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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Management of oligometastatic lung cancer and brain metastases

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University of Heidelberg

Disclosures

Research funding from Elekta/Carl Zeiss Meditec

Medical advisor for Elekta

Teaching center for Elekta/Carl Zeiss Meditec

Journal of Clinical Oncology, Vol 13, No 1 (January), 1995: pp 8-10

Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mecha-

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or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*.

Journal of Clinical Oncology, Vol 13, No 1 (January), 1995: pp 8-10

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EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized

treatments. Tumors early in their progression should be amenable to localized therapy. Patients with oligometastases, either de novo or following systemic treatment, should be cured by ablation of these lesions. More advanced disease will require more aggressive and effective systemic treatment.

FORSCHUNGS CAMPUS M²OLIE

Oligometastases

Cancer as a chronic disease

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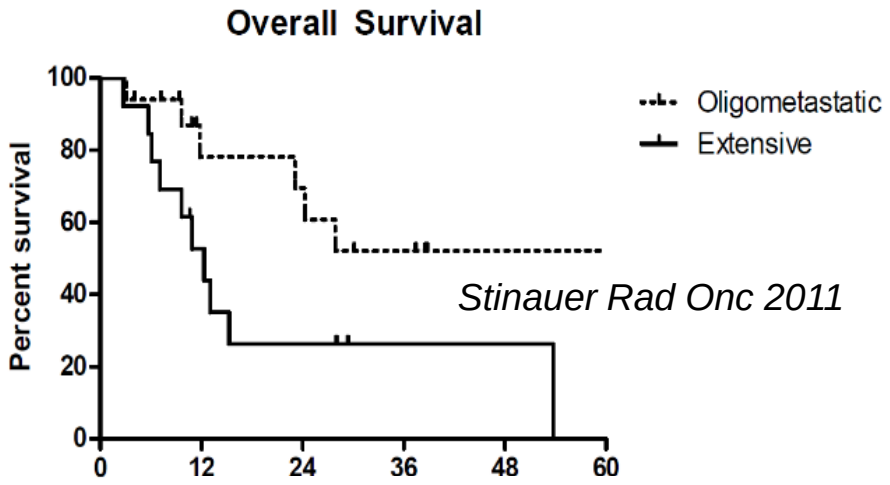
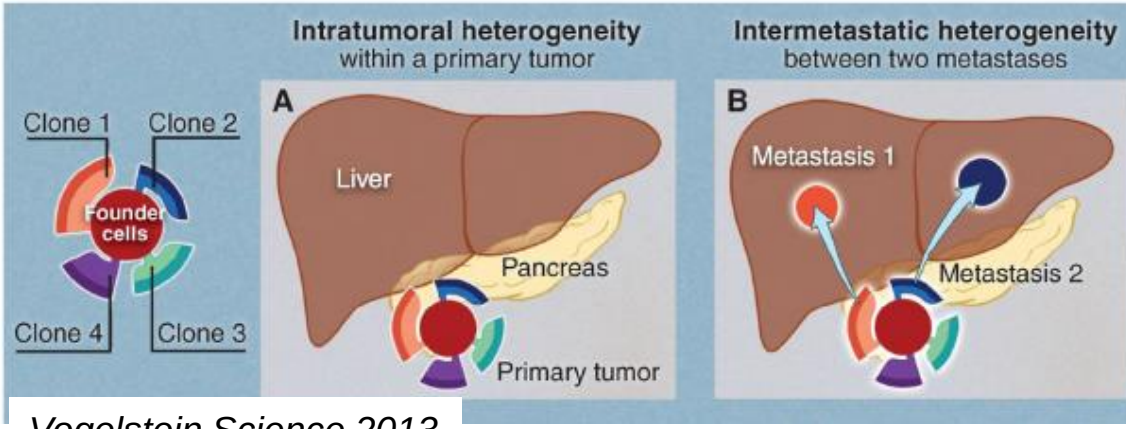
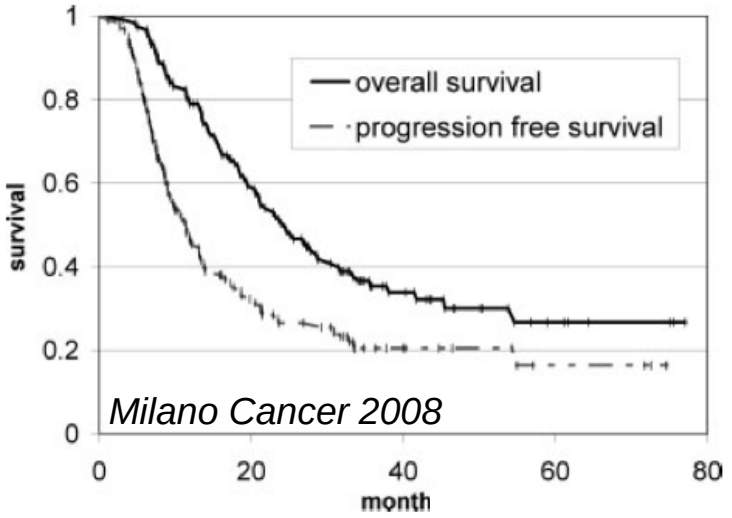
- curative potential @ M1
  → **patient selection**
- demographic development
  → **minimally invasive Dx/Tx**
- clonal heterogeneity
  → **local ablative therapy**





Vogelstein Science 2013



GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

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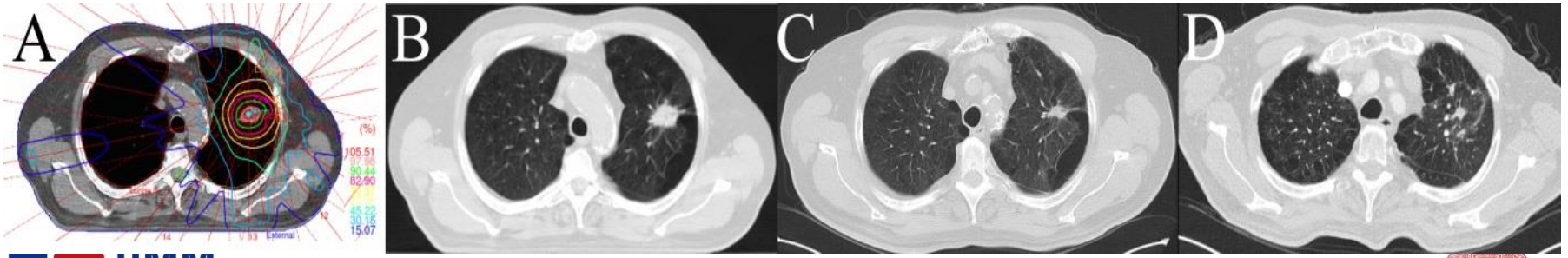
Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Journal of Clinical Oncology, Vol 31, No 11 (April 10), 2013: pp 1384-1390

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, *University of Chicago Medical Center, Chicago, IL*

Radiation Series	Year	No. Patients	No. Lesions	Local Control (%)	Survival (%)	Site
Blomgren et al	1995	31	42	80	Not reported	Liver, lung, and retroperitoneum
Wulf et al	2004	41	51	80	33[g]	Lung
Hoyer et al (colorectal cancer)	2006	64	141	86[g]	38[g], 13[h]	Lung, liver, and adrenal
Hof et al	2007	61	71	63[i]	47.8[i]	Lung
Rusthoven et al	2009	47	63	92[g]	30[g]	Liver
Rusthoven et al	2009	38	63	96[g]	39[g]	Lung
Kang et al (colorectal cancer)	2010	59	78	66[i]	49[i]	Multiple
Okunieff et al	2006	49	125	83[i]	25[j]	Lung
Katz et al	2007	69	174	57[k]	24[l,m]	Liver
Lee et al	2009	70	143	71[m]	47[n]	Liver
Milano et al	2011	121				Multiple[p]
Breast cancer		39		87[o]	74[g], 47[o]	
All others		82		65[o]	39[g], 9[o]	
Salama et al	2011	61	111	66.7[g,q]	56.7[g]	Multiple
Bae et al (colorectal cancer)	2012	41	50	64[i], 57[h]	64[i], 38[h]	Lung, liver, and lymph node
Norihisa et al	2008	34		90[g]	84.3[g]	Lung



from Simoenova et al 2012

Radical Irradiation of Extracranial Oligometastases

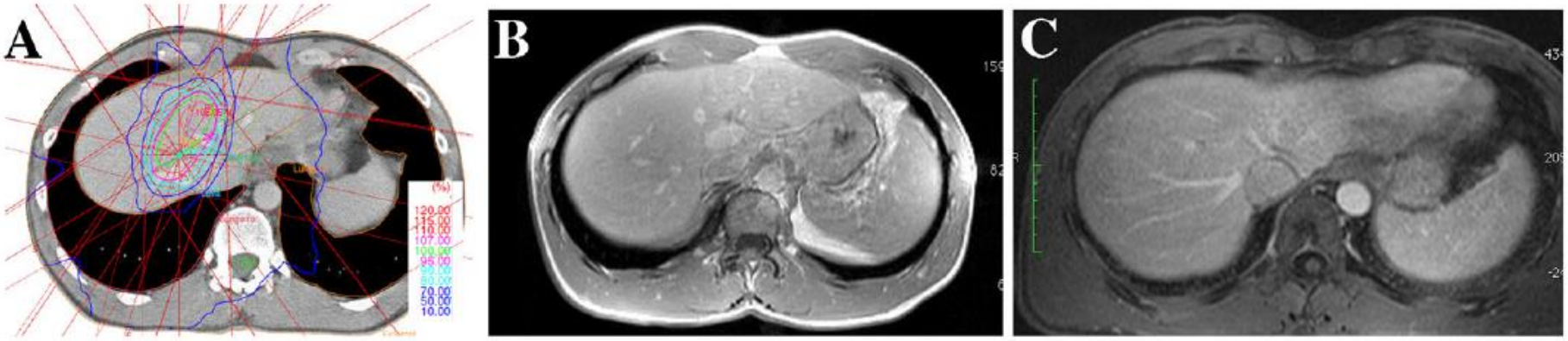
Joseph K. Salama and Michael T. Milano

J Clin Oncol 32:2902-2912. © 2014

Table 2. Selected Studies of Oligometastatic Patients Treated With Irradiation of All Known Metastases

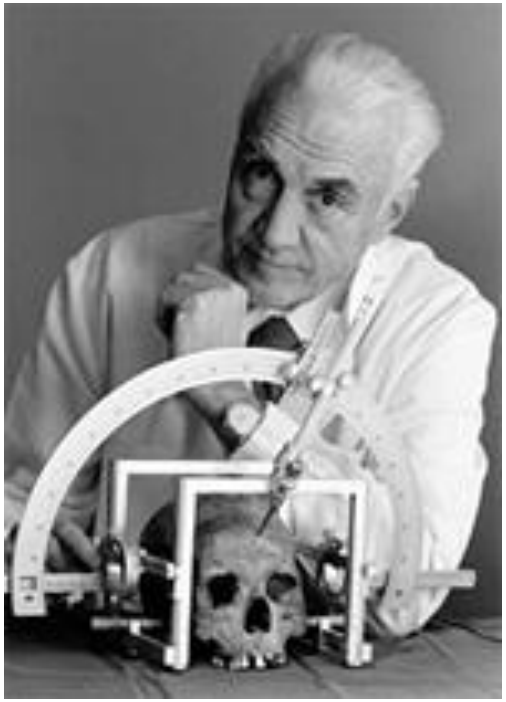
Study	No. of Patients	No. of Metastases per Patient		Dose (Gy)		Follow-Up (months)		Metastasis Control (%)	OS (%)	Toxicity Grade ≥ 3 (%)
		Median	Range	Total	No. of Fractions	Median	Range			
Mt Sinai (New York, NY)[82]	21	1	1-5	40-60	10	10	2-18	1 year: 85	1 year: 75	NA
University of Rochester (Rochester, NY)[41]	121	2	1-5	50	10	85	55-125*	2 years: 67	4 years: 28	1†
University of Chicago (Chicago, IL)[20]	61	2	1-5	24-48	3	21	3-61	2 years: 53	2 years: 57	10†
Vrije University (Brussels, Belgium)[83]	309	2	1-5	40-50	10	12	1-84	2 years: 33	3 years: 32	NS

Abbreviations: NA, not applicable; NS, not stated; OS, overall survival.
*Surviving patients with breast cancer.
†Crude rate.

