+ T cells) have antitumoral effects to tumors outside the treatment field after SBRT/SABR was delivered...

Brown JM, Brenner DJ, et al. (USA)
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Int J Radiat Oncol Biol Phys. 2013;85(5):1159-60

Corbin KS, et al. (USA)
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Extracranial oligometastases: a subset of metastases curable with SBRT

"New Biology" for IORT?

...Surgical wound fluids (WF) stimulated proliferation, migration and invasion of breast cancer cell lines. The stimulatory effect was almost completely abrogate when fluids from IORT treated patients were used.

This novel antitumoral effect could , at least partially, explain the very low recurrence rates found in trials with IORT in breast...

Modified from Belleti B., Baldassarre G., et al.
TARGIT impairs the stimulation of Breast Cancer Cell proliferation and invasion caused by surgical wounding
Clin Cancer Res 14. 1325-1331. 2008.

"New Biology" for IORT?

... Two signaling pathways differentially activated by surgical wound fluids (WF) from control and IORT treated patients, namely p70S6K and STAT3.

Their activation is necessary to stimulate local recurrences...

Modified from Segatto I., Baldassarre G., et al.
p70S6 kinase mediates breast cancer cell survival in response to surgical wound fluid stimulation-
Molecular Oncology 8. 766-780. 2014.

"New Biology" for HDR-IGBT?

Any of these factors
(Sphingolipid ceramide, CD8+ T cells, signaling pathways p70S6K and STAT3, etc) colloquially termed a "new biology", could make HDR-IGBT more effective than would be predicted from new technologies in BT?

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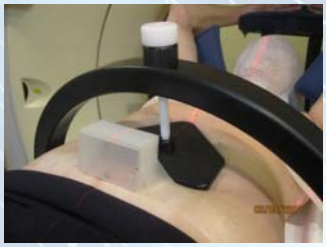
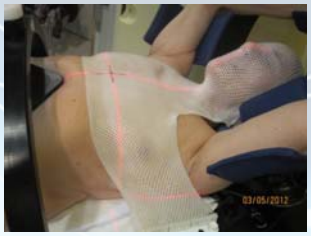
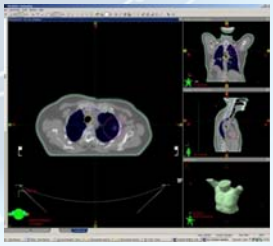
Clinical Trial for lung SBRT at ICO

1. **Phase II SBRT in stage I NSCLC (from 4-2008 to 6-2012)**

* 3 fractions of 18 Gy in T <2 cm at >2 cm from mediastinum.

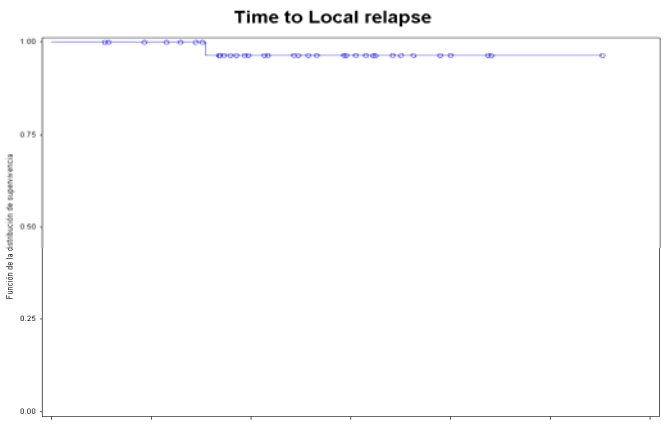
Phase II trial at ICO with outcomes at 2 years of patients with stage I NSCLC non operables treated with SBRT (3x18Gy)

Of 160 patients treated at ICO for Lung Tumors, results of the first 43 patients:

<u>Median FU: 24m.</u>

<u>LC: 96.4% at 24m.</u>

<u>OS: 79.1% at 24m</u>.



Stereotactic Ablative Body Radiotherapy (SABR or SBRT)

in Lung is non competitive with:

Image Guided Brachytherapy with High Dose Rate (IGBT-HDR)

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ELIOT Phase III Trial (Milan, Italy)

1305 pts were randomized (654 pts to WBI with 50 Gy + 10 Gy & 651 to IORT with electrons 21 Gy).

After a medium FU of 5,8y., 35 patients in IORT group and 4 patients in WBI had had a LR (p<0·0001). The 5y rate for LR was 4,4% in IORT group and 0,4% in WBI.

In patients with data available (n=464 for IORT & n=412 for WBI) they noted significantly less skin side-effects in the IORT group vs the WBI group (p=0,0002).

Veronesi U, et al. (Italy)
Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial
Lancet Oncol. 2013;14(13):1269-77

Pacients out the ELIOT Phase III Trial (Milan, Italy)

To evaluate outcomes among early-stage breast cancer patients after WBI & IORT (ELIOT) by applying the GEC-ESTRO recommendations.

1815 cases could be classified according to GEC-ESTRO groups: 573 patients were included in the "good candidates" group, 46 in the "possible candidates" group and 767 in the "contraindication" group.

The 5y rate of in-breast LR for "good candidates", "possible candidates" and "contraindication" groups were 1.9%, 7.4% and 7.7%, respectively (p=0.001).

