The **radiation oncologist** point of view…

Defining the strategy in oligometastatic rectal cancer

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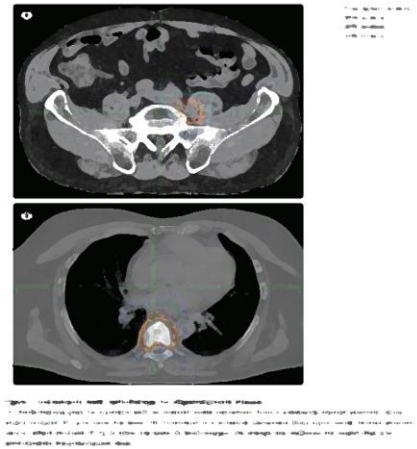
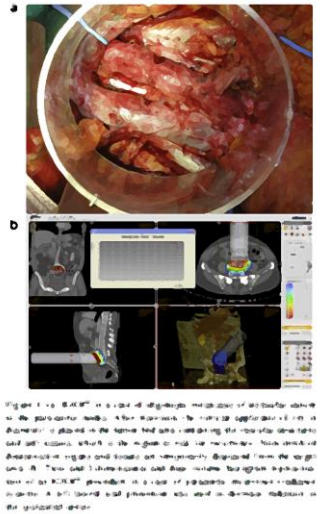
ESMO GI 2017

No disclosures

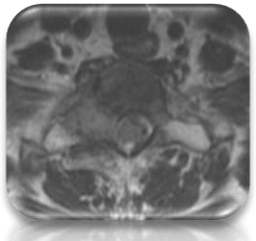
The paradigm, the challenge, the opportunity… The evidence!

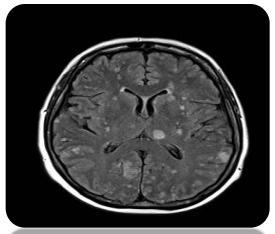
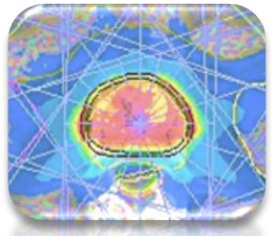


- Oligo-metastasis
- Oligo-recurrence
- Oligo-progression



- Technology
- Innovation
- Clinical tailoring




1. Definitions, paradigm, clinical value
2. Oligo-metastasis: clinical models
3. Oligo-recurences: clinical models
4. Oligo-biology
5. Update 2017: improved practice & reserach

Definitions & Paradigm Transit… Clinical value

- **Oligo-metastasis 1995:**

"…limited number of secondary lesions…"

- **Oligo-recurrences 2006:**

"…the rate of metastasis development…< 5… primary recurrent…"

- **Sync-oligomets 2012:**

"primary + < 5"

Oligo-progression 2016

"primary controlled…< 5 mets… > 2 years

- **Oligocancer 2017**:

*any of the above conditions **+ biology***

Definitions & Paradigm Transit… Clinical value

- **Oligometastasis 1995:**

"…limited number of secondary lesions…"

- **Oligorecurrences 2006:**

"…the rate of metastasis development…< 5…recurrence with primary controlled…"

- **Sync-olimets 2012:**

"primary + < 5"

- **Oligocancer 2017**:

any of the above conditions + biology

Limmited # of lesions

Ablative treatment avilability

Spatially confined sites involvement

OLIGOMETASTASES

CLASSIFICATION STAGING PROPOSAL

- **M:**
  - -MIC: circulating cancer cells persisting after surgery or radiation treatment of the primary tumor and regional nodes, 0.1 mm or 100 m M1MIC: micrometastases, 0.2 mm to 2.0 mm in size (200 m to 2000 m).
  - **-M1: a solitary metastasis in a single organ.**
  - **-M2: oligometastases,** designate number and limited to 1 organ (5 nod., 5 cm in total)**.**
  - -M3: multiple metastases, lim. 1 organ site
  - -M4: multiple metastases, multiple organs.

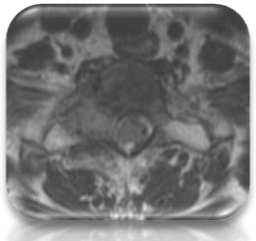
- **Serum molecular markers:**
  - S0: not detectable.
  - S1: detectable, low level.
  - S2: intermediate level.
  - S3: high level.

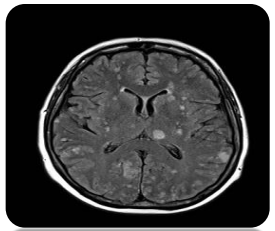
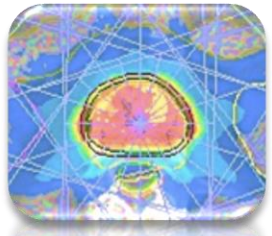
- **Host status** (modified Karnofsky scale):
  - -H0: normal activity; asymptomatic
  - -H1: symptomatic; fully ambulatory
  - -H2: symptomatic; in bed 50% of time
  - -H3: symptomatic, in bed 50% of time, not bedridden
  - -H4: 100% bed ridden

- **Stage IV needs to be modified**
  - -A. No systemic signs: minimal 5% weight loss, minimal lab abnormalities.
  - -B. Systemic signs: 100% weight loss, cachexia, fevers not explained, la abnormalities, i.e. altered lung function, abnormal liver enzymes, etc.

✧***Binomial age/general condition.***

Solitary Metastases: Illusion Versus Reality. Rubin et al.Semin Radiat Oncol 2006 16:120-130




1. Definitions, paradigm, clinical value
2. Oligo-metastasis: clinical models **based on surgical metastatectomy**
3. Oligo-recurences: clinical models
4. Oligo-biology
5. Update 2017: improved practice & research

OPINION

Oligometastases revisited

Ralph R. Weichselbaum and Samuel Hellman

Abstract | We previously proposed a clinical state of metastasis termed 'oligometastases' that refers to restricted tumor metastatic capacity. The implication of this concept is that local cancer treatments are curative in a proportion of patients with metastases. Here we review clinical and laboratory data that support the hypothesis that oligometastasis is a distinct clinical entity. Investigations of the prevalence, mechanism of occurrence, and position in the metastatic cascade, as well as the determination of molecular markers to distinguish oligometastatic from polymetastatic disease, are ongoing.

Weichselbaum, R. R. & Hellman, S. *Nat. Rev. Clin. Oncol.* **8**, 378–382 (2011); published online 22 March 2011; doi:10.1038/nrclinonc.2011.44

Table 1 | Summary of four large series of resection of hepatic metastasis

Study	*n*	5-year survival rate (%)	10-year survival rate (%)
Hughes *et al.* (1986)[3]	607	33	No 10-year follow up
Nordlinger *et al.* (1996)[4]	1,568	28	No 10-year follow up
Fong *et al.* (1999)[5]	1,001	37	22
Pawlik *et al.* (2005)[6]	557	58	No 10-year follow up

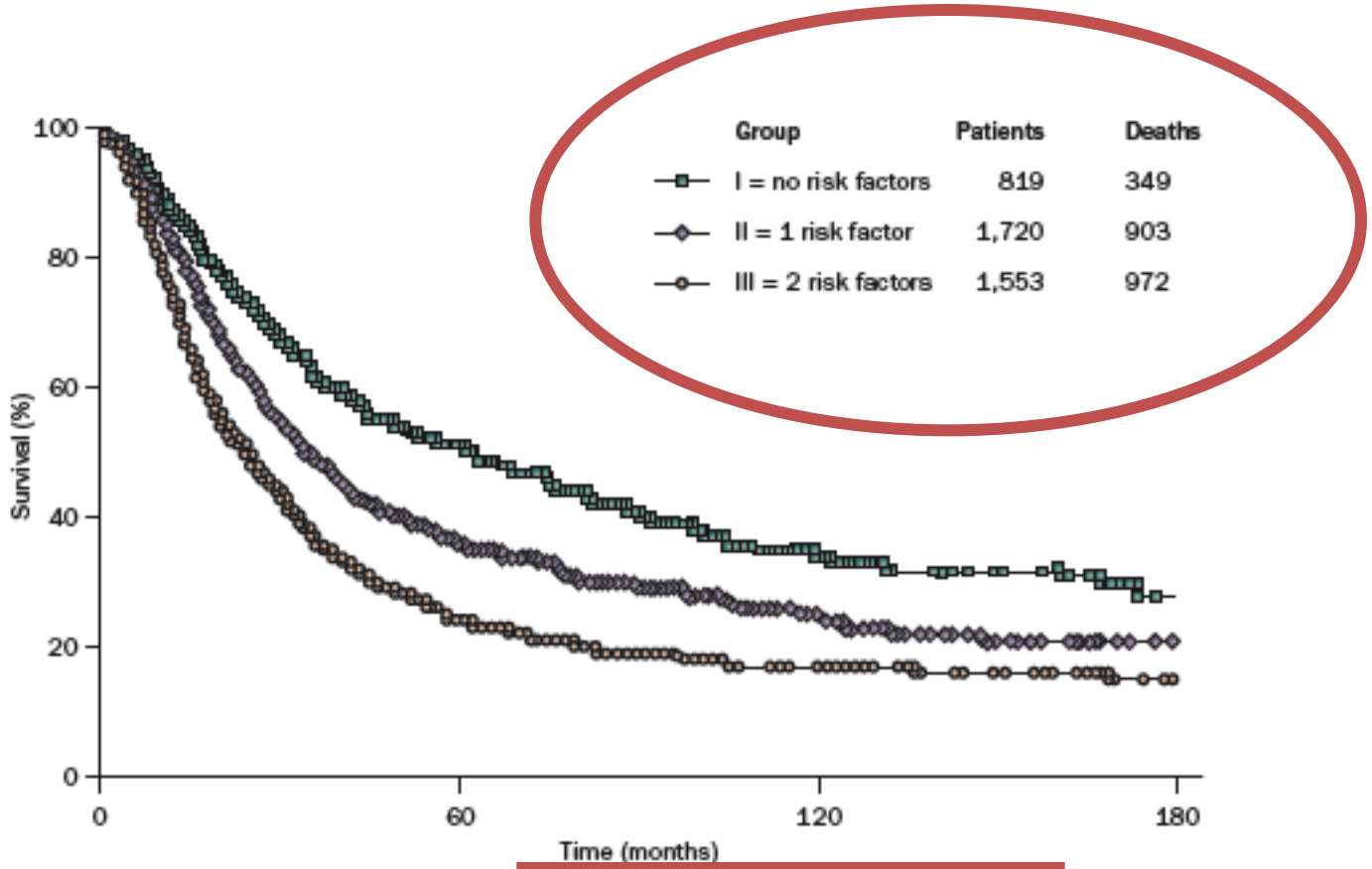
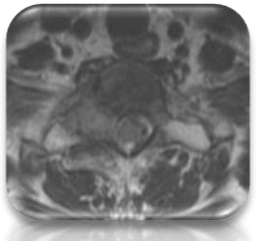
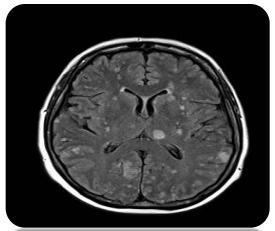
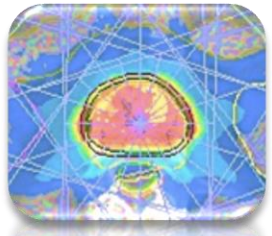


Figure 1 | Survival of patients undergoing pulmonary resection of metastatic tumors. Each curve represents the survival of patients with an increasing number of risk factors for recurrence as determined by a retrospective review of the data.[7] These categories are: group I, a single resectable metastasis with a disease-free interval from primary tumor to metastasis of ≥36 months; group II, multiple metastases or a disease-free interval <36 months; group III, multiple metastases and a disease-free interval <36 months. The size, number and tumor type are risk factors for recurrence. Permission obtained from Elsevier © Pastorino, U. *et al. J. Thorac. Cardiovasc. Surg.* **113**, 37–49 (1997).