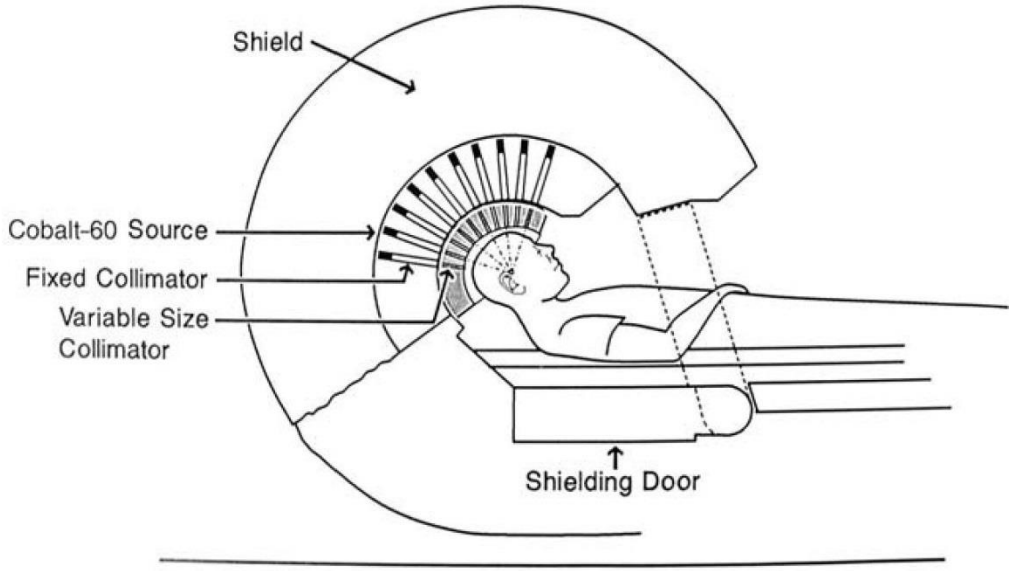


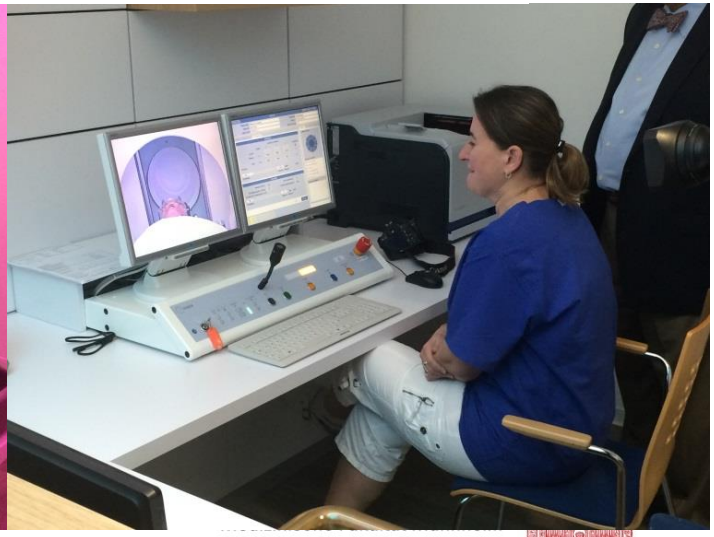
from Boda-Heggemann et al 2012

It all began with the gamma knife …



Lars Leksell
1907-1986



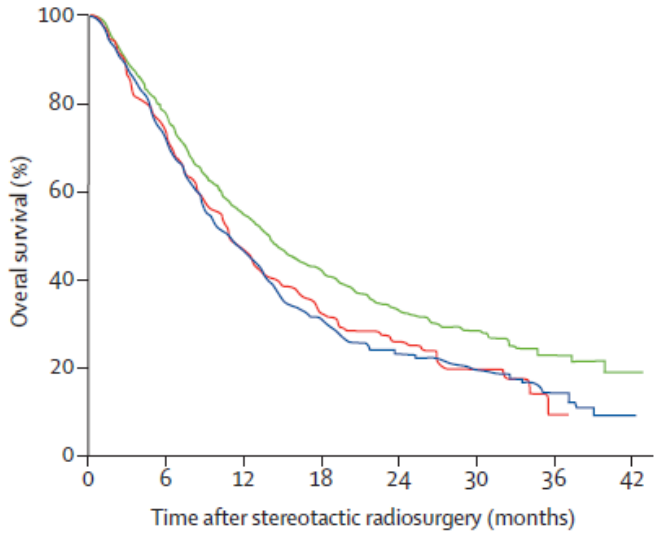


Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Lancet Oncol 2014; 15: 387–95

Masaaki Yamamoto, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya*

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

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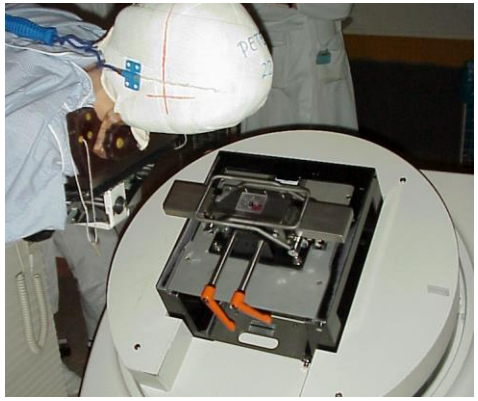
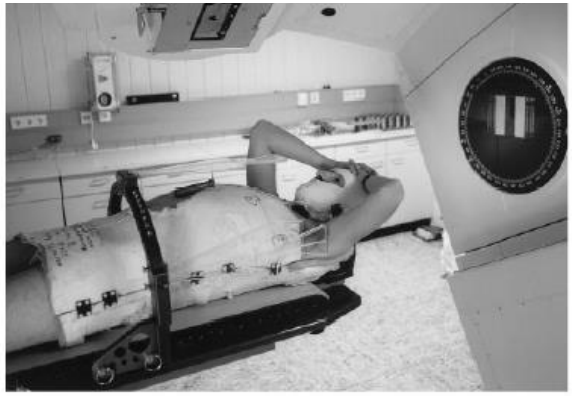
From SRS to SBRT

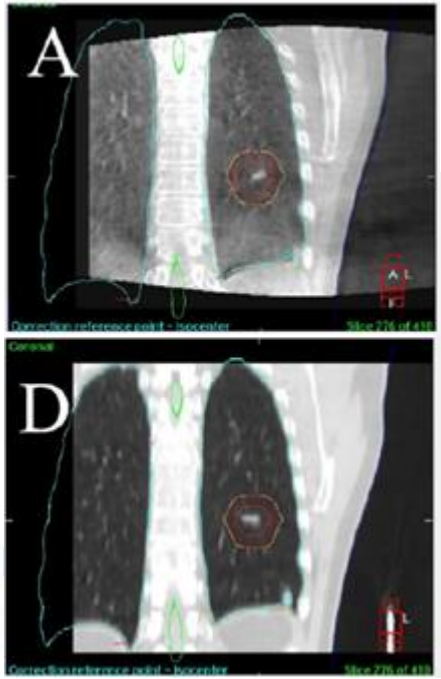
Linac RS mid 1980‘



torso/Lohr et al 1999

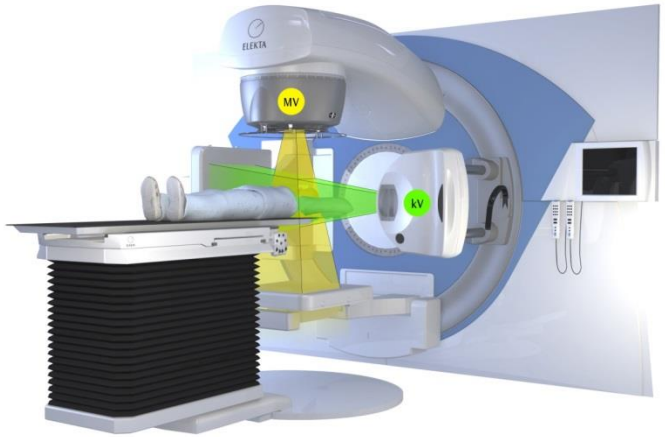


ABC/Boda-Heggemann et al 2006



mbh-CBCT/Boda-Heggemann et al 2011

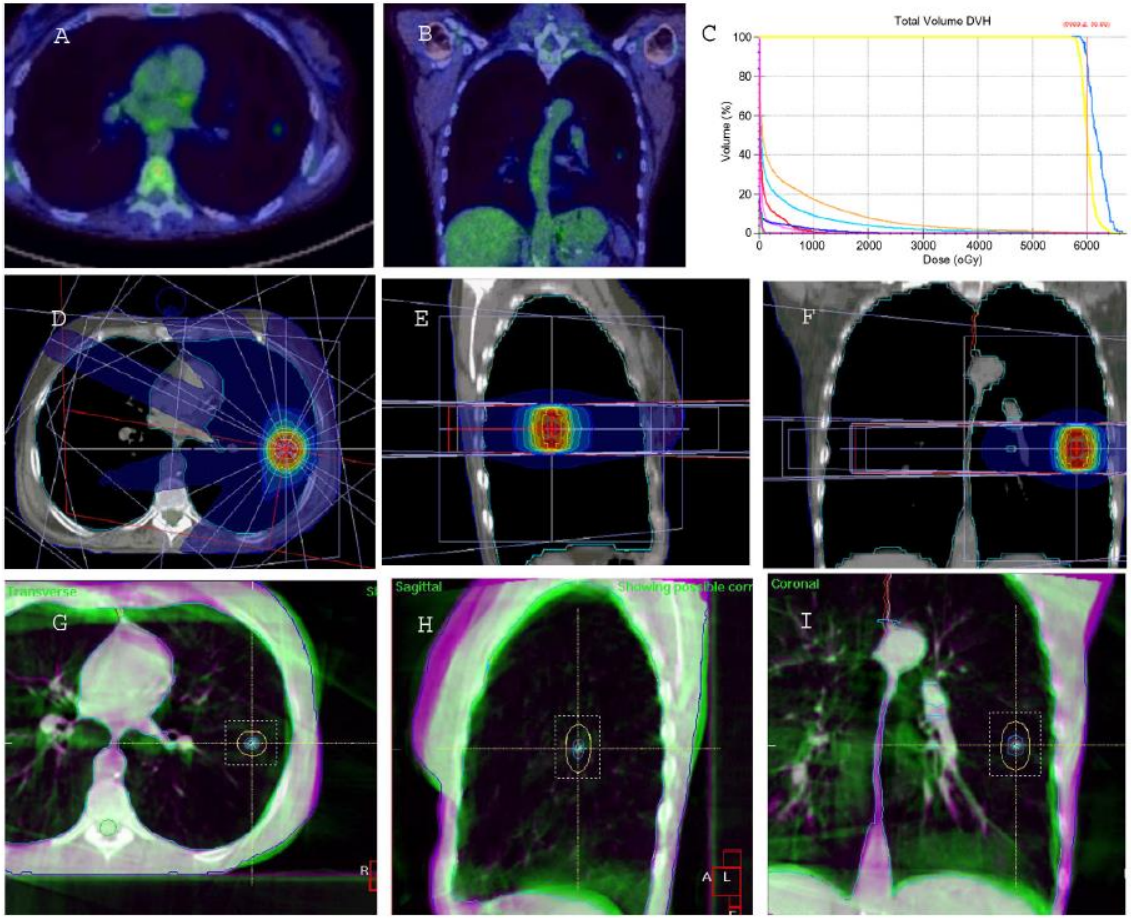
kVMV-CBCT/Wertz et al 2010



Flattening-filter-free intensity modulated breath-hold image-guided SABR (Stereotactic ABlative Radiotherapy) can be applied in a 15-min treatment slot

Radiotherapy and Oncology 109 (2013) 505–509

Judit Boda-Heggemann *,[1], Sabine Mai [1], Jens Fleckenstein, Kerstin Siebenlist, Anna Simeonova
Michael Ehmann, Volker Steil, Frederik Wenz, Frank Lohr, Florian Stieler



Planning CT (DIBH, no frame, no rigid fixation, no abdominal pressure)

↓

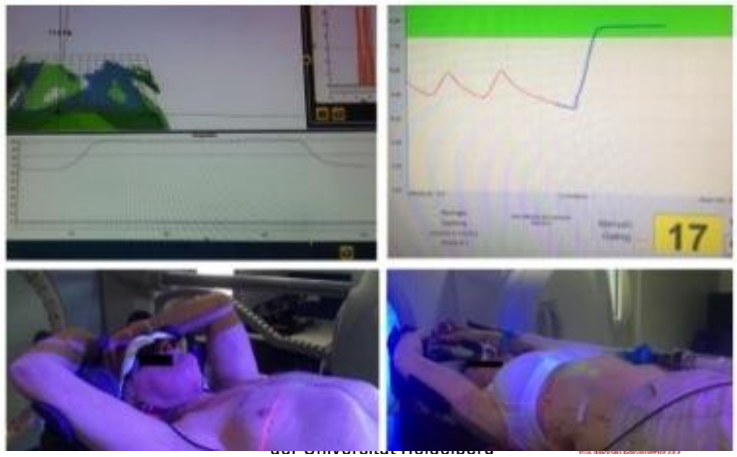
Planning on single phase DIBH dataset.
No need to contour on multiple breathing phases