Leonardi MC, Veronesi U, Orecchia R, et al. (Italy)
Radiat Oncol 2013 106(1):21-7
Accelerated partial breast irradiation with intraoperative electrons:
using GEC-ESTRO recommendations as guidance for patient selection

Targit Phase III Trial

The 5y LR was 3·3% for TARGIT (20 Gy +/- 50 Gy WBI if adverse features were detected on final pathology) vs 1,3% for WBI (50 Gy + boost) with p=0,042.

TARGIT concurrently with lumpectomy (2298 pts) had much the same results as WBI: 2,1% vs 1,1% (p=0,31).

With delayed TARGIT (1153 pts) LR for TARGIT was 5,4% vs 1,7% for WBI with p=0,069.

Vaidya JS, Wenz F, et al. (USA)
Lancet. 2013;S0140-6736(13)61950-9
Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Hungarian APBI Phase III Trial

In a series of 258 pts, APBI delivered by interstitial HDR BT (7x5,2 Gy) or EB for early breast cancer pts produces similar 10y. results to those achieved with conventional WBI (LR of 5,9% vs 5,1%, p=0,77 & OS of 80 vs 82% & DFS of 85 vs 84%).

Significantly better cosmetic outcome can be achieved with HDR BT compared with WBI (81 vs 63%, p<0,01)

Polgár C, Fodor J, Major T, Sulyok Z, Kásler M (Hungary)
Radiother Oncol. 2013;108(2):197-202
Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial

GEC-ESTRO APBI Phase III Trial

After a median FU of 4 y. of GEC-ESTRO phase III trial of 1195 pts

comparing WBI (50 Gy + 10 Gy)

vs

HDR-APBI catheters technique

(8x4 Gy in majority of cases),

they found less skin toxicity in HDR group (p<0,0001).

Strnad V., et al.
Radiother Oncol. 2012. abstract presented during the meeting.
Preliminary results of Breast-conserving therapy with partial or whole breast irradiation: GEC-ESTRO phase III trial

Breast model at ICO

1. Standard treatment:

Low risk Breast cancer:
*** 46-50 Gy 3D CRT**
+ Electrons (16-20 Gy) or BT (3 fractions of 4,5-5 Gy)

2. APBI:

Following the recommendations GEC-ESTRO for selection criteria:
*** 8-10 fractions of 4-3,4 Gy.**

Polgar C, Van Limbergen, Polo A, Guedea F, et al.
Radiother Oncol. 94(3): 264-73. 2010.
Patient selection for APBI after breast-conserving surgery: recommendations of the GEC-ESTRO breast cancer working group based on clinical evidence.

Intraoperative Radiation therapy (IORT)

in Breast is competitive with:

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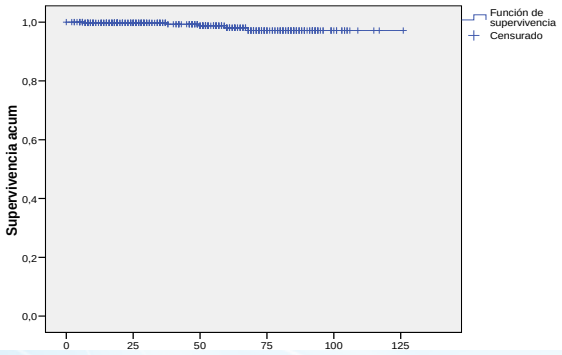
Results of 377 pts with High Risk Prostate cancer treated with EBRT (60 Gy) + HDR-BT (9 Gy) + AD 3y at ICO. Median FU: 48,7 months.

Survival free of biochemical relapse: 91% at 5y. & 89% at 10y.



Boladeras A., Guedea F., Submited to Rad & Oncol.

Prostate model at ICO

1. Standard treatments:

Low–intermediate risk prostate cancer:
* Seeds in Low risk and EBRT and seeds for intermediate risk.

High risk prostate cancer:
* 60 Gy IMRT + 9 Gy HDR +AD.

2. Clinical Trials:

Phase II study of high dose SBRT for low & intermediate risk:
* 5 fractions of 7 Gy.

Phase II study of high dose SBRT for high risk prostate cancer:
* 60 Gy IMRT + 9 Gy SBRT +AD.

S, Langley, F. Guedea, et al.
BJU 2009

JM. Pistis, F. Guedea, et al. (USA)
Brachytherapy 2010

Stereotactic Ablative Body Radiotherapy (SABR or SBRT) or EBRT

in Prostate are competitive or complementary with:

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...Tremendous advances in radiation therapy technology

Improved tumour control
(eg, SBRT on lung cancer, SRC, BT with I-125 or HDR)
Less toxicity
(eg, IMRT for H&N, IMRT for Prostate, IGBT)
& Shortened treatment courses
(eg, Moderate Hypofractionation, Extreme Hipofractionation, APBI, IORT)

decrease the indirect costs of cancer care, including lost time and economic productivity secondary to treatment ...

Modified from R Sullivan et al (UK & other countries)
Delivering affordable cancer care in high-income countries
The Lancet Oncology Commission
Lancet Oncol. 12. 933-80. 2011.

But in some tumors (Breast, Prostate,…) these new technologies in EBRT (SBRT,…), in IORT, & new technologies in Surgery are competitive techniques with HDR-IGBT