1. Definitions, paradigm, clinical value
2. Oligo-metastasis: clinical models **based on radiotherapy**
3. Oligo-recurences: clinical models
4. Oligo-biology
5. Update 2014: models for improved practice

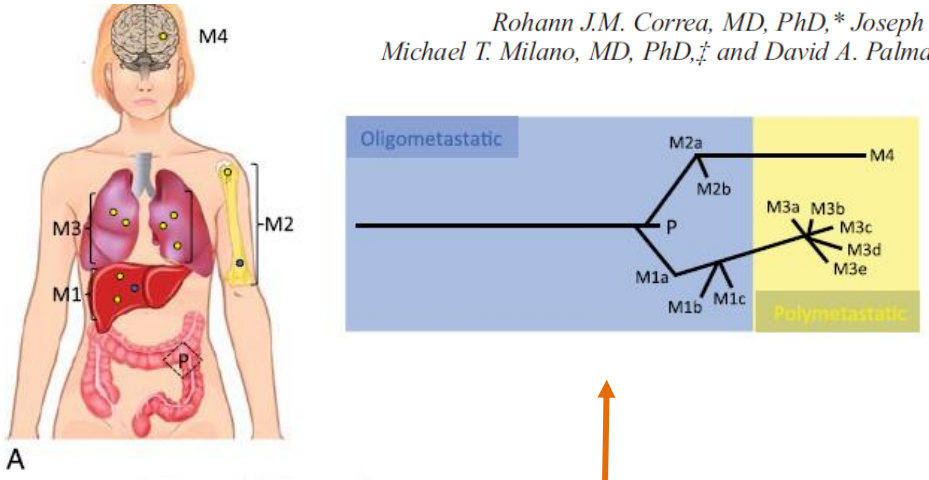
(*Cancer J* 2016;22: 247–256)

Stereotactic Body Radiotherapy for Oligometastasis

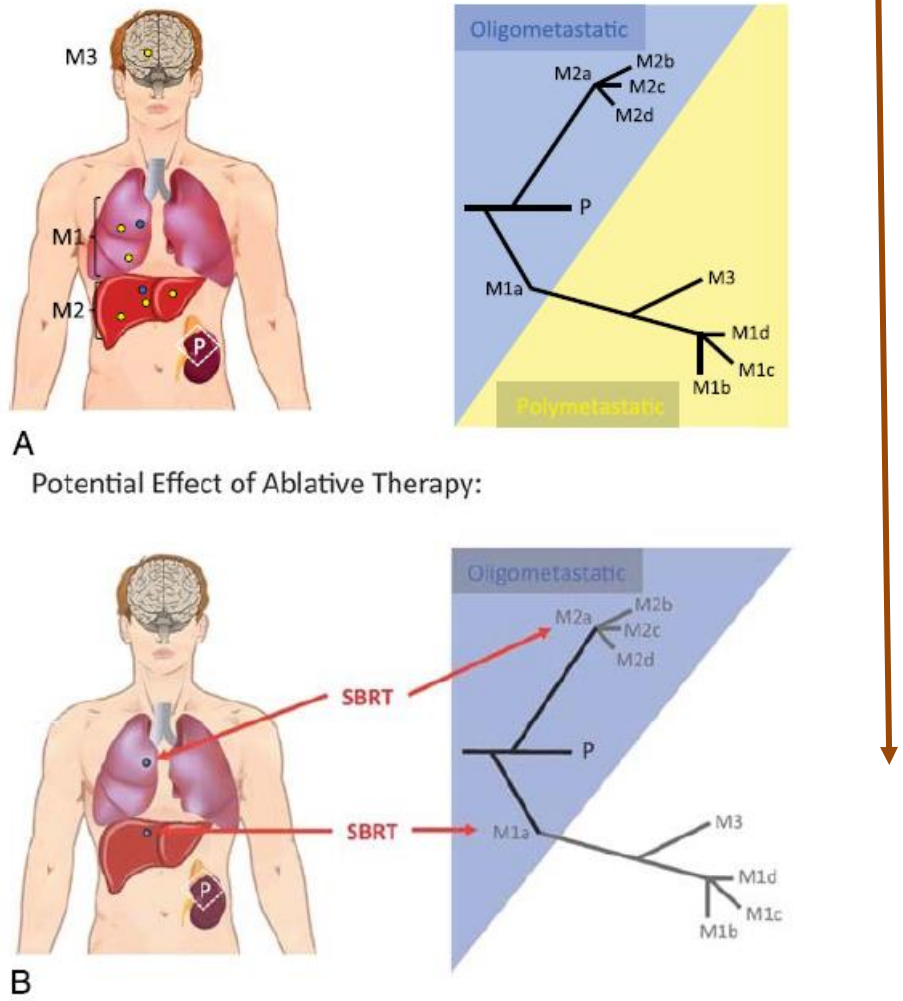
Opportunities for Biology to Guide Clinical Management

Rohann J.M. Correa, MD, PhD, Joseph K. Salama, MD,† Michael T. Milano, MD, PhD,‡ and David A. Palma, MD, MSc, PhD, FRCPC**

Parallel progression model

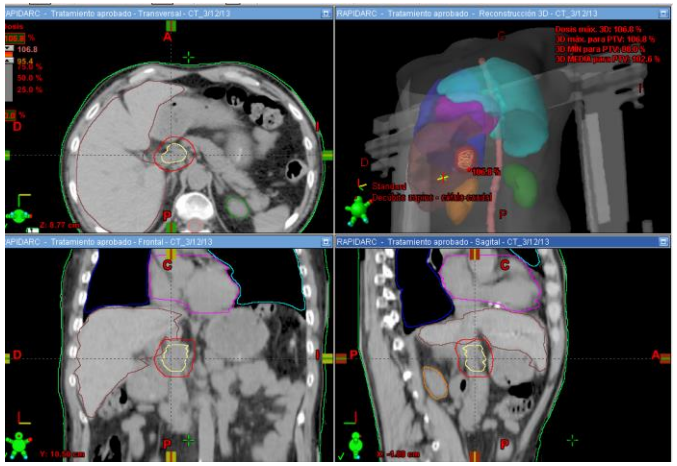


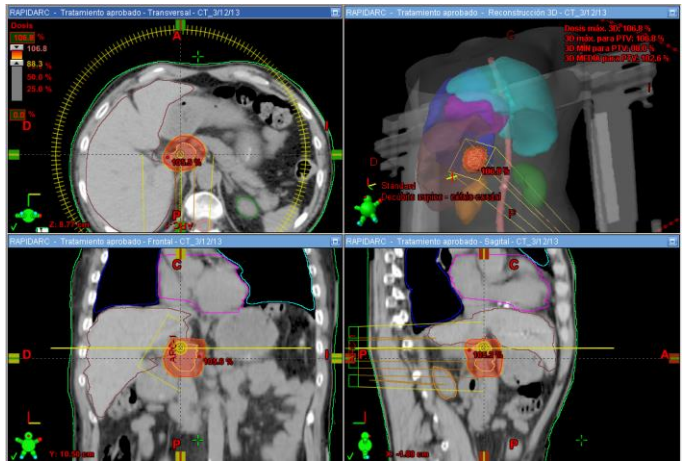
Linear progression model

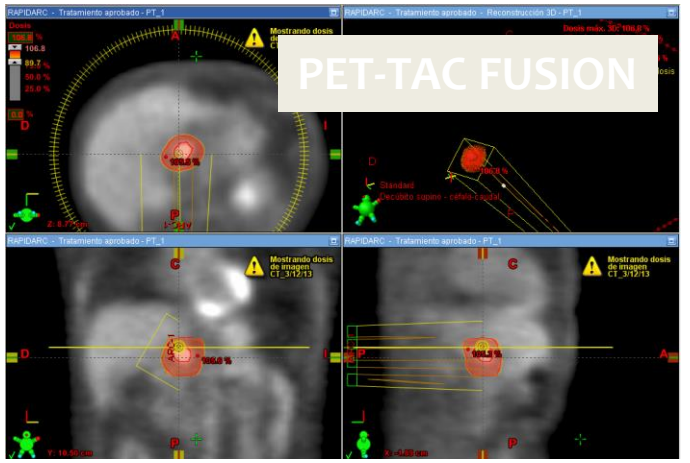


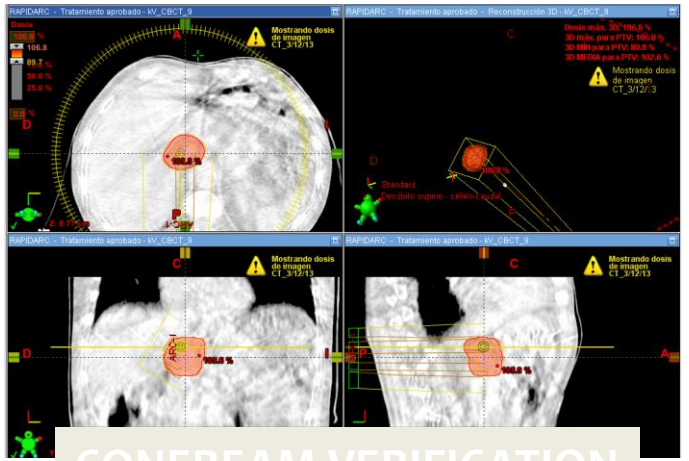
Extreme Precision = i-fusion + cone beam CT = Extreme Hipofractionation

1 – 3 *SBRT* fractions









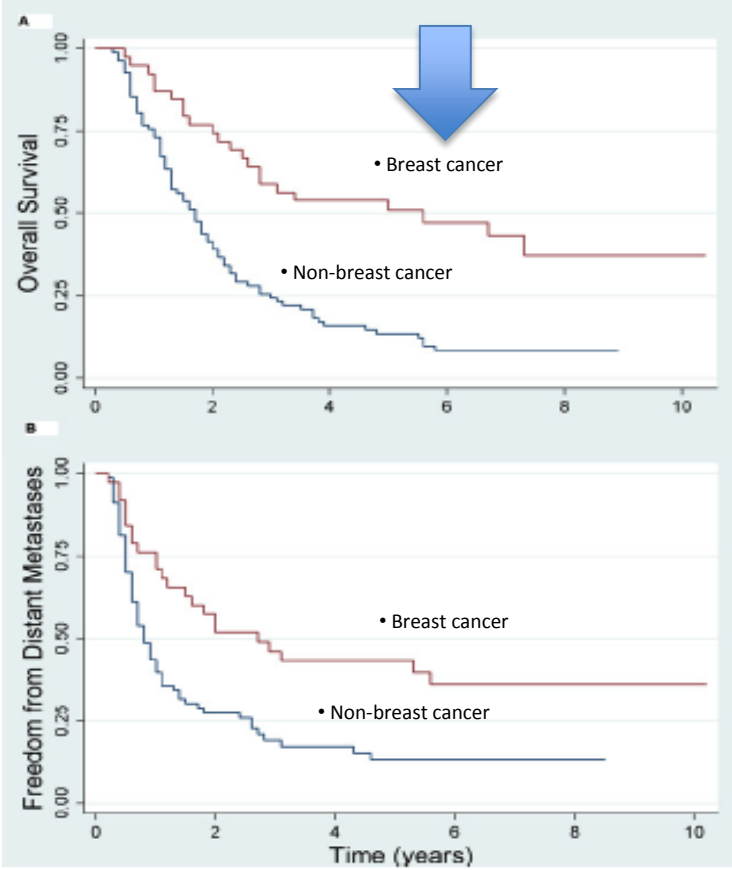
Clinical Investigation: Metastases

Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study

Michael T. Milano, M.D., Ph.D.,* Alan W. Katz, M.D., M.P.H.,*
Hong Zhang, Ph.D., M.D.,* and Paul Okunieff, M.D.*,†

**Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY; and †Department of Radiation Oncology, University of Florida, Gainesville, FL*

Received May 16, 2011, and in revised form Jul 3, 2011. Accepted for publication Aug 8, 2011



SBRT body (no brain SRS)
121 pts
< 5 mets
Breast cancer 16 / 39 alive
Other sites 7 / 82 alive

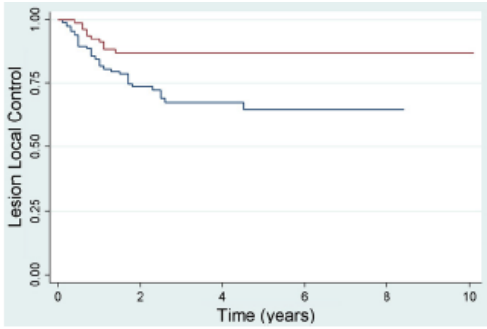


Table 2 Summary of stereotactic body radiotherapy for pulmonary metastasis

Ref.	Study	Patients (*n*) (primary sites)	Meta (*n*)	Institution	MFU (mo)	Dose (Gy)/	Time (d)	Prescription specification	LC (mo)	OS (mo)	Toxicity	*P* value
Wulf *et al*[70]	Retro	CRC (*n* = 4) others (*n* = 37)	51	Wuerzburg Univ	10	30-37.5/3 or 26/1	2-3 interval	PTV periphery: 65% isodose of maximum	80% (24)	33% (24)	NMT	
Okunieff *et al*[71]	Retro	CRC (*n* = 14) others (*n* = 35)	125	Rochester Univ.	19	Oct-50	1-5 times per week	Isocenter	91% (24)	38% (24)	Grade 3 pleural effusion: 2%	
Norihisa *et al*[72]	Retro	CRC (*n* = 14) others (*n* = 35)	43	Kyoto Univ.	27	48-60/4	4-18 (med: 12)	Isocenter	90% (24)	84.3% (24)	Grade 3 RP: 3%	
Kim *et al*[73]	Retro	CRC (*n* = 13)	18	Korea Cancer Center	28	39-51/3	3	PTV periphery: 75%-80% isodose of maximum	53% (24)	76% (24)	NMT	
Rusthoven *et al*[74]	P I/II	CRC (*n* = 9) others (*n* = 29)	63	multi-institution	15	48-60/3	< 14	Isocenter, PTV surrounded by 80%-90% isodose	96% (24)	39% (24)	Grade 3 RP: 8%	
Takeda *et al*[44]	Retro	CRC (*n* = 15) others (*n* = 19)	CRC (*n* = 21) others (*n* = 23)	Ofuna Chuo Hospital	29 15	May-50	5	PTV periphery: 75%-80% isodose of maximum	72% (24) 94% (24)	- -	NMT	*P* < 0.05
Oh *et al*[75]	Retro	57	67 CRC, HCC (*n* = 16) others (*n* = 51)	Samsung Medical Center	21	50-60/4-5	-	PTV periphery: 75%-80% isodose of maximum	92% (24) 81% (24) 100% (24)	57% (24)	Grade 5 RP: 2%	*P* = 0.01
Ricardi *et al*[76]	Retro	61	77	Giovanni Battista Univ	20	26/1 or 36-45/3	3	PTV periphery:	89% (24)	66.5% (24)	Grade 3 RP: 2%	
Inoue *et al*[77]	Retro	22	31	Hokkaido Univ.	25	Apr-48	4-7	80% isodose of maximum isocenter	100% (24)	80% (24)	NMT	
Widder *et al*[78]	Retro	CRC (*n* = 31) others (*n* = 11)	≥ 65	Groningen Univ	43	3/8/1960	-	PTV periphery: adapted risk of toxicity	94% (24)	86% (24)	-	
Inoue *et al*[79]	Retro	CRC (*n* = 37) others (*n* = 50)	≥ 150	Miyakojima IGRT Clinic	15	48/4, 52-60/4 or 50/5	4-5	-	80% (24)	47% (24)	Grade 3 RP: 6% Grade4 RP: 1%	

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer

Atsuya Takeda, Naoko Sanuki, Etsuo Kunieda

World J Gastroenterol 2014 April 21; 20(15): 4220-4229

+ 300 lung mets

LC 53% - 100%

+ OS 34% 2 years

Table 1 Summary of stereotactic body radiotherapy for liver metastasis

Ref.	Study	Patients (*n*) (primary sites)	Meta (*n*)	Institution	MFU (mo)	Dose (Gy)/fr	Time (d)	Prescription specification	LC (mo)	OS (mo)	Toxicity	*P* value
Herfarth *et al*[50]	P Ⅰ	CRC (*n* = 18) others (*n* = 14)	60-	Heidelberg Univ	15	14-26/1	1	Isocenter, PTV surrounded by	0% (24)	32% (24)	N MT	*P* < 0.01
	P Ⅱ					26/1	1	80% isodose	81% (24)	83% (24)		
Wulf *et al*[51]	Retro	39	CRC (*n* = 23) others (*n* = 28)	Wuerzburg Univ	15	28-30/3-4 36-37.5/3 or 26/1	2-3 interval	PTV periphery: 65% isodose of maximum	58% (24) 82% (24)	81% (24 for all)	N MT	*P* = 0.08
Katz *et al*[52]	Retro	CRC (*n* = 20) others (*n* = 49)	174	Rochester Univ	15	50/5f preferred	14	Maximum, PTV surrounded by the 80% isodose	57% (20)	37% (20)	N MT	
Rusthoven *et al*[53]	P Ⅰ / Ⅱ	CRC (*n* = 20) others (*n* = 49)	63	Multi-institution	16	36-60/3	< 14	Isocenter, PTV surrounded by 80%-90% isodose	92% (24)	30% (24)	Grade 3: 2%	
Lee *et al*[54]	P Ⅰ	CRC (*n* = 40) others (*n* = 28)	-	Princess Margaret Hospital	11	27.7-60/6 (median: 41.8)	> 14	PTV periphery: 71% isodose of maximum	71% (12)	47% (18)	N MT	
van der Pool *et al*[55]	Retro	CRC (*n* = 20)	31	Erasmus Univ	26	37.5-45/3f preferred	5-6	D95 of PTV	74% (24)	83% (24)	N MT	
Rule *et al*[56]	P Ⅰ	CRC (*n* = 12) others (*n* = 15)	36	Texas Southwestern Univ	20	3/30	< 14	PTV periphery, 70%-85% isodose of maximum	59% (24)	56% (24)	N MT	
						50/5	≤ 17		89% (24)	67% (24)		
						60/5	≤ 17		100% (24)	50% (24)		
Vautravers-Dewas *et al*[57]	Retro	CRC (*n* = 30) others (*n* = 15)	62	Centre Oscar Lambret	14	40/3 45/3	4-17 (mean: 9)	PTV periphery, 80% isodose of the maximum	86% (12) 100% (12)	48% (24 for all)	N MT	*P* = 0.07
		CRC (*n* = 30) others (*n* = 15)							86% (12) 100% (12)			*P* = 0.07
Scorsetti *et al*[58]	P Ⅱ	CRC (*n* = 29) others (*n* = 32)	76	Humanitas Cancer Center	12	52.5-75/3	3	Mean dose to PTV	90.6% (24)	37% (24)	N MT	

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer

Atsuya Takeda, Naoko Sanuki, Etsuo Kunieda

+ 400 liver mets

LC 57% - 100%

+ OS 32% @ 2 years

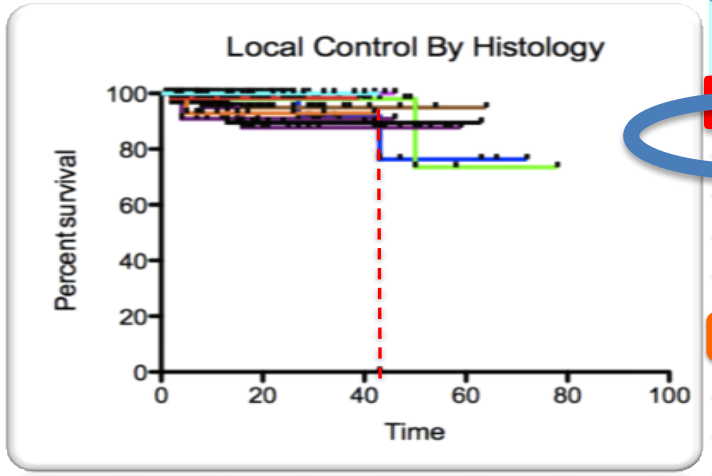
CLINICAL INVESTIGATION Metastasis

PREDICTORS OF LOCAL CONTROL AFTER SINGLE-DOSE STEREOTACTIC IMAGE-GUIDED INTENSITY-MODULATED RADIOTHERAPY FOR EXTRACRANIAL METASTASES

Carlo Greco, M.D.,* Michael J. Zelefsky, M.D.,* Michael Lovelock, Ph.D.,† Zvi Fuks, M.D.,* Margie Hunt, M.S.,† Kenneth Rosenzweig, M.D.,* Joan Zatcky, B.S., N.P.,* Balem Kim, B.A.,* and Yoshiya Yamada, M.D.*

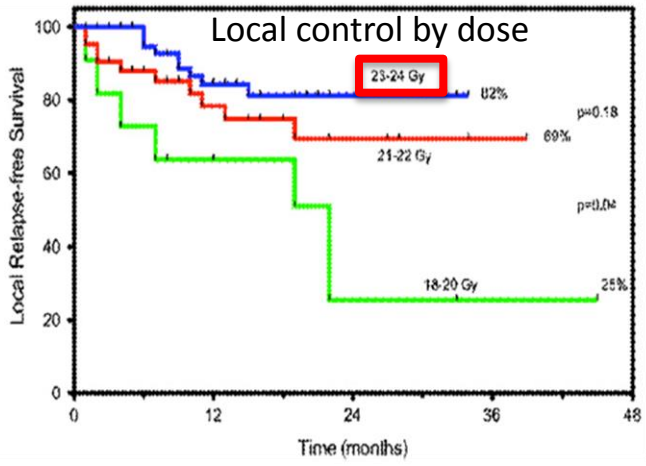
Departments of *Radiation Oncology and †Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY

- **Single dose of 21-24Gy … 90% local control.**



Histology	3 Yr Local Control
	98%
GI	98%
H&N	93%
Lung	98%
Melanoma	90%
Unknown	91%
Prostate	98%
Renal	89%
Sarcoma	96%
Thyroid	92%

413 patients



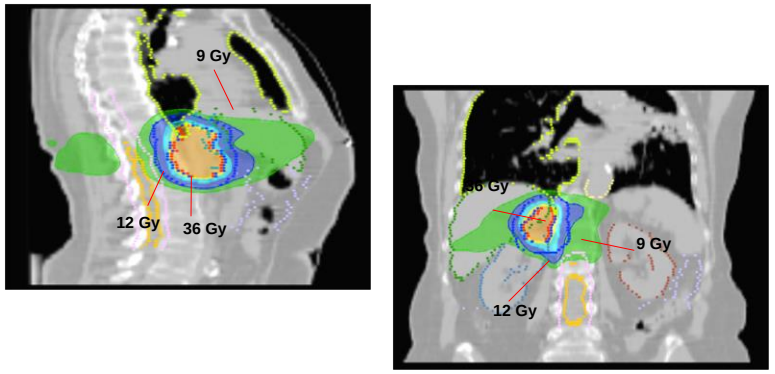
Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 1151–1157, 2011