↓

IGRT with CBCT acquired in repetitive DIBH

↓

Fast Delivery (DIBH, FFF, fast MLC) with static anatomical geometry identical to planning CT



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from Boda-Heggemann et al under review

Pulmonary oligometastases: Metastasectomy or stereotactic ablative radiotherapy? ☆

Radiotherapy and Oncology 107 (2013) 409–413

Joachim Widder [a,*], Theo J. Klinkenberg [b], Jan F. Ubbels [a], Erwin M. Wiegman [a], Harry J.M. Groen [c], Johannes A. Langendijk [a]

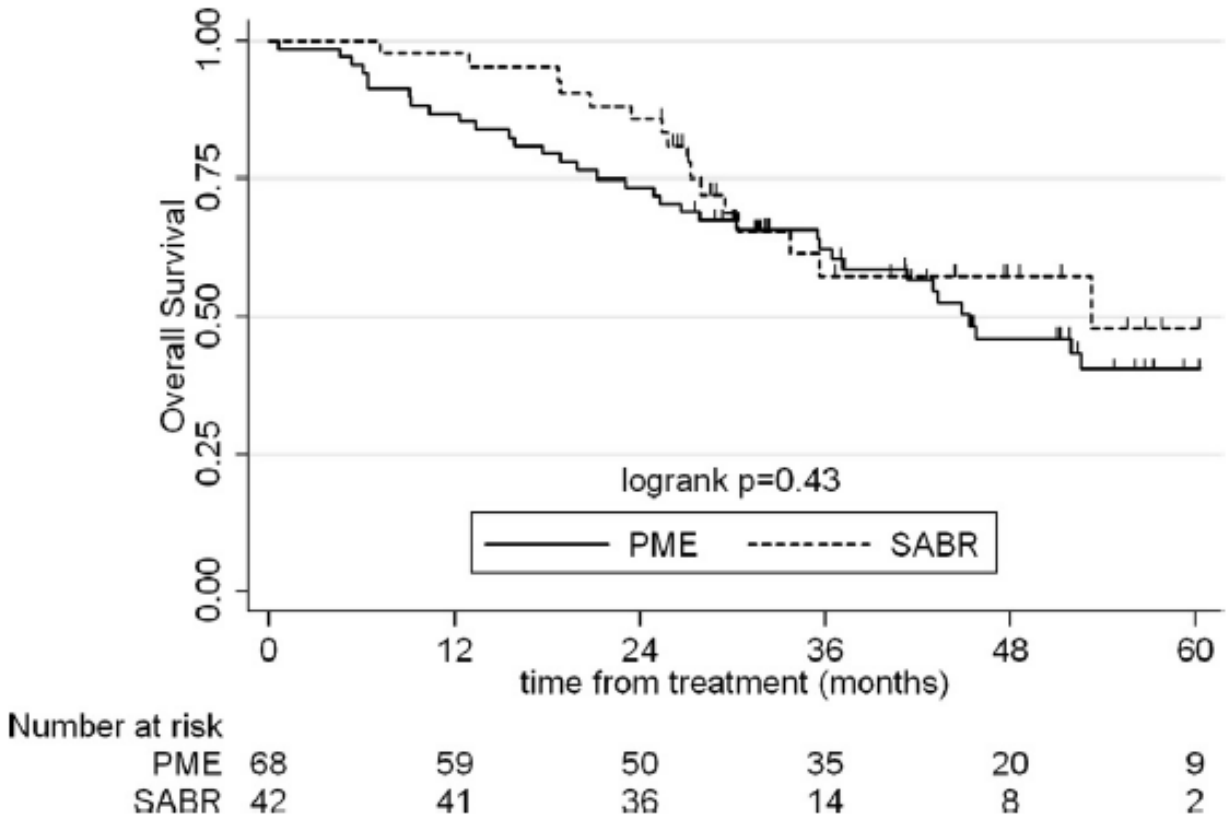
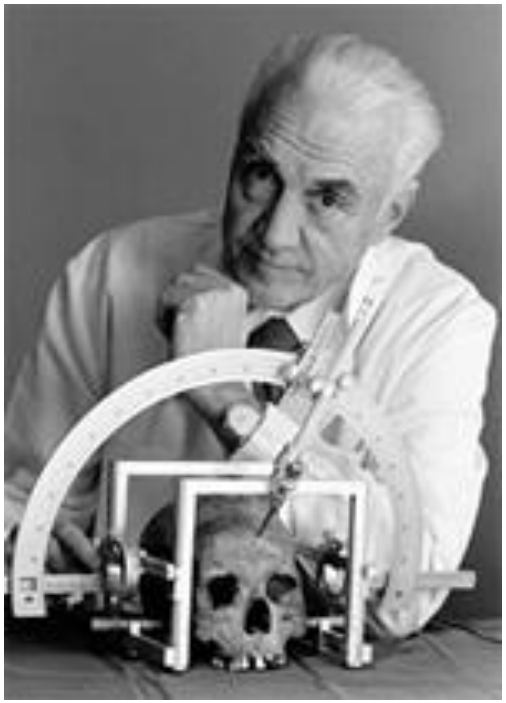


Fig. 1. Overall survival, PME (pulmonary metastasectomy) versus SABR (stereotactic ablative radiotherapy).

It all began with the gamma knife … lessions learnt



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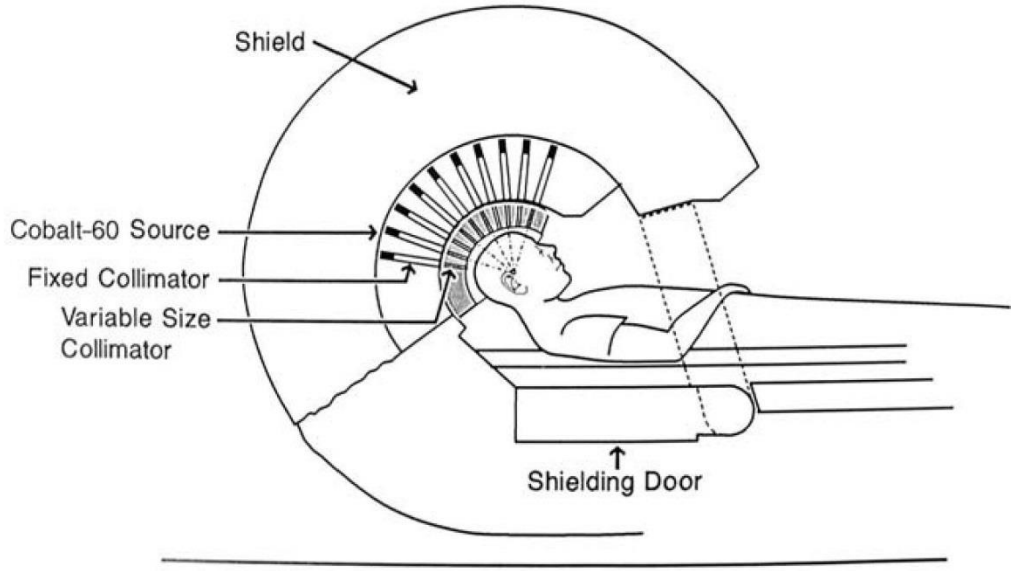

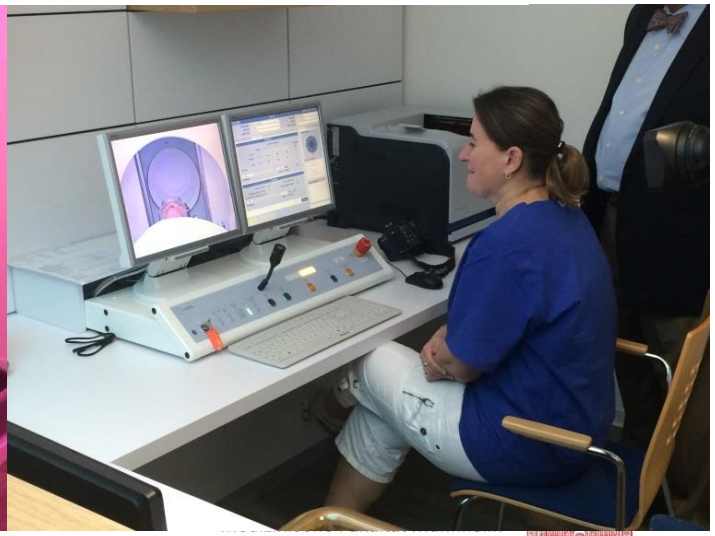

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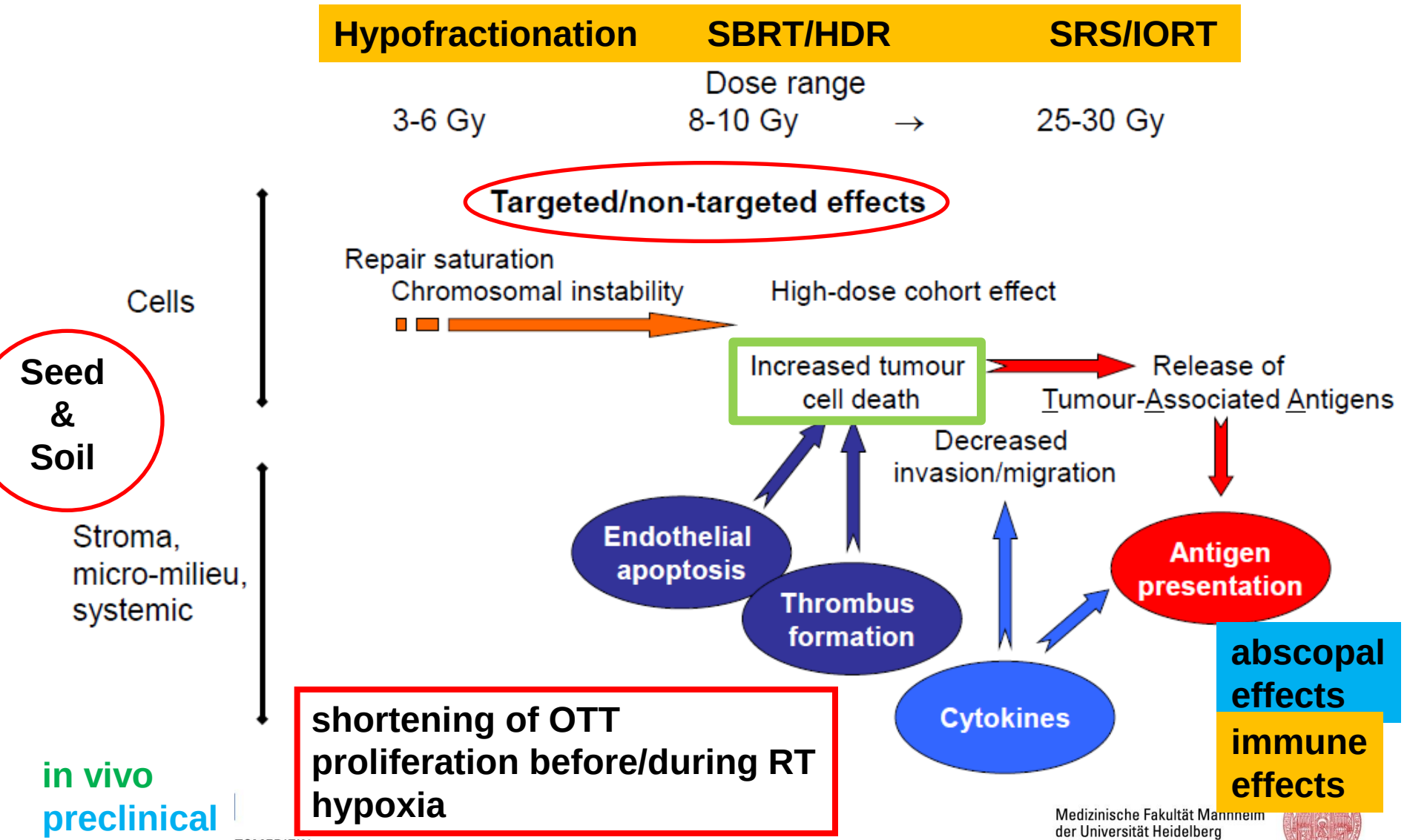
Radiobiological aspects of intraoperative tumour-bed irradiation with low-energy X-rays (LEX-IORT)

Transl Cancer Res 2014;3(1):3-17

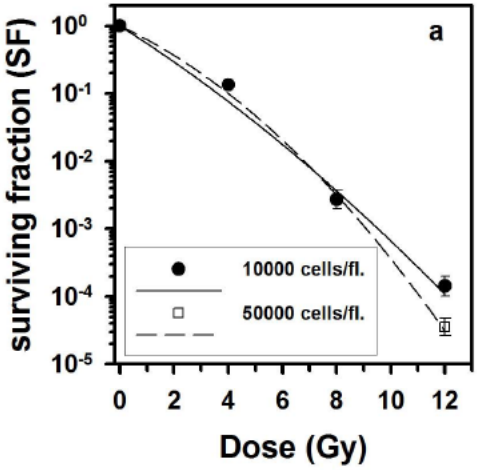
Carsten Herskind, Frederik Wenz

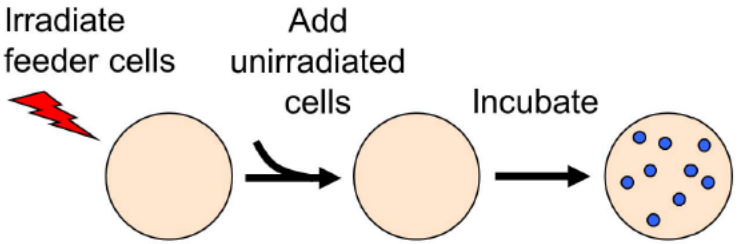


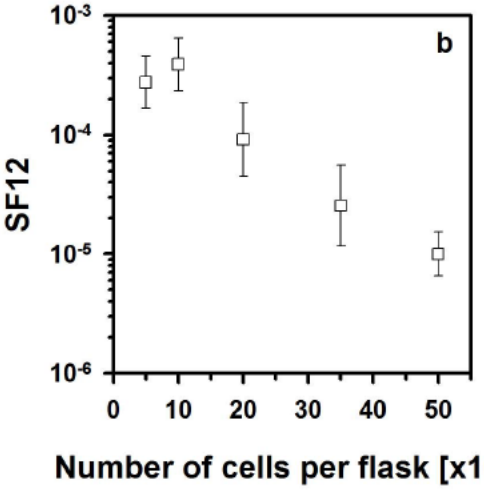
The Biological Effect of Large Single Doses: A Possible Role for Non-Targeted Effects in Cell Inactivation

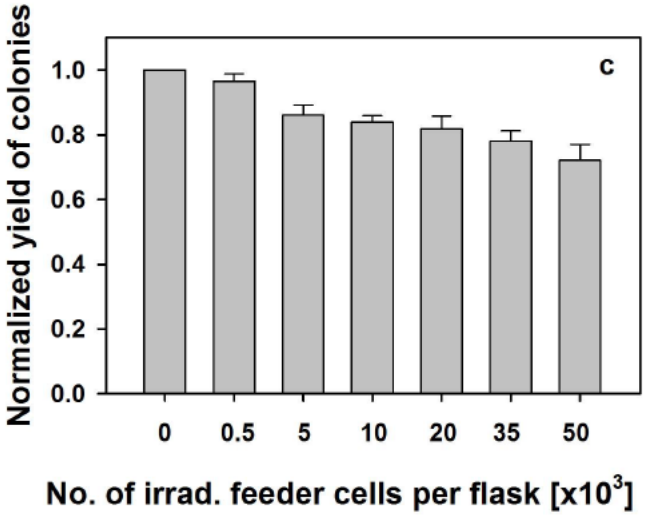
Marlon R. Veldwijk, Bo Zhang, Frederik Wenz, Carsten Herskind*

PLoS ONE 9(1): e84991.









Effect of cell density on cell survival after high-dose irradiation.

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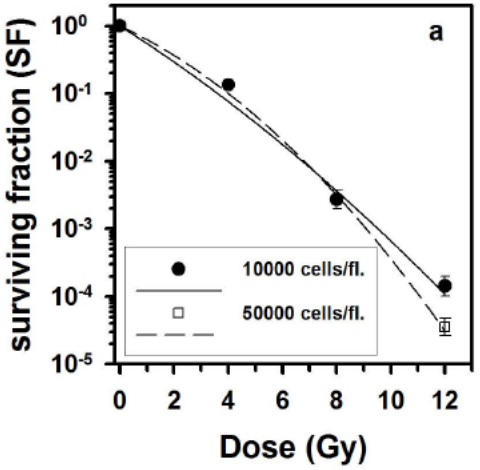
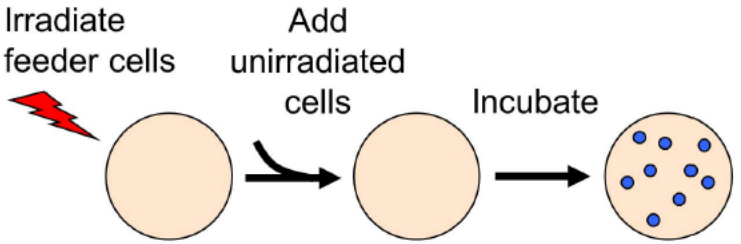
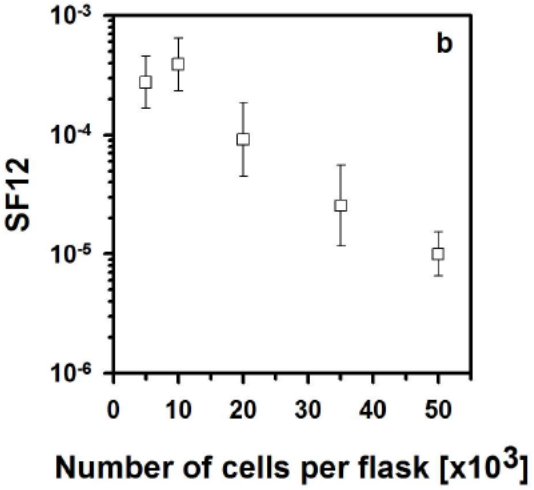
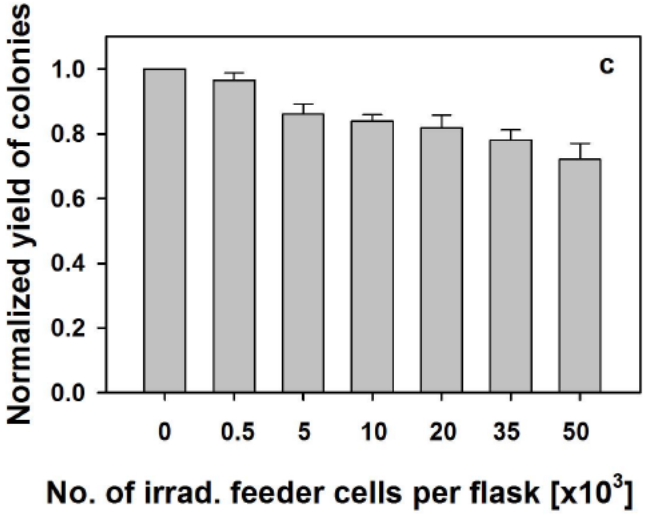


effect depends on cell number







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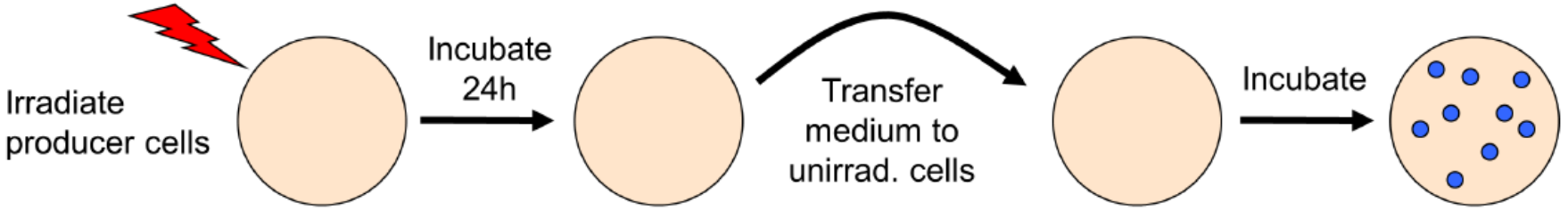

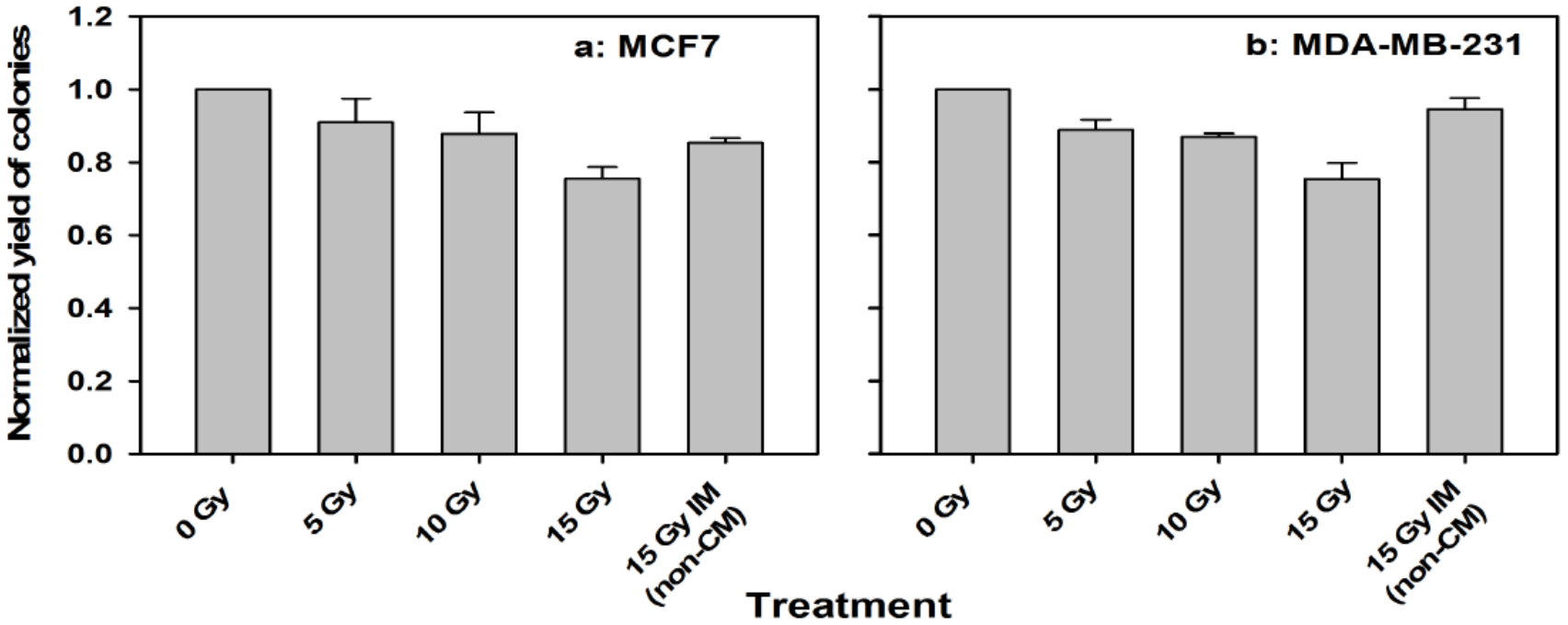

Medium transfer experiments to test effect of transferrable factor.