SBRT COLO- RECTAL + miscelaneous CANCER

Single Dose

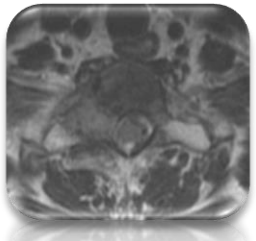
Habermehl et al. Radiat Oncol 2013

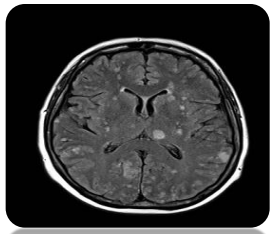
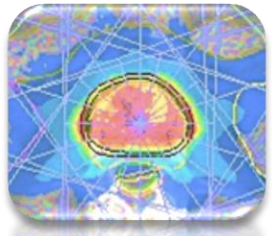
- METHODS
  - 1997-2009, 90 patients, 138 lesions
  - 17-30 Gy (median dose 24 Gy)
  - **Colo-rectal 70 lesions**



- RESULTS (Median overall survival 24.3 months)

Event	SBRT-single fr
Local PFS @ 6, 12 and 18 months	87% / 70% / 59%
Median time to local progression	25.5 months
Colo-rectal vs breast	p=0.05
Single lesion (sustained)	43,1 months




1. Definitions, paradigm, clinical value

2. Oligo-metastasis: clinical models **based on updated systematic reviews**
3. Oligo-recurences: clinical models

4. Oligo-biology

5. Update 2014: models for improved practice

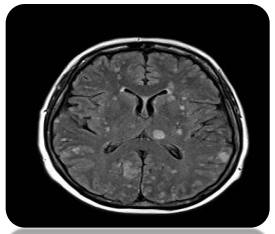
Huang et al. Radiation Oncology 2014, 9:230
http://www.ro-journal.com/content/9/1/230

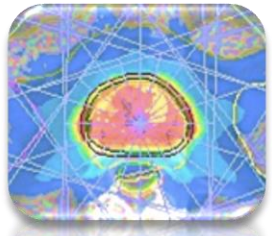
RADIATION ONCOLOGY

REVIEW Open Access

Oligometastasis and oligo-recurrence: more than a mirage

Fang Huang, Gang Wu* and Kunyu Yang*





Metastatectomy *vs* SBRT: systematic review (*Radiat Oncol 2014*)

Lung	SURGERY	SBRT
(References) years pub	(10) 1998-2011	(6) 2006-2013
Patients	**3.443**	**321**
Primaries	Melanoma/colorectal/renal/STS/Germ/GYN	Mixed/colorectal/NSCLC
Outcome	**21-69% OS @ 5y**	48-97% LC @ 1y

Hepatic	SURGERY	SBRT
(References) years pub	(5) 2005-2010	(6) 2001-2011
Patients	**2.040**	**240**
Primaries	Non-colorectal/breast/STS	Mixed/colorectal
Outcome	26-49% OS @ 5y	56-92% LC @ 1y

15 references 20% >2011 **5.483 > 20% OS @ 5y** **561 > 48% local control @ 1y**

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The biology and treatment of oligometastatic cancer

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[2]Departments of Pharmacology and Molecular Sciences, and Chemical and Biomolecular Engineering, The Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA

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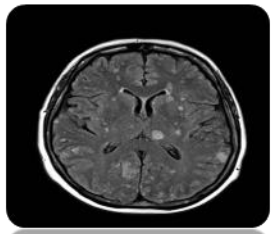
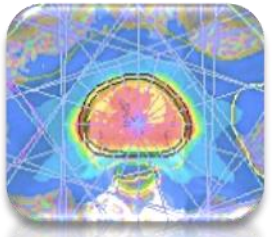
Keywords: metastasis, therapy, tumor, spectrum theory, diaspora

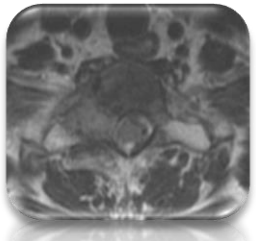
Received: *February 06, 2015* ***Accepted:*** *February 24, 2015* ***Published:*** *April 13, 2015*

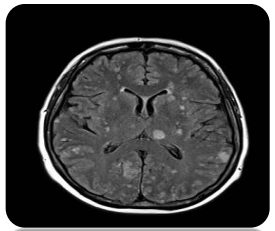
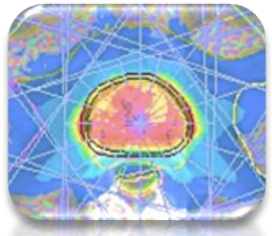




CANCER	(R) YEARS	STUDY/DEF	PATIENTS	TREATMENT	OUTCOME
Breast	(6) 2002-2014	4 R; <5 1-2 org	408	3CT; 2S; 4RT	OS @ >3y 39-59%
Lung	(20) 2006-2014	17R; <5 brain	**3.917**	CT; S; CRT; SBRT; RS	OS @ 5y 15-38%
Colo-rectal	(9) 2010-2014	6 R; 1 to <5	**1.377**	3S; 6 SBRT	OS @ 5y 29-52%
Sarcoma	(2) 2008-2014	2 R; 1 to >7	297	1S; 1RT; 2CT	MST 43.5 mo
Renal	(5) 2001-2014	3 R; <5	384	3S; 2 SBRT	OS @ 5y 27%
Melanoma	(2) 2004-2012	2 R; 1 or <3 N+	954	1S; 1RT; 1IT	OS @ 5y 17%
Prostate	(13) 2004-2014	12 R; <5 or LN+(3)	**2.714**	HT; S; RT; 6 SBRT	OS @ 5y 73-96%

7 primaries ***54 references; 65% >2010*** ***84% retrospective*** ***10.051*** ***CMT + 65% RT*** ***OS @ 5y 15-96%***

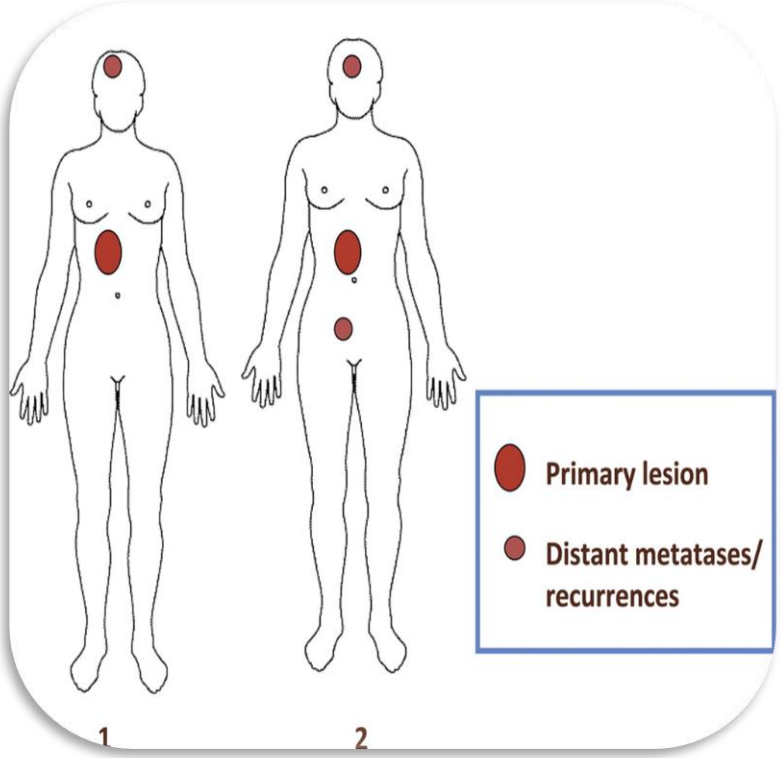


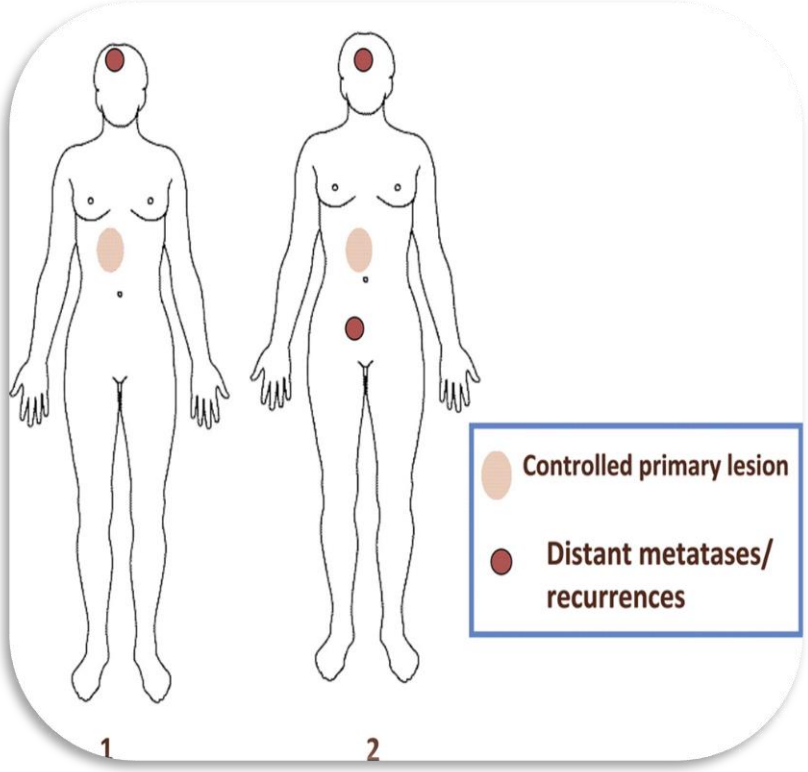

1. Definitions, paradigm, clinical value
2. Oligo-metastasis: clinical models
3. **Oligo-recurrences: rectal cancer**
4. Oligo-biology
5. Update 2014: improved practice & research

OLIGOMETASTASES vs. OLIGORRECURRENT

migration



- Situation in which a patient has distant disease in a limited number of regions.
  - Controlled primary tumor or not.



- 1 or more distant metastasis / recurrence (gen. 1) in 1 or more organs (gen. 1).
- Primary is controlled. 1 or more met/ rec. can be treated with local therapy.
  - No more met / rec. as described.

resistant

S +/- RT +/- CT

Hellman S, Weichselbaum RR. Oligometastases. J ClinOncol1995;13:8–10.
Niibe Y , Hayakawa K Jpn. J. Clin. Oncol. 2010;40:107-111

Japanese Journal of Clinical Oncology

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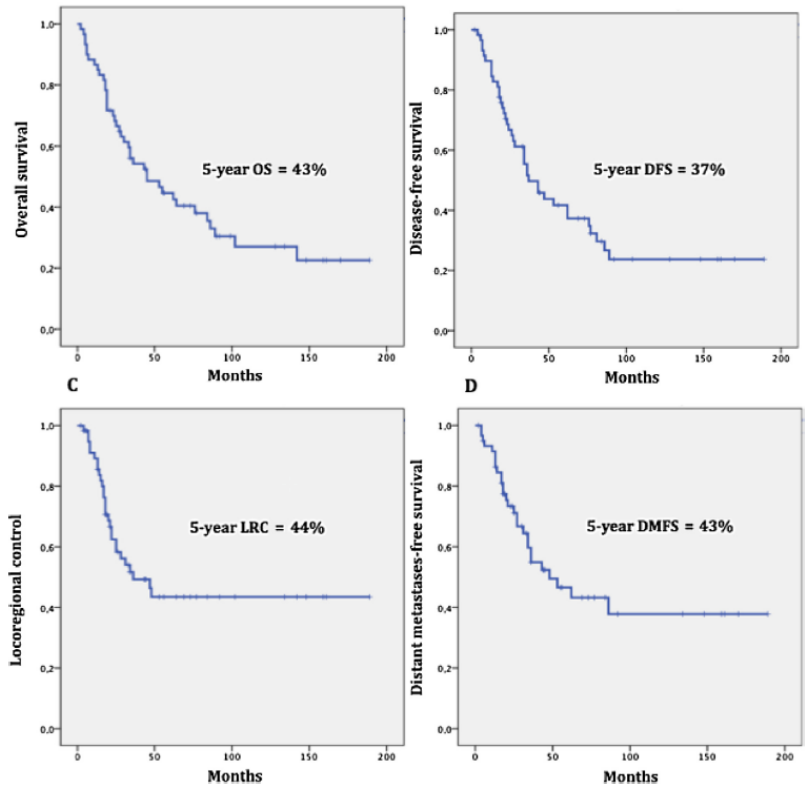
Clinical Investigation: Gastrointestinal Cancer

Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution

Felipe A. Calvo, MD, PhD,[*,§,||] Claudio V. Sole, MD,[*,§,||,¶] Pedro Alvarez de Sierra, MD, PhD,[†,||] Marina Gómez-Espí, MD,[*,‡,§] Jose Blanco, MD,[*,§] Miguel A. Lozano, MD,[*,‡,§] Emilio del Valle, MD,[†,§] Marcos Rodriguez, MD,[†,§] Alberto Muñoz-Calero, MD,[†,§] Fernando Turégano, MD,[†,§] Rafael Herranz, MD,[*,‡,§,||] Luis Gonzalez-Bayon, MD, PhD,[†,§] and Jose Luis García-Sabrido, MD, PhD[†,§,||]



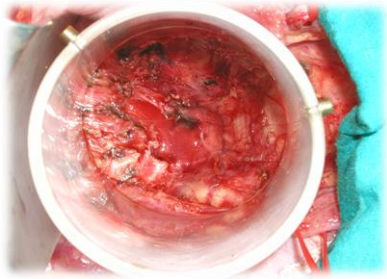


Table 1 Patient, tumor, and treatment characteristics

Characteristics	All patients n=60 (%)	Extended surgery n=38 (%)	Nonextended surgery n=22 (%)	*P* value
Patient variables				
Median age, y (range)	55.7 (35-79)	57.9 (35-73)	54.2 (35-79)	.63
Sex				
M/F	33 (55)/27 (45)	21/17	12/10	.96
Karnofsky performance status				
≥90/<90	22 (37)/38 (63)	14/24	8/14	.97
Median interval from primary to LR, mo (range)	27.2 (3-158)	26.1 (3-98)	28.1 (5-158)	.89
Macroscopic tumor variables				
Extent of infiltration of recurrence on pelvic sidewall: F0/F1/F2/F3/F4	2 (3)/17 (28)/7 (12)/16 (27)/18 (30)	0/0/4/16/18	2/17/3/0/0	<.001
Pelvic relapse topography: posterior/posterolateral/anterocentral	32 (53)/20 (33)/8 (14)	23/11/4	9/9/4	.33
Maximum recurrent tumor diameter, ≥5 cm vs <5 cm	23 (38)/37 (62)	17/21	6/16	.25
Median recurrent tumor size, cc (range)	4.5 (2-9)	4.8 (2-9)	4.1 (2-6)	.35
Tumor fragmentation: yes vs no	26 (43)/34 (57)	18/20	8/14	.41

Oligo-recurrent rectal cancer: IOERT component for rescue HGUGM (16 years experience)

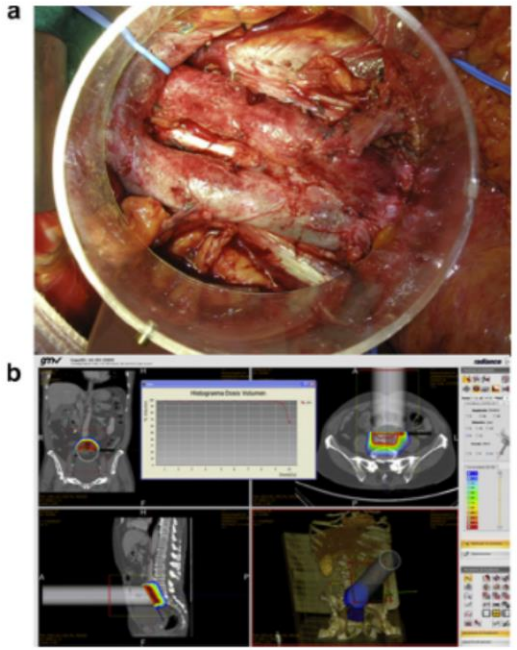


Figure 1. (a) IOERT in a case of oligotopic metastasis of testicular cancer to the para-aortic nodes. After resection, the circular applicator (8 cm in diameter) is placed in the tumor bed area containing the vascular structures and soft tissues, which is the region at risk for recurrence. Non-involved dosesensitive organs and tissues are temporarily displaced from the target area. (b) Two- and 3-dimensional and dose-volume histogram representation of an IOERT procedure in a case of paraaortic recurrence (radiance system). A left lateral lead protection was used to decrease radiation to the ipsilateral ureter.

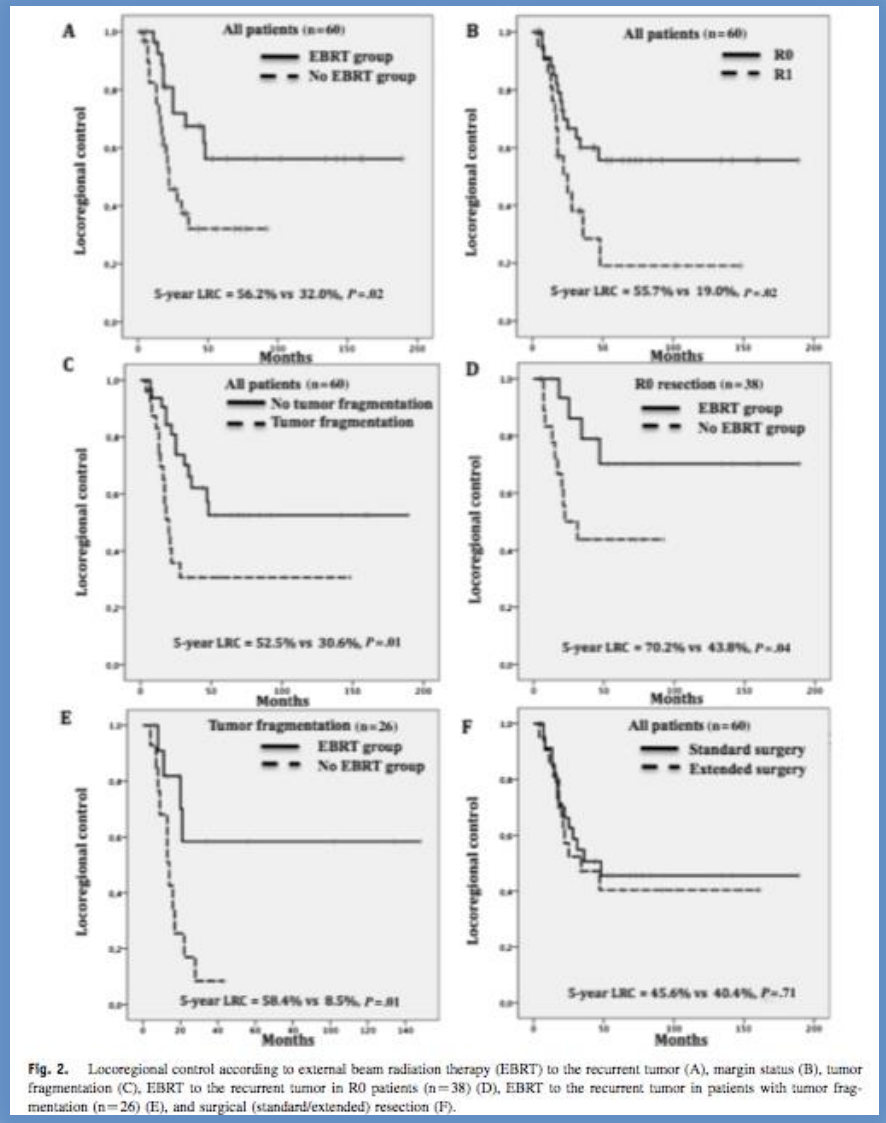


Fig. 2. Locoregional control according to external beam radiation therapy (EBRT) to the recurrent tumor (A), margin status (B), tumor fragmentation (C), EBRT to the recurrent tumor in R0 patients (n = 38) (D), EBRT to the recurrent tumor in patients with tumor fragmentation (n = 26) (E), and surgical (standard/extended) resection (F).

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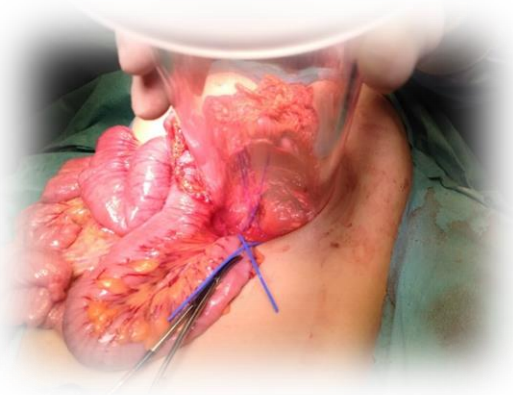
Clinical Investigation: Gastrointestinal Cancer

Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution

Felipe A. Calvo, MD, PhD,*,§,|| Claudio V. Sole, MD,*,§,||,¶ Pedro Alvarez de Sierra, MD, PhD,†,|| Marina Gómez-Espí, MD,*,‡,§ Jose Blanco, MD,*,§ Miguel A. Lozano, MD,*,‡,§ Emilio del Valle, MD,†,§ Marcos Rodriguez, MD,†,§ Alberto Muñoz-Calero, MD,†,§ Fernando Turégano, MD,†,§ Rafael Herranz, MD,*,‡,§,|| Luis Gonzalez-Bayon, MD, PhD,†,§ and Jose Luis García-Sabrido, MD, PhD†,§,||



IORT Results: colo-rectal recurrent cancer Mayo Clinic > 25 years

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 143–150, 2011

0360-3016/$–see front matter

2011

doi:10.1016/j.ijrobp.2009.10.046

CLINICAL INVESTIGATION **Large Bowel**

COMBINED MODALITY THERAPY INCLUDING INTRAOPERATIVE ELECTRON IRRADIATION FOR LOCALLY RECURRENT COLORECTAL CANCER

Michael G. Haddock, M.D.,* Robert C. Miller, M.D.,* Heidi Nelson, M.D.,†
John H. Pemberton, M.D.,† Eric J. Dozois, M.D.,† Steven R. Alberts, M.D.,‡
and Leonard L. Gunderson, M.D.§

*Department of Radiation Oncology, †Division of Colon and Rectal Surgery, and ‡Division of Medical Oncology, Mayo Clinic, Rochester, MN, and §Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ

LC 68% @ 5-y, 30% OS
Central-control *vs* prior EBRT (18% vs 14%),
R0/R+(11% vs 9%)

1981-2008, Mayo Clinic (>25 years experience)

607 patients (rectal 70%), recurrent 45% previous RT, R0 85%

Survival affected by Rstatus, CT, before/after 1997

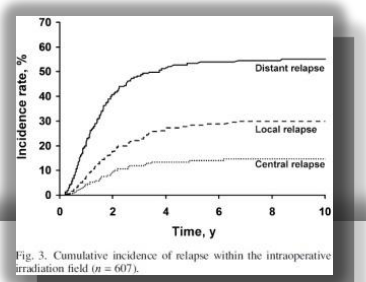


Fig. 3. Cumulative incidence of relapse within the intraoperative irradiation field (n = 607).