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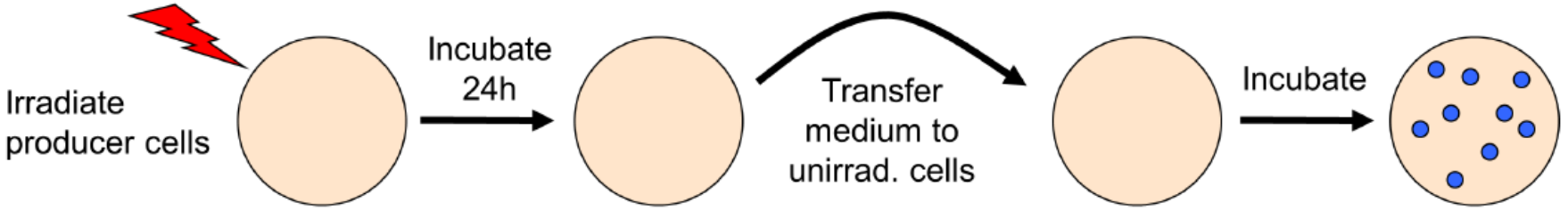
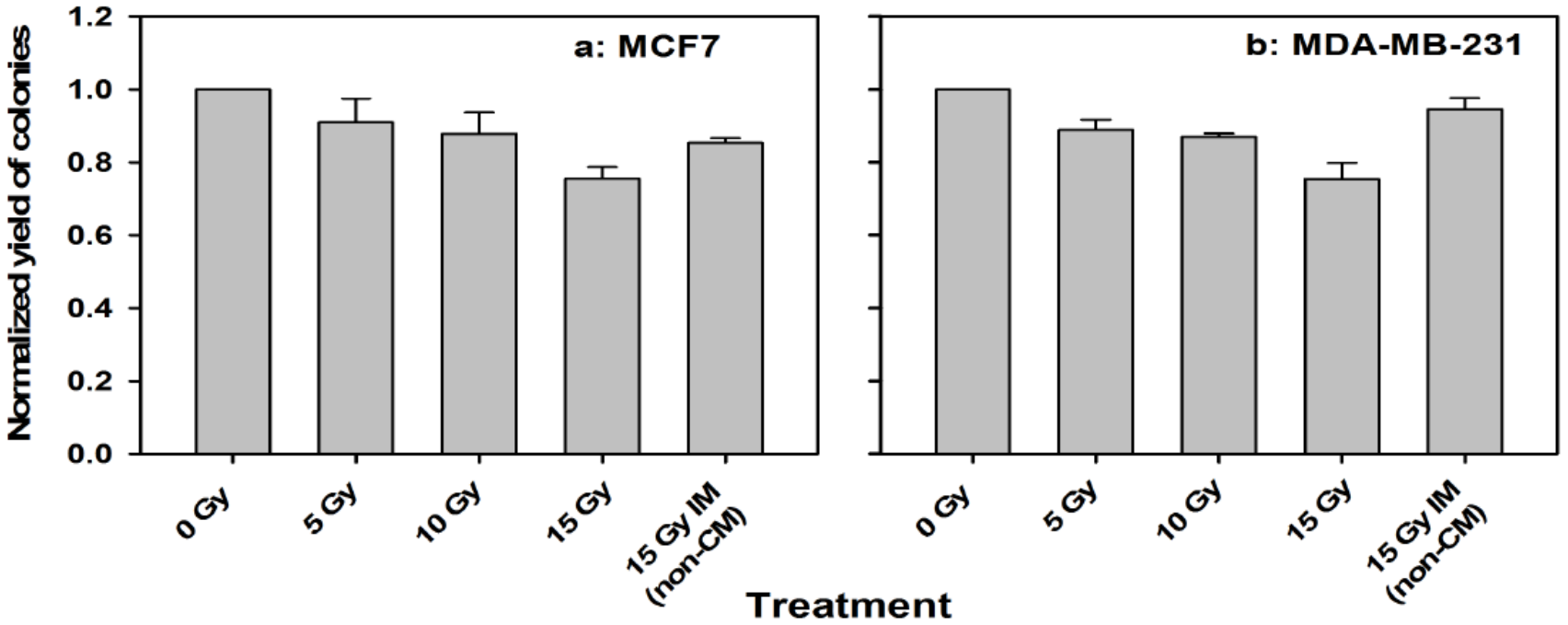
PLoS ONE 9(1): e84991.

effect depends on cell number & dose





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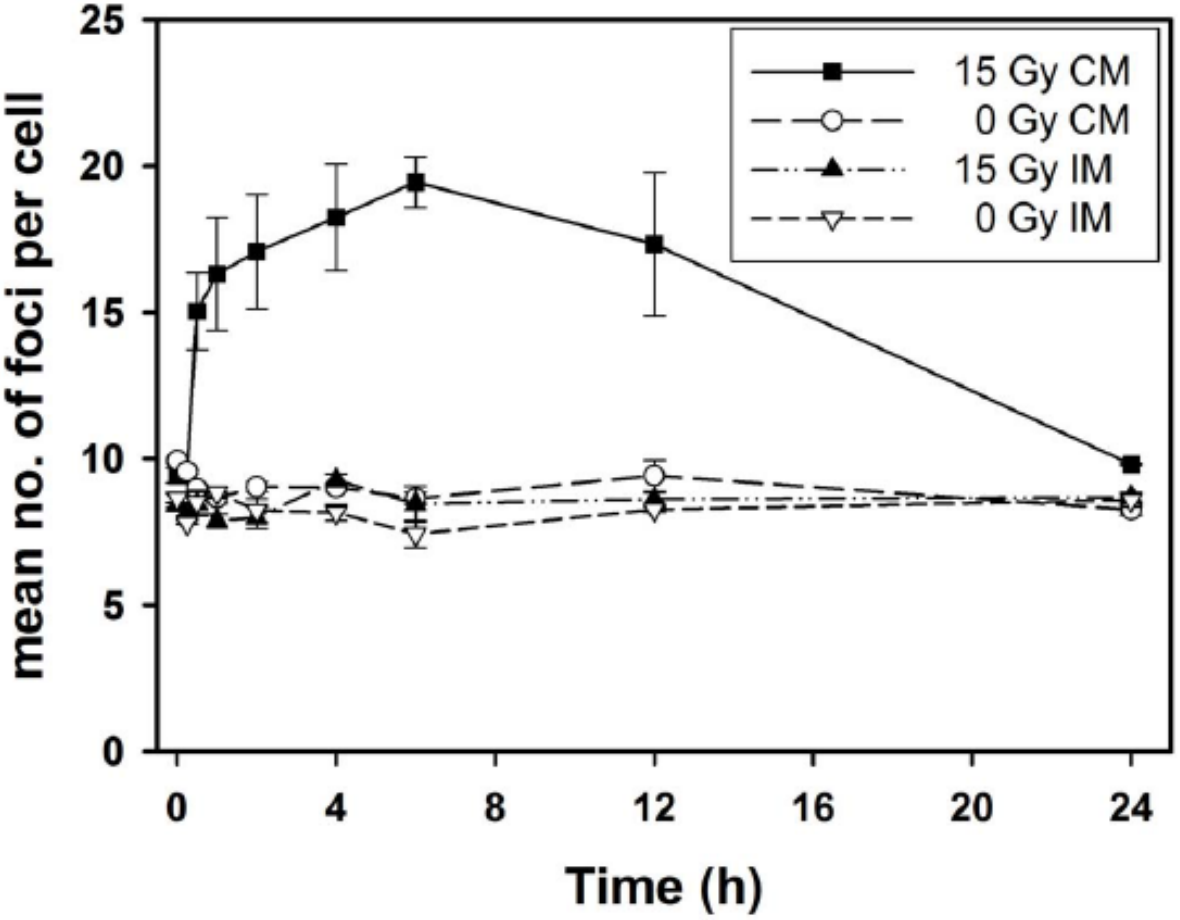

Conditioned medium (CM) induces prolonged γ- H2AX foci in MCF7 cells.

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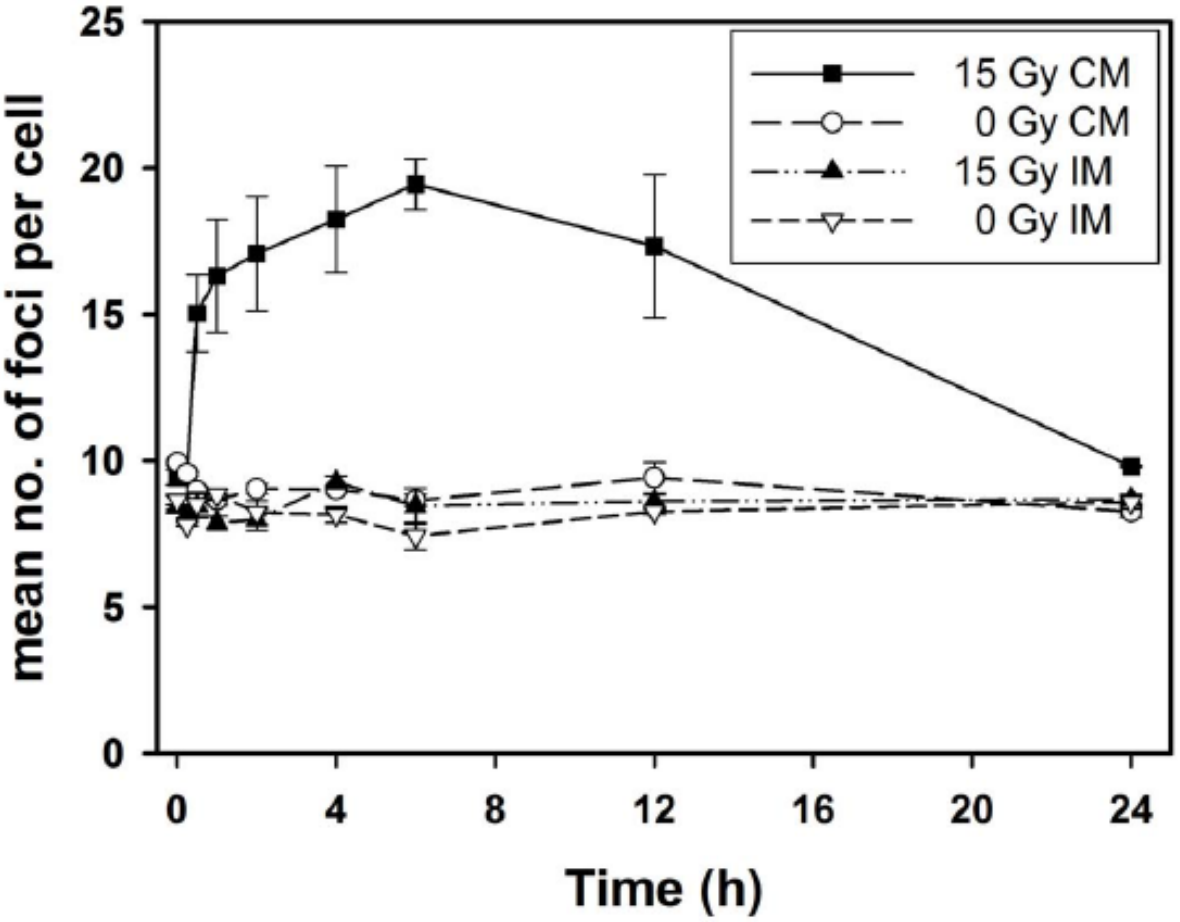
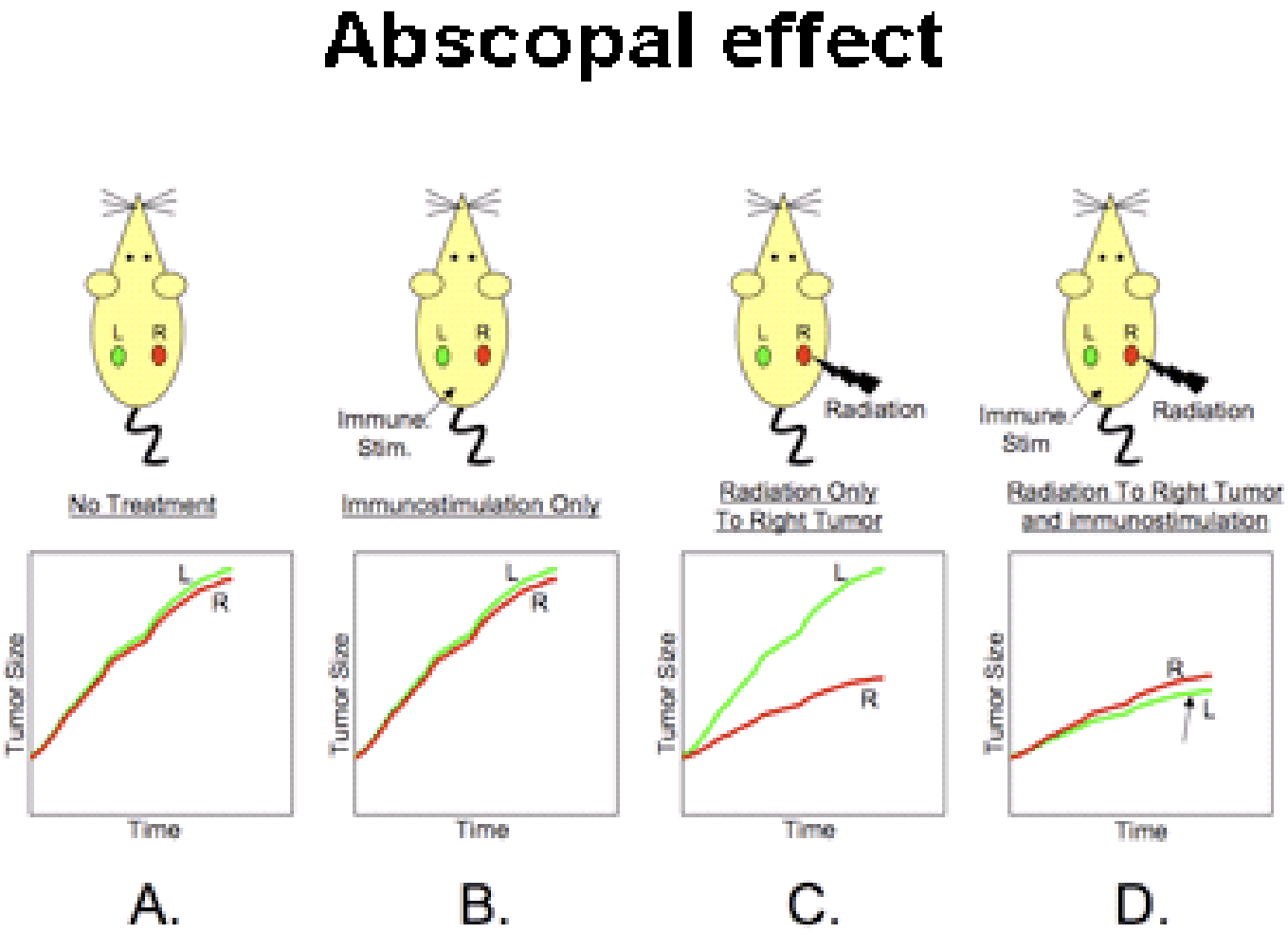
effect depends on cell number & dose

„supposed“ dsb



Conditioned medium (CM) induces prolonged γ- H2AX foci in MCF7 cells.