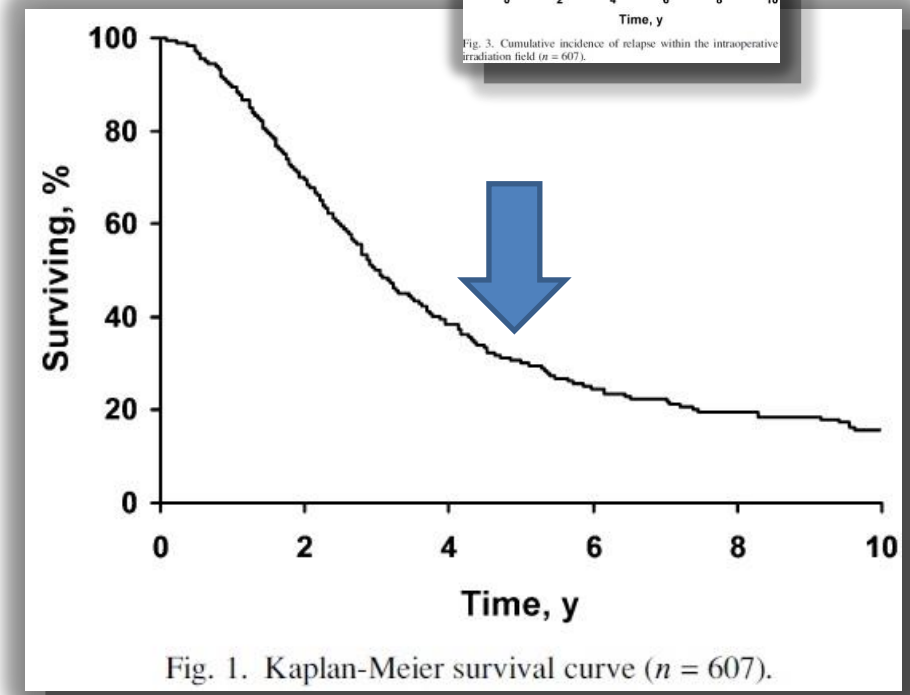
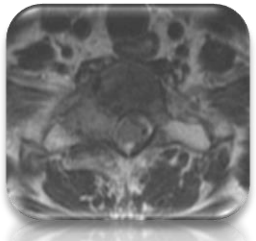
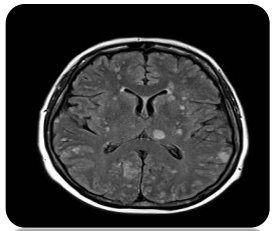
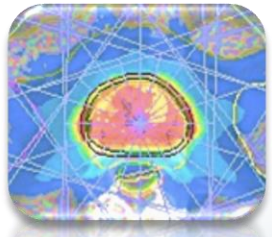


Fig. 1. Kaplan-Meier survival curve (n = 607).

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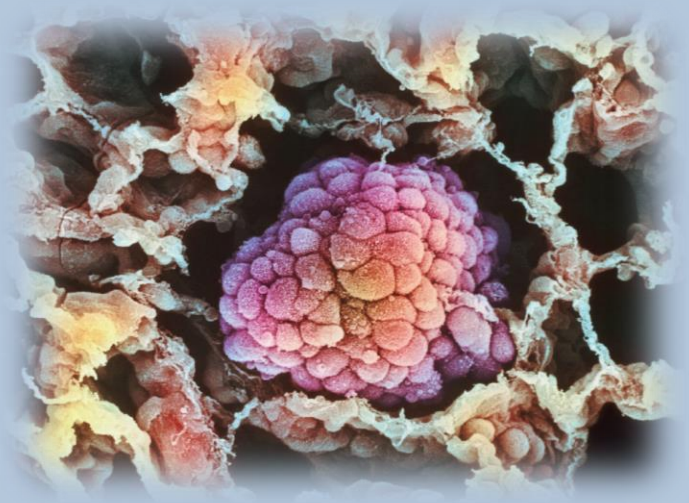
3. Oligo-recurences: clinical models
4. **Oligo-biology**
5. Update 2014: improved practice & research



Clin Exp Metastasis (2014) 31:735–748
DOI 10.1007/s10585-014-9664-3

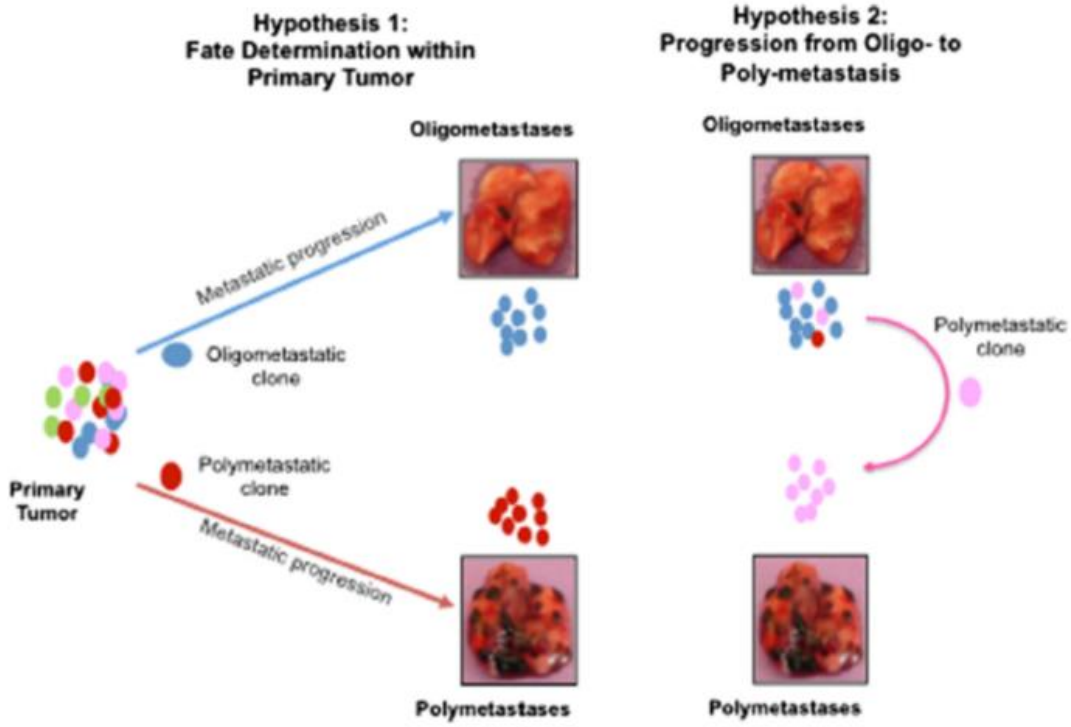
REVIEW

Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs

Abhineet Uppal · Mark K. Ferguson · Mitchell C. Posner · Samuel Hellman · Nikolai N. Khodarev · Ralph R. Weichselbaum

Received: 26 January 2014 / Accepted: 9 June 2014 / Published online: 27 June 2014

Fig. 1 Pathways of oligo-and polymetastases development. Two hypotheses of Oligometastastic Disease: *Hypothesis 1* Oligometastases and Polymetastases may be distinct metastasis phenotypes determined by dissemination of clonal populations with differing metastatic potential. *Hypothesis 2* Metastasis may be a continuum of phenotypes identified early (oligometastases) or late (polymetastases) in the progression of disease



Pathways for metastatic development

Heterogeneity + clonal migration

Clin Exp Metastasis (2014) 31:735–748
DOI 10.1007/s10585-014-9664-3

REVIEW

Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs

Abhineet Uppal · Mark K. Ferguson · Mitchell C. Posner · Samuel Hellman · Nikolai N. Khodarev · Ralph R. Weichselbaum

Received: 26 January 2014 / Accepted: 9 June 2014 / Published online: 27 June 2014

3 overlaping micro-RNAs

A

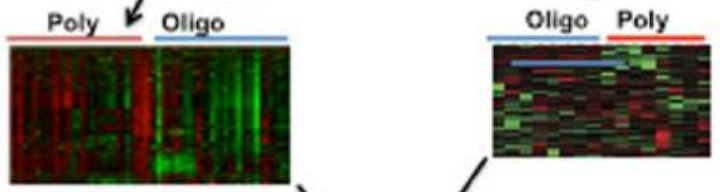
Unsupervised clustering: succesfull segretation

Oligo vs Polymetastatic

Upregulated

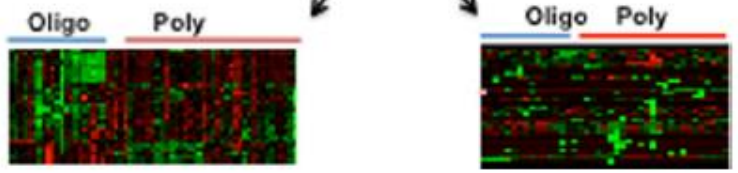
Downregulated

B

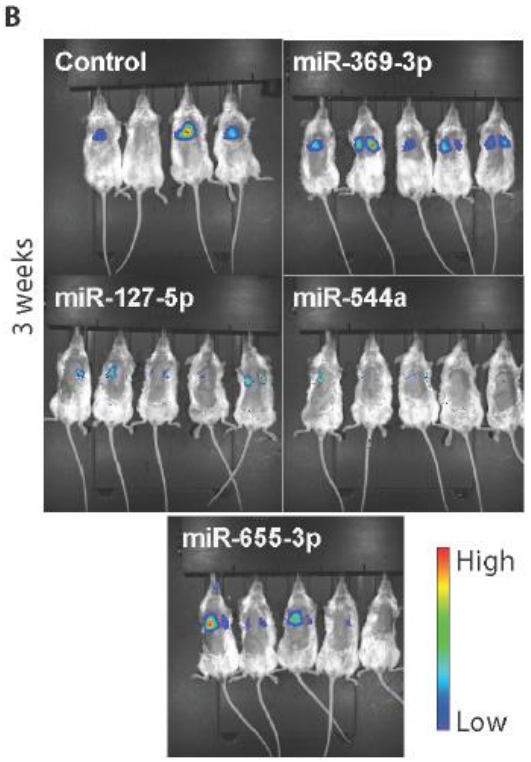


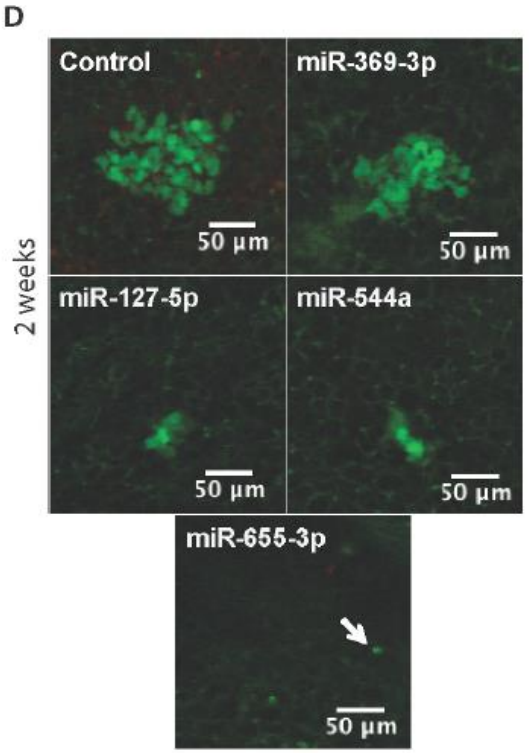
Polivalent signature: surgery vs SBRT

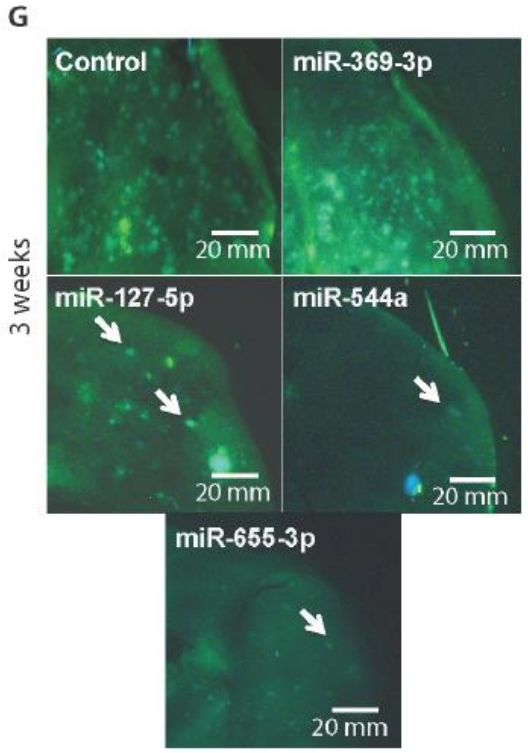
C



Ectopic expression of 14q32-encoded miRNAs limits lung colonization of metastatic tumor cells.