High dose non-target effects - local vs abscopal



Role of T lymphocytes in tumor response to radiotherapy

Sandra Demaria[1]* and Silvia C. Formenti[2]

August 2012 | Volume 2 | Article 95 |

frontiers in ONCOLOGY

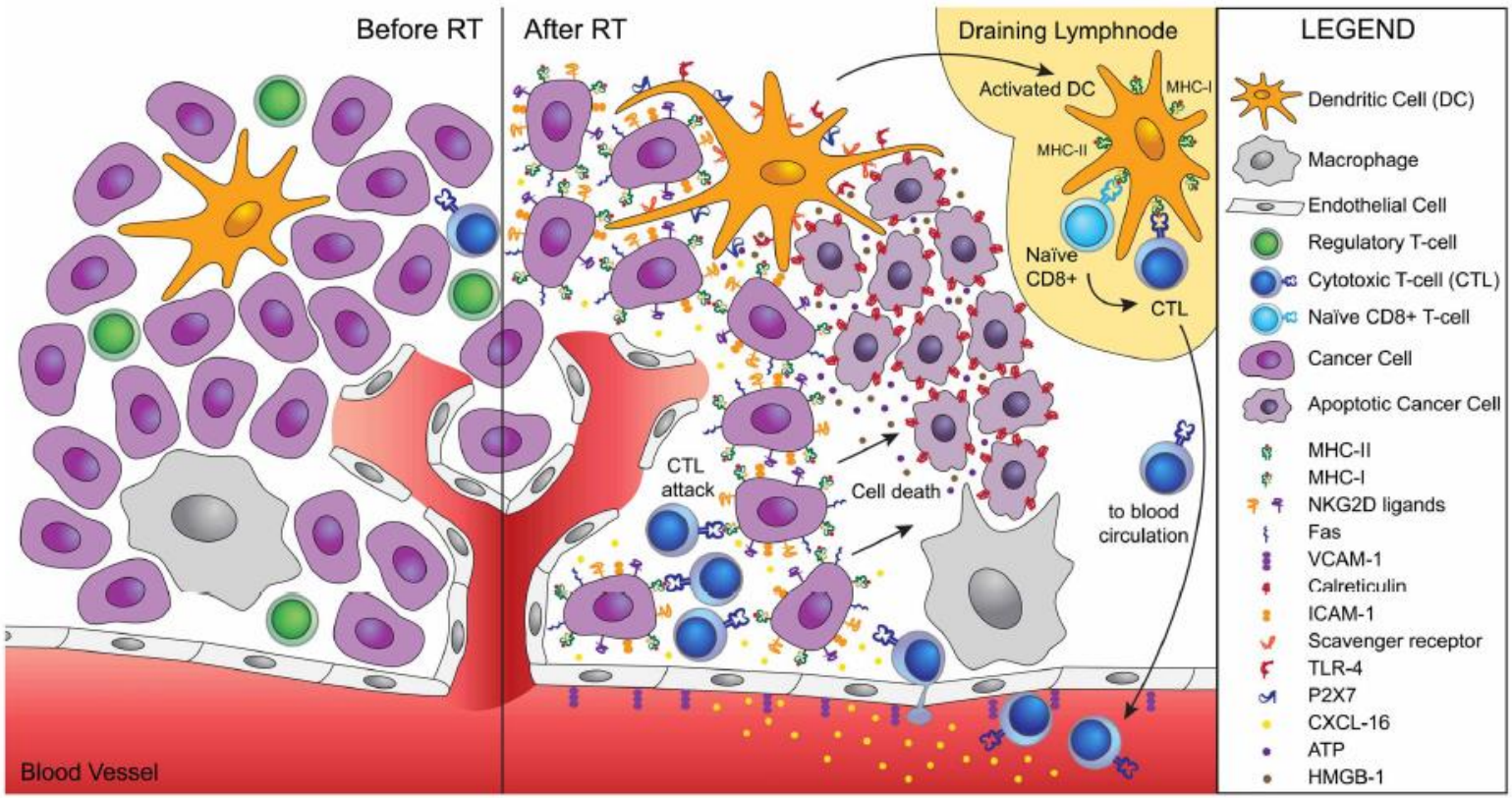


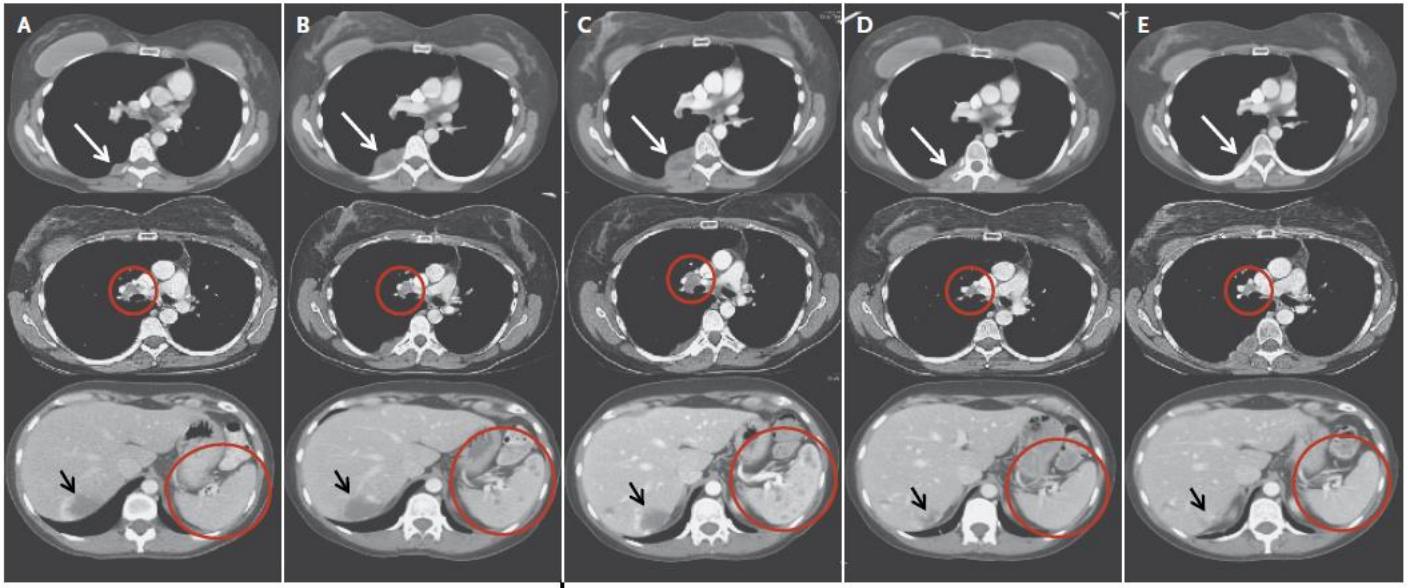
FIGURE 1 | Ionizing radiation acts as a modifier of the tumor microenvironment converting the tumor into an *in situ* vaccine. Radiation induces an immunogenic cell death of tumor cells characterized by calreticulin translocation to the surface of dying cells, and release of HMGB-1 and ATP. Calreticulin allows uptake of dying cells by dendritic cells via scavenger receptor(s). HMGB-1 binds to TLR4 and promotes the cross-presentation of tumor antigens, while ATP binds to P2X7 and triggers the activation of the inflammasome. Activated dendritic cells migrate to the draining lymph node, where they activate naïve T cells specific for tumor antigens. Activated CD8 T cells acquire effector functions and traffic to the tumor guided by radiation-induced chemokines. Tumor infiltration by CTLs is facilitated by radiation-induced upregulation of VCAM-1 on the vascular endothelium. Once in the tumor, CTLs interact efficiently with tumor cells expressing increased levels of MHC-I, ICAM-1, NKG2D ligands, and Fas that promote the formation of stable immunological synapses between targets and effectors and facilitate the killing of tumor cells by CTLs. Tumor cells killed by CTLs become a source of antigens for cross-presentation, thus fueling the process.

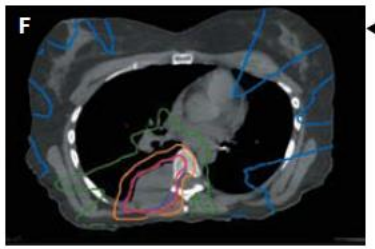
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

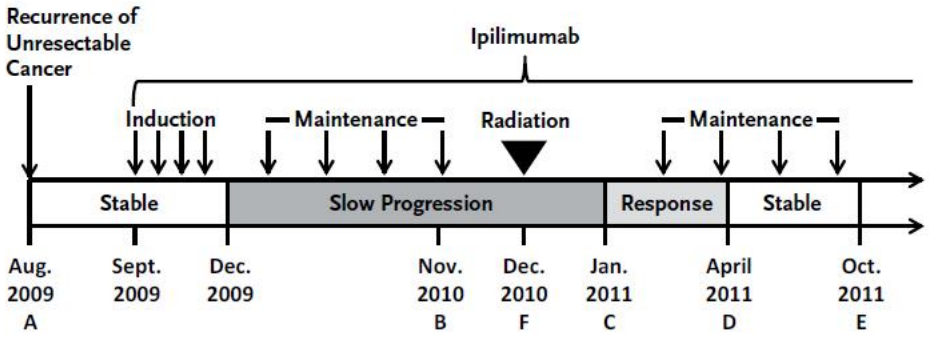
N Engl J Med 2012;366:925-31.

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. Ipilimumab is a monoclonal antibody that inhibits an immunologic checkpoint on T cells, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). We report a case of the abscopal effect in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer–testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy. (Funded by the National Institutes of Health and others.)