www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No.6

14q32-encoded microRNAs mediate an oligometastatic phenotype

Abhineet Uppal[1], Sean C. Wightman[1], Stephen Mallon[2,3], Go Oshima[1], Sean P. Pitroda[2,3], Qingbei Zhang[4], Xiaona Huang[2,3], Thomas E. Darga[2,3], Lei Huang[5], Jorge Andrade[5], Huiping Liu[6], Mark K. Ferguson[1,3], Geoffrey L. Greene[3,7], Mitchell C. Posner[1,3], Samuel Hellman[2,3], Nikolai N. Khodarev[2,3,*], Ralph R. Weichselbaum[2,3,*]

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[4]Department of Pathology, Committee on Cancer Biology, The University of Chicago, Chicago, IL 60637, USA
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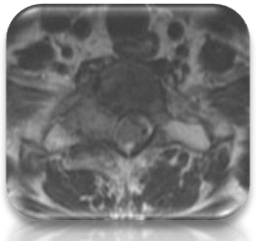
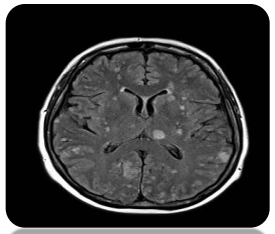
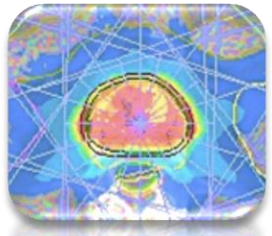
Keywords: metastasis, oligometastasis, microRNA, gene expression, gene regulation
Received: November 17, 2014 ***Accepted:*** December 11, 2014 ***Published:*** February 18, 2015

MDA-MB-231 polymetastatic breast cancer cells co-labeled with luciferase and GFP.
Transfected with miR-127-5p, miR-369-3p, miR-544a, miR-655-3p.
Non-targeting control. Injected into NOD/SCID mice.

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4. Oligo-biology
5. **Update 2017: improved practice & research**

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.45.9651

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

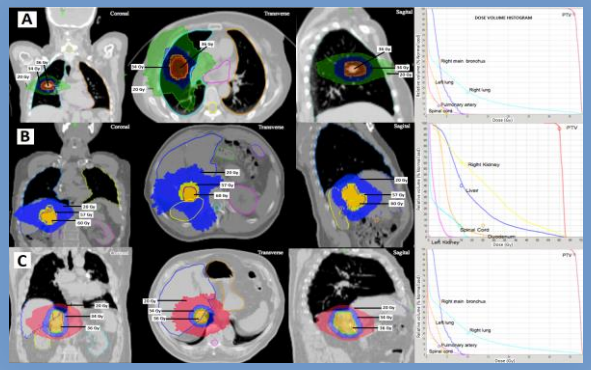
Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

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

Review

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



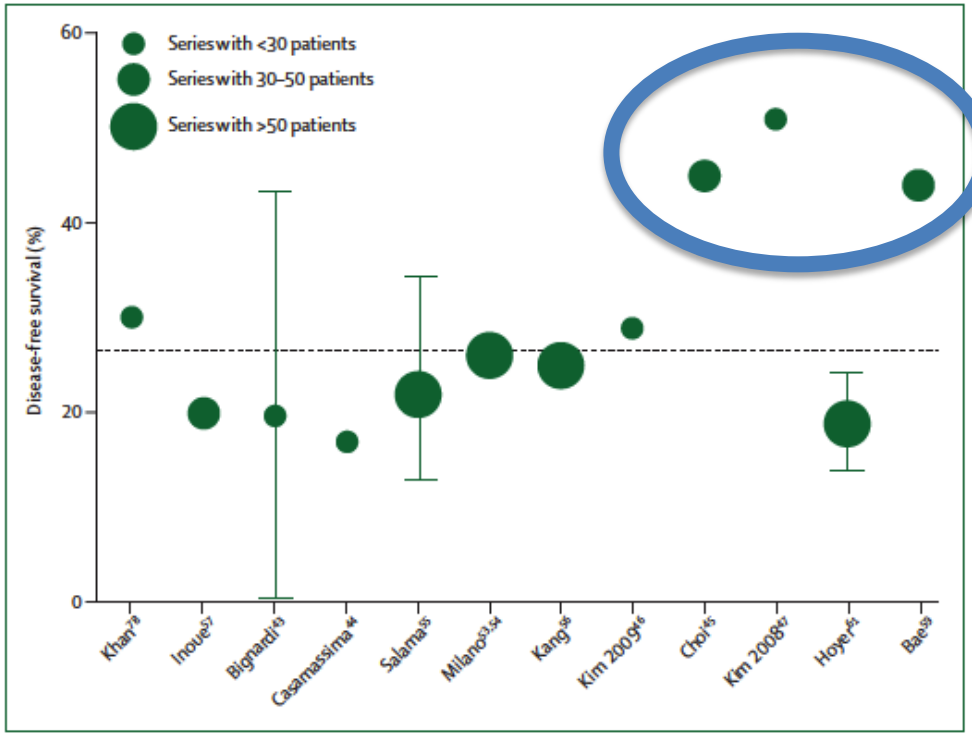


Figure 2: **Disease-free survival in patients with oligometastatic disease at 17–48 months' follow-up**
Dotted line represents mean proportion of patients who were disease free at the reported timepoint, weighted for number of patients in each cohort. Error bars represent 95% confidence intervals.

1fr-18-24 Gy
3fr-24-60 Gy
4fr-40 Gy
5fr-40-60 Gy
6fr-42 Gy
10fr-50 Gy

	Study year	Number of patients (number of lesions)	Dose	Primary site	Treated site(s)	Treated metastasis control	Toxicity
Milano et al[53,54]	2008	121 (293)	Various; median 50 Gy in 10 fractions	All (mostly breast and colorectal)	Lung, liver, bone, lymph node, 7 CNS	2-year LLC 77%; 4-year LLC 74%	Grade 3 in 1 patient (1%)
Salama et al[55]	2011	61 (113)	Increasing from 24 Gy in 3 fractions to 48 Gy in 3 fractions	All (26% NSCLC)	Lung, liver, lymph node, bone	2-year LLC 66·7%; 88·0% if dose ≥30 Gy in 3 fractions	Acute grade 3 in 2 (3%), 6 possible late grade 3 (10%)
Kang et al[56]	2010	59 (78)	42 Gy in 3 fractions	Colorectal	Lung, liver, lymph node, other	3-year local control 66% (note 69% of patients had PD after chemotherapy)	No grade 3, 3% grade 4 (gastrointestinal perforation/ obstruction)
Inoue et al[57]	2010	44 (60)	48 Gy in 8 (adrenal), 35–60 Gy in 4–8 fractions (see text for details)	Mostly lung	Lung, adrenal, brain	3-year local control 80%	9·8% grade 2; no grade 3 or higher
Stinauer et al[58]	2011	30 (53)	40–50 Gy in 5 fractions or 42–60 Gy in 3 fractions	Renal-cell and melanoma	Lung, liver, bone	18-month local control 88%	One grade 3 hypoxia (3%)
Bae et al[59]	2012	41 (50)	Median 48 Gy in 3 fractions	Colorectal	Lymph node, lung, liver	3-year local control 64%	No acute grade 3, 7% late grade 3
Jereczek-Fossa et al[60]	2011	34 (38)	30 Gy in 5 fractions to 36 Gy in 3 fractions	Prostate	Lymph node, bone, prostate recurrence	88% local control	6% grade 3 urinary, 3% grade 3 rectal (all prostate recurrence patients), 6% grade 3 late urinary
Hoyer et al[61]	2006	64 (141)	45 Gy in 3 fractions	Colorectal	Liver, lung, nodes, other	2-year local control 63% (86% LLC)	30% grade 3: pain, nausea, skin reaction; 9% grade 4
Wersall et al[62]	2005	58 (162)	30–40 Gy in 3 fractions was most common dose	Renal-cell carcinoma	Lung (majority), renal bed, lymph node, adrenal	Local control 90% or higher	40% had grade 1 or higher toxicity, with a high proportion of grade 3 events (some perhaps in the same patient); one death (gastric haemorrhage)
Svedman et al[63]	2006	30 (82)	Various: 40 Gy in 4 fractions was most common dose	Renal-cell carcinoma	Lung (majority), renal bed, adrenal	Only 2% documented progression at median follow-up 52 months	4% of side-effects were grade 3
Nuyttens et al[64]	2007	14 (15)	Median 7 Gy/fraction, median 6 fractions	Mixed	Mixed	100% local control at median follow-up 18 months	No grade 3
Greco et al[65]	2011	103 (126)	18–24 Gy in 1 fraction	Prostate, renal, colorectal	Majority bone, lymph node, soft tissue	Local control at 2 years 64% (82% if >22 Gy, 25% for 18–20 Gy)	<4% grade 3 late (stricture, neuritis)

LLC=lesion local control. NSCLC=non-small cell lung cancer. PD=progressive disease.

Table 2: **Stereotactic body radiotherapy for mixed oligometastatic sites**

Toxicity

G3 3-30%
G4 3-9%

Lancet Oncol 2013; 14: e28–37 (12 modern SBRT olimetastatic trials)

Radiosensitivity of Colon and Rectal Lung Oligometastasis Treated With Stereotactic Ablative Radiotherapy

Clinical Colorectal Cancer, Vol. ■, No. ■, ■-■ © 2016

Rémy Kinj,[1] Pierre-Yves Bondiau,[1] Eric François,[2] Jean-Pierre Gérard,[1] Arash O. Naghavi,[3] Axel Leysalle,[1] Emmanuel Chamorey,[4] Ludovic Evesque,[2] Bernard Padovani,[5] Antoine Ianessi,[6] Karen Benezery,[1] Jérôme Doyen[1,7]

Table 1 Patient Demographics and Treatment Characteristics

Demographic or Clinical Characteristic	No. of Patients (%)
Median age, year (range)	69 (47-84)
Missing data	0
Median follow-up, mos (range)	33 (4-85)
Gender	
Male	35 (34%)
Female	18 (66%)
Missing data	0
Primary lesion	
Rectal	17 (32.1%)
Colon	36 (67.9%)
Missing data	0
KRAS mutation	
Present	20 (54%)
Absent	17 (46%)
Missing data	16
Metastases at cancer diagnosis	
Presence of metastases	37 (69.8)
Absence of metastases	16 (30.2)

Figure 3 Overall Survival According the Number of Metastases at Time of Stereotactic Radiotherapy