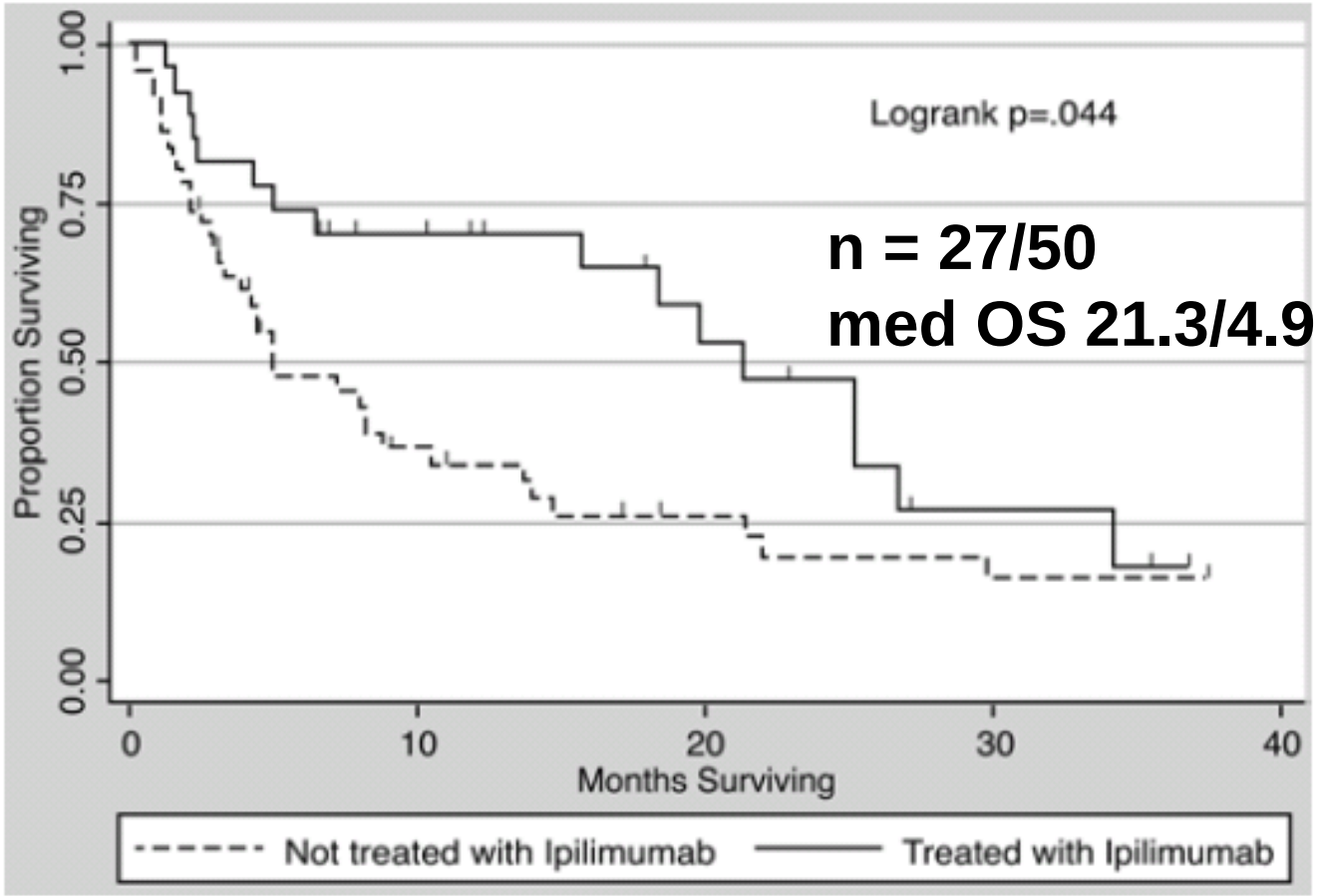
See the corresponding editorial in this issue, pp 225–226.

J Neurosurg 117:227–233, 2012

Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival

Clinical article

Jonathan P. S. Knisely, M.D.,[1] James B. Yu, M.D.,[3,4] Jaclyn Flanigan, M.D.,[2,3] Mario Sznol, M.D.,[2,3] Harriet M. Kluger, M.D.,[2,3] and Veronica L. S. Chiang, M.D.[3,5]

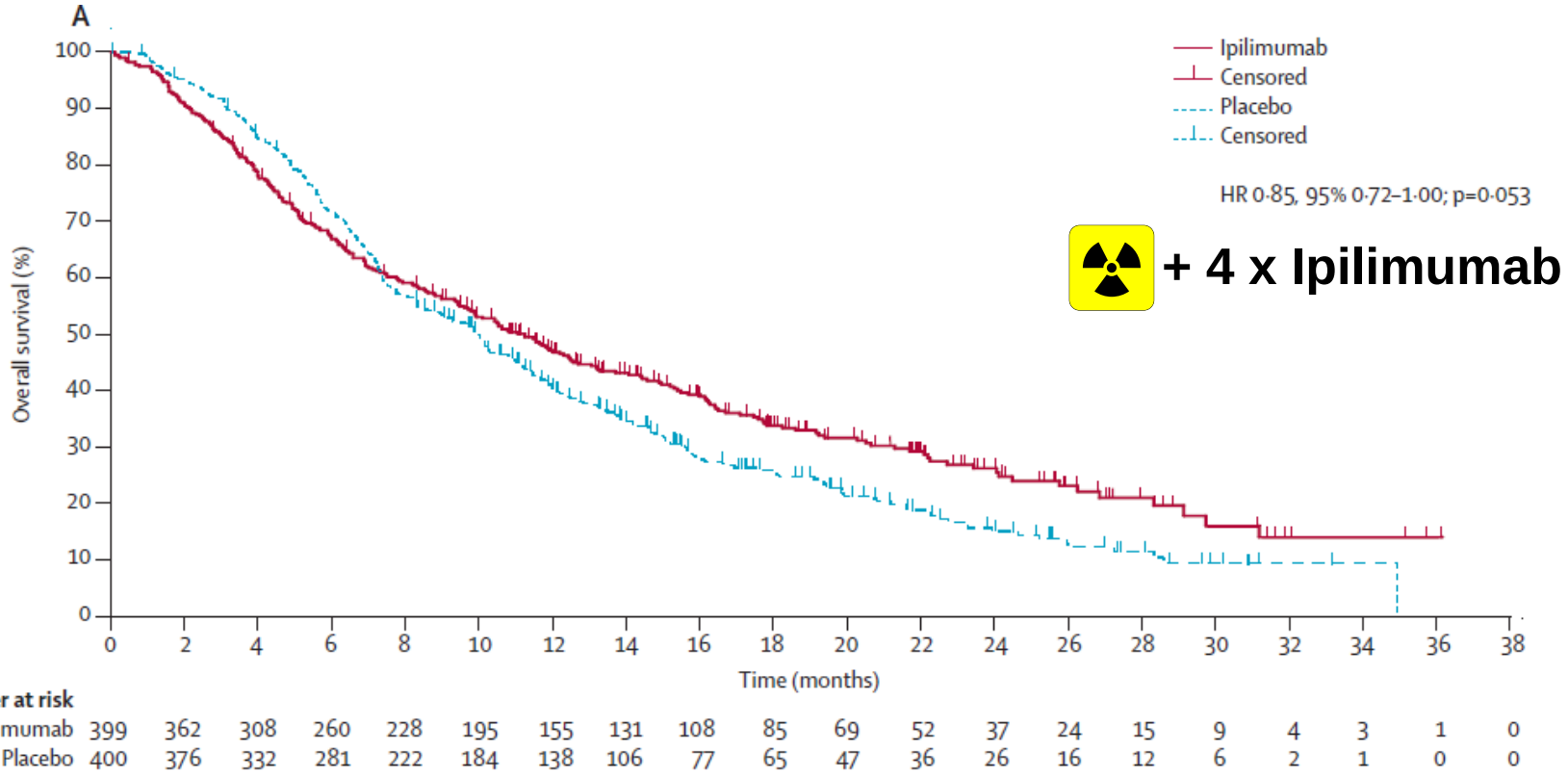


n = 27/50
med OS 21.3/4.9 mon

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Lancet Oncol 2014; 15: 700–12

*Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengeløv, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gagnier, David Liu, Winald R Gerritsen, for the CA184-043 Investigators**



+ 4 x Ipilimumab

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der Universität Heidelberg

Universitätsklinikum Mannheim

Stereotactic body radiotherapy for oligometastases

Alison C Tree, Vincent S Khoo, Rosalind A Eeles, Merina Ahmed, David P Dearnaley, Maria A Hawkins, Robert A Huddart, Christopher M Nutting, Peter J Ostler, Nicholas J van As

Lancet Oncol 2013; 14: e28–37

	Study year	Number of patients	Dose	Primary site	Treated site(s)	Treated metastasis control	Toxicity
Bignardi et al[43]	2010	19	45 Gy in 6 fractions (reduced in 6/19 cases)	Mixed	Abdominal lymph nodes	77·8% at 2 years	Grade 3 in 1 patient (5%)
Casamassima et al[44]	2011	25	Most common dose 30 Gy in 3 fractions	Prostate	Pelvic, para-aortic, or mediastinal lymph nodes	3-year local control 90%	No grade 2 or higher
Choi et al[45]	2009	30	Most received 33–45 Gy in 3 fractions	Mostly cervix, some endometrial	Para-aortic nodes	4-year local control 67·4%	20% grade 3 (but 16% haematological because most patients also had chemotherapy)
Kim et al[46]	2009	7	Median 48 Gy in 3 fractions	Gastric	Para-aortic nodes	100% (median follow-up 26 months)	No grade 3 recorded
Kim et al[47]	2008	23	Median 39 Gy in 3 fractions	Rectal	Pelvic/presacral lymph nodes	4-year local control 74·3%	Grade 3 in 1 patient (4%): rectal perforation
Casamassima et al[48]	2012	48	Most common dose 36 Gy in 3 fractions	Mixed (mostly NSCLC and colon)	Adrenal	2-year local control 90% (2-year overall survival 14·5%)	No grade 3 recorded
Chawla et al[49]	2009	30 patients (only 14 had <5 metastases)	Median dose 40 Gy in 10 fractions	Mostly NSCLC	Adrenal	2-year local control 27%	No grade 2 or higher
Holy et al[50]	2011	13 with only adrenal metastases	Median dose 40 Gy in 5 fractions	All NSCLC	Adrenal	21-month local control 77%	2 patients had gastric ulcer (probably grade 2 toxic effect)
Scorsetti et al[51]	2012	34	Median dose 32 Gy in 4 fractions	64% NSCLC	Adrenal	1-year local control 66%, 2-year local control 33%	No grade 3, 6% grade 2 nausea
Torok et al[52]	2011	7 patients (9 metastases)	Median 16 Gy in 1 fraction	NSCLC in 4 of 7	Adrenal	1-year local control 63%	Not known

NSCLC=non-small-cell lung cancer.

Table 1: Stereotactic body radiotherapy for lymph-node or adrenal oligometastases

Stereotactic body radiotherapy for oligometastases

Alison C Tree, Vincent S Khoo, Rosalind A Eeles, Merina Ahmed, David P Dearnaley, Maria A Hawkins, Robert A Huddart, Christopher M Nutting, Peter J Ostler, Nicholas J van As

Lancet Oncol 2013; 14: e28–37

	Study year	Number of patients (number of lesions)	Dose	Primary site	Treated site(s)	Treated metastasis control	Toxicity
Muacevic et al[67]	2011	40 (64)	20 Gy in 1 fraction (median)	Prostate	Bone (34/64 spine)	2-year control 95·5%	No grade 3 or higher
Wang et al[68]*	2012	149 (166)	27–30 Gy in 3 fractions	Mixed (32% renal)	Spine	72% (median follow-up 15·9 months)	7% grade 3 (non-cardiac chest pain, other pain, nausea, fatigue)
Yamada et al[69]*	2008	93 (103)	18–24 Gy in 1 fraction	Mixed (high proportion of renal-cell carcinoma)	Vertebrae	90% at 15 months	1 acute grade 3 (1%), 1 late grade 3 (1%)
Gerstzen et al[70]*	2007	393 (500)	Mean maximum dose 20 Gy in 1 fraction	Mixed	Vertebrae	88% at median follow-up 21 months (100% for breast and lung primaries, 75% for melanoma)	No significant neurological effects recorded
Zelefsky et al[71]	2011	105 (105)	Varied, but mostly 24 Gy in 1 fraction or 30 Gy in 5 fractions	Renal-cell carcinoma	99% bone metastases	3-year local control 44%, but 88% for 24 Gy in 1 fraction	1 grade 4 skin (1%), 4 fractures (not graded)
Nguyen et al[72]*	2010	48 (55)	24 Gy in 1 fraction, 27 Gy in 3 fractions, or 30 Gy in 5 fractions	Renal-cell carcinoma	Spine (one or two sites)	82% 1-year spine progression-free survival	2% pain, 2% anaemia

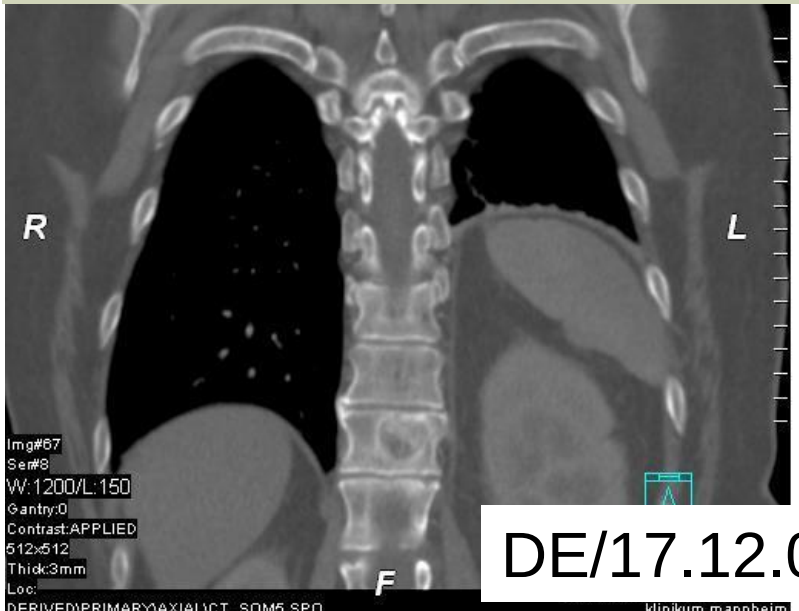
*Percentage of patients with oligometastatic disease is not known for these studies.

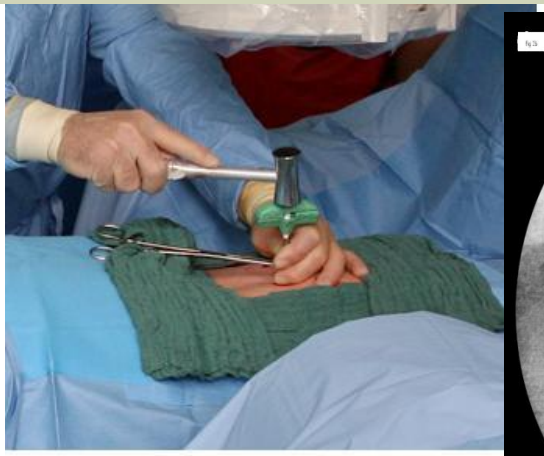
Table 3: **Stereotactic body radiotherapy for treatment of spinal metastases**

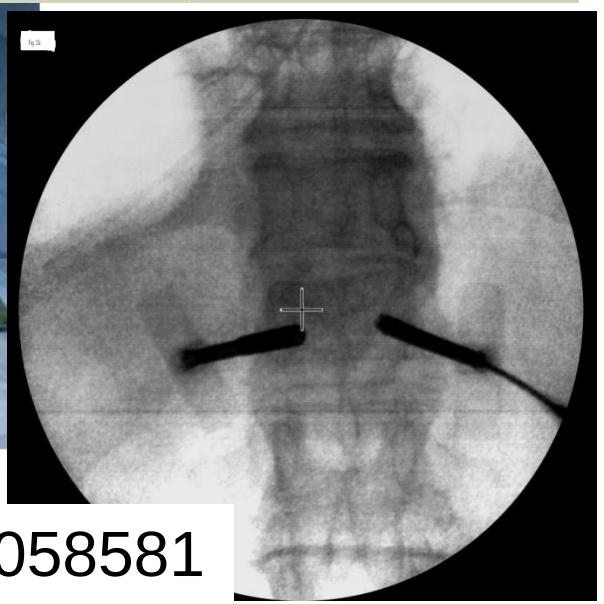
Kypho-IORT - a novel approach of intraoperative radiotherapy during kyphoplasty for vertebral metastases

Radiation Oncology 2010, **5**:11

Frederik Wenz[1*], Frank Schneider[1], Christian Neumaier[1], Uta Kraus-Tiefenbacher[1], Tina Reis[1], René Schmidt[2], Udo Obertacke[2]





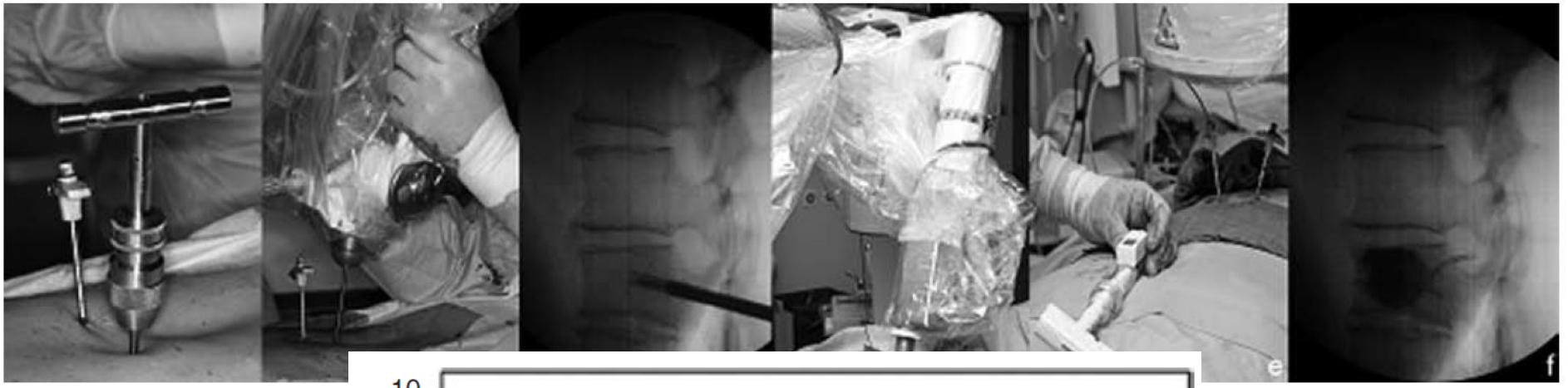


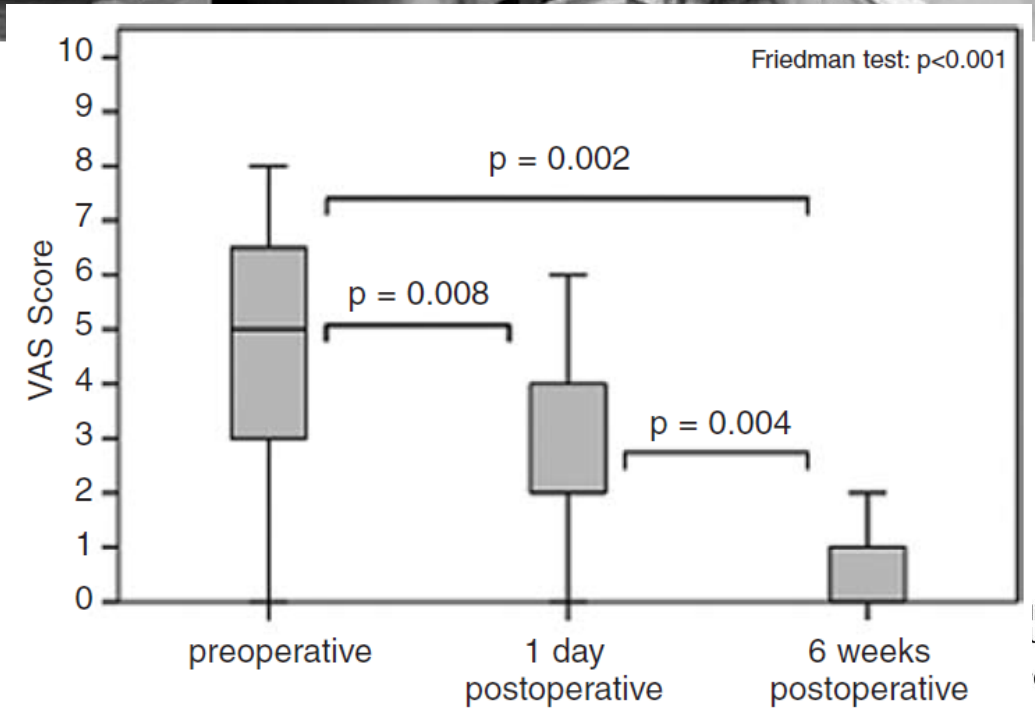
DE/17.12.09/DEA10200905058581

Intraoperative radiotherapy during kyphoplasty for vertebral metastases (Kypho-IORT): first clinical results

Tumori, 98: 434-440, 2012

Tina Reis[1], Frank Schneider[1], Grit Welzel[1], Renè Schmidt[2], Udo Obertacke[2], Frederik Wenz[1]





n = 18

phase II
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Stereotactic body radiotherapy for oligometastases

Alison C Tree, Vincent S Khoo, Rosalind A Eeles, Merina Ahmed, David P Dearnaley, Maria A Hawkins, Robert A Huddart, Christopher M Nutting, Peter J Ostler, Nicholas J van As

Lancet Oncol 2013; 14: e28–37

Panel: Evidence-based practice for extracranial oligometastases

- Stereotactic body radiotherapy results in a high control rate of treated metastases (~80%)
- About 20% of patients are progression free at 2–3 years after stereotactic body radiotherapy
- Toxicity is low
- Stereotactic body radiotherapy should be considered in patients with isolated metastases, especially if the disease-free interval is longer than 6 months
- Randomised trials are needed to establish whether stereotactic body radiotherapy improves progression free and/or overall survival
- Patients most likely to benefit from stereotactic body radiotherapy have:
  - Long disease-free interval
  - Breast histology
  - One to three metastases
  - Small metastases
  - Higher radiation dose delivered (biologic effective dose >100 Gy)

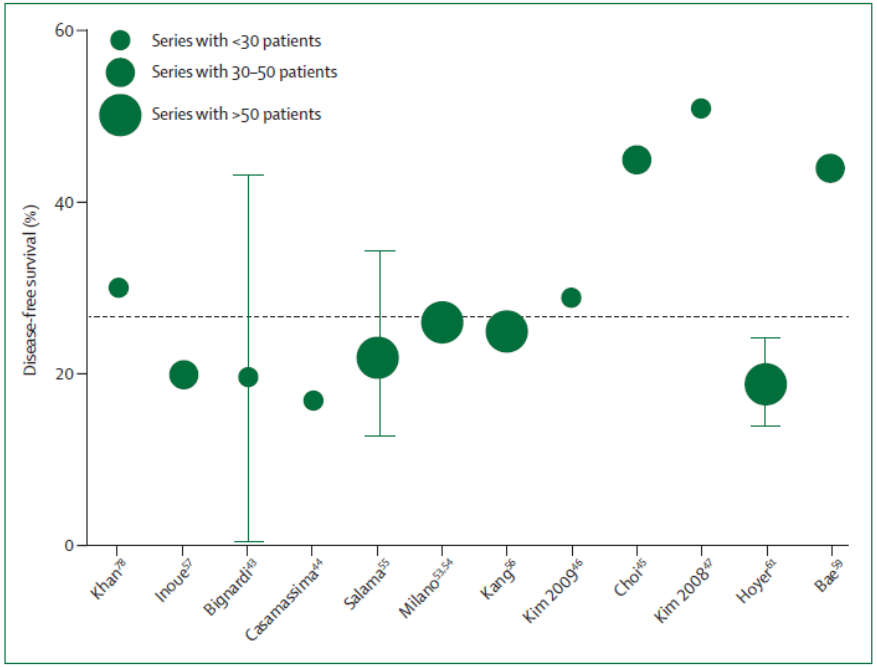

Figure 2: **Disease-free survival in patients with oligometastatic disease at 17–48 months' follow-up**
Dotted line represents mean proportion of patients who were disease free at the reported timepoint, weighted for number of patients in each cohort. Error bars represent 95% confidence intervals.

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Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, *University of Chicago Medical Center, Chicago, IL*

Journal of Clinical Oncology, Vol 31, No 11 (April 10), 2013: pp 1384-1390

Table 2. Selected Ongoing Prospective Trials for Oligometastases

Trial Name or Number	Design	Eligibility	Intervention
SABR-COMET	Randomized	All metastatic sites treatable; maximum of three tumors to any single organ system; controlled primary tumor	Standard arm: palliative-scheme radiation; experimental arm: stereotactic ablative radiation
UPCI 10-028	Phase II	≤ Five metastases from solid malignancy	SBRT to affected sites
UPCI 10-027	Phase II	≤ Five metastases diagnosed at initial presentation	SBRT to affected sites in combination with treatment of primary tumor
NCT01565837	Phase II	Melanoma with ≤ five metastatic sites (not resectable)	Ipilimumab with SBRT to all sites, timed to be delivered before third cycle
NCT01185639	Phase II	NSCLC with ≤ five metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have ≤ three	SBRT to affected sites, delivered in three or five fractions
PulMiCC	Randomized	Pulmonary metastases from colorectal cancer	Standard: active monitoring; experimental: active monitoring with pulmonary metastasectomy

Abbreviations: NSCLC, non–small-cell lung cancer; PulMiCC, Pulmonary Metastasectomy in Colorectal Cancer; SABR-COMET, Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors; SBRT, stereotactic body radiotherapy; UPCI, University of Pittsburgh Cancer Institute.