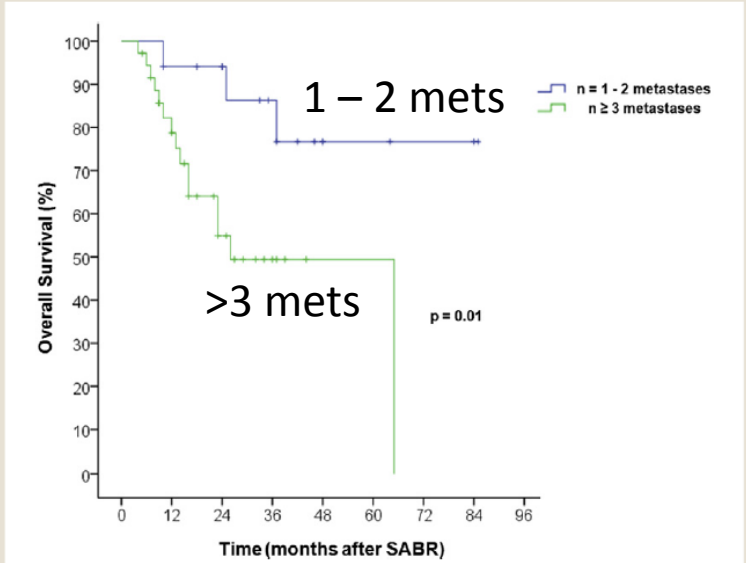


Table 6 Comparison Between Rectal and Colon Metastases

Variable	Rectal Tumors	Colon Tumors	*P* Value
Mutation of *KRAS*, %			
No	**26.7**	**59.6**	**.02**
Yes	**73.3**	**40.4**	
Mean Number of metastases[a]	3.4	3.7	.4
Mean number of involved organs[a]	1.5	1.7	.2
Mean number of chemotherapy lines before SABR[a]	**0.9**	**1.7**	**.001**
Mean BED, Gy	**169.3**	**153.3**	**.01**
Mean GTV, mL	11.6	12.5	.9
Mean tumor size, mm	22.1	20.5	.5

Figure 2 Metastasis-Free Survival (A), Progression-Free Survival (B) and Overall Survival (C) in the Whole Cohort

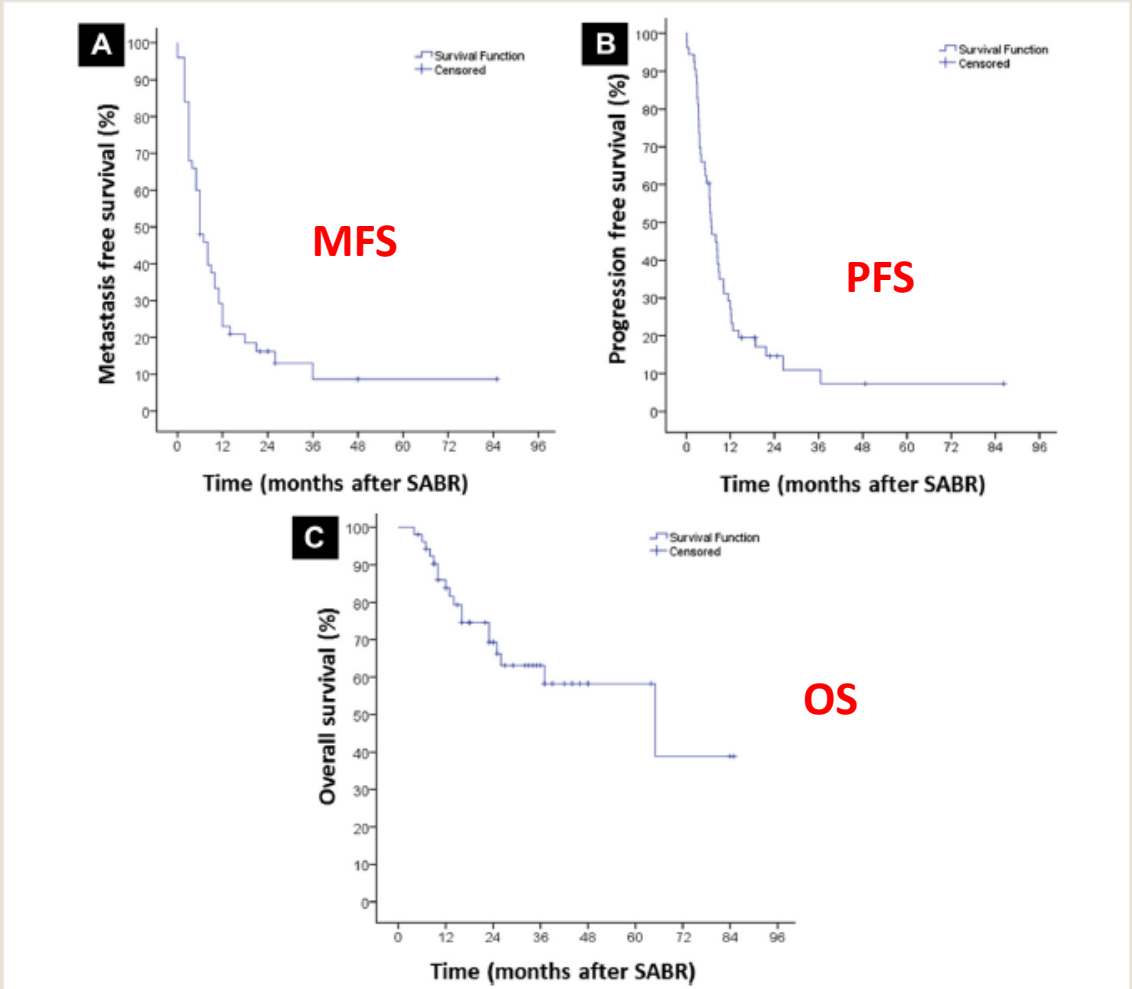
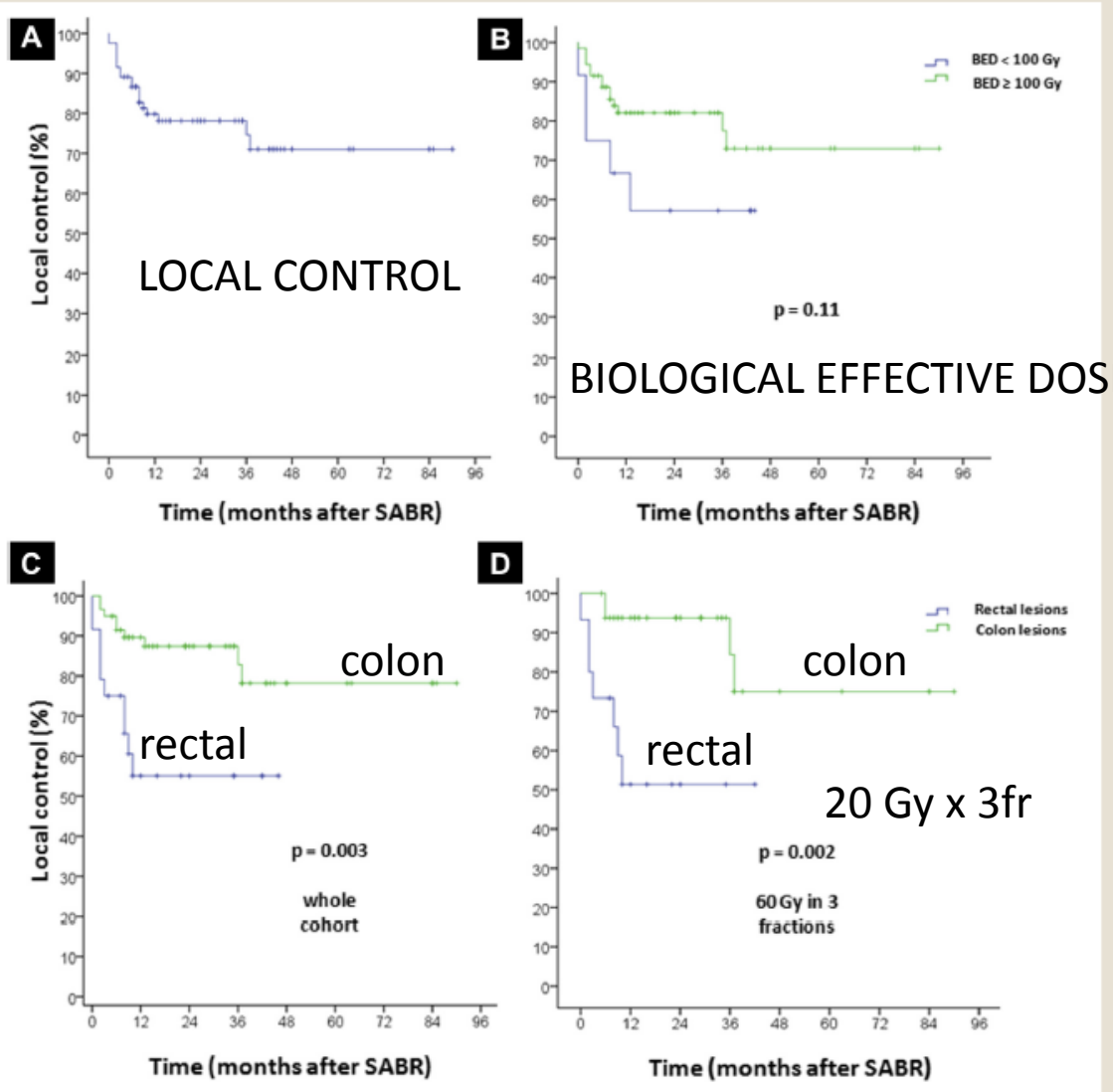


Table 3 Prognostic Factors for Local Control

Variable	2-Year Local Control, %	Log-Rank *P*	HR (Cox Regression)
Primary tumor			
Rectal (n = 24)	**55.1**	**.003**	***P* = .001**
Colon (n = 63)	**87.4**		**HR = 4.7 (1.8-12.2)**
Mutation of *KRAS*			
No (n = 35)	78.0	.8	NI
Yes (n = 32)	71.6		

Reducir (Ctrl+1)

Figure 1 Local Control in the Whole Cohort (A), According to the Biological Effective Dose (BED) (B), Primary Origin (C), and Primary Origin When Treated With 60 Gy in 3 Fractions (D)



VOLUME 32 · NUMBER 26 · SEPTEMBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Emergence of Stereotactic Body Radiation Therapy and Its Impact on Current and Future Clinical Practice

Robert D. Timmerman, Joseph Herman, and L. Chinsoo Cho

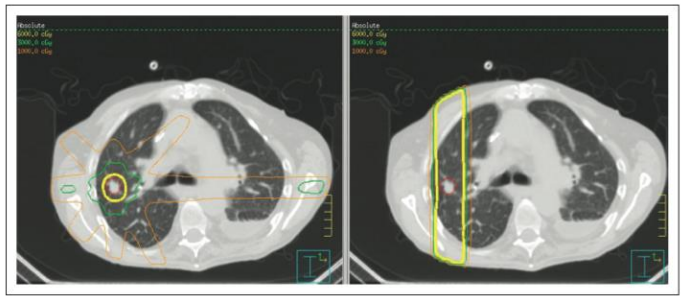


Fig 1. Comparison of stereotactic body radiation therapy (SBRT) plan in the left panel versus historical postage stamp anterior/posterior-directed field arrangements shown in the right panel. The SBRT plan uses advanced imaging and guidance to reduce the necessary margin around the tumor. In addition, it spares the high-dose (60 Gy, yellow) and intermediate-dose (30 Gy, green) volumes in exchange for a considerably larger low-dose (10 Gy, orange) volume.

"Local treatment of metastatic disease
with SBRT would effectively be a new indication for radiotherapy,
resulting in potentially dramatic growth
in the average raditherapy practice.
Interestingly, the rational becomes even stronger
with the discovery of more effective systemic therapies".

Studies Oligometastatic Disease: Cancer-Type Oriented

Clinical Trials. Gov CTG @ 2 / 1 / 2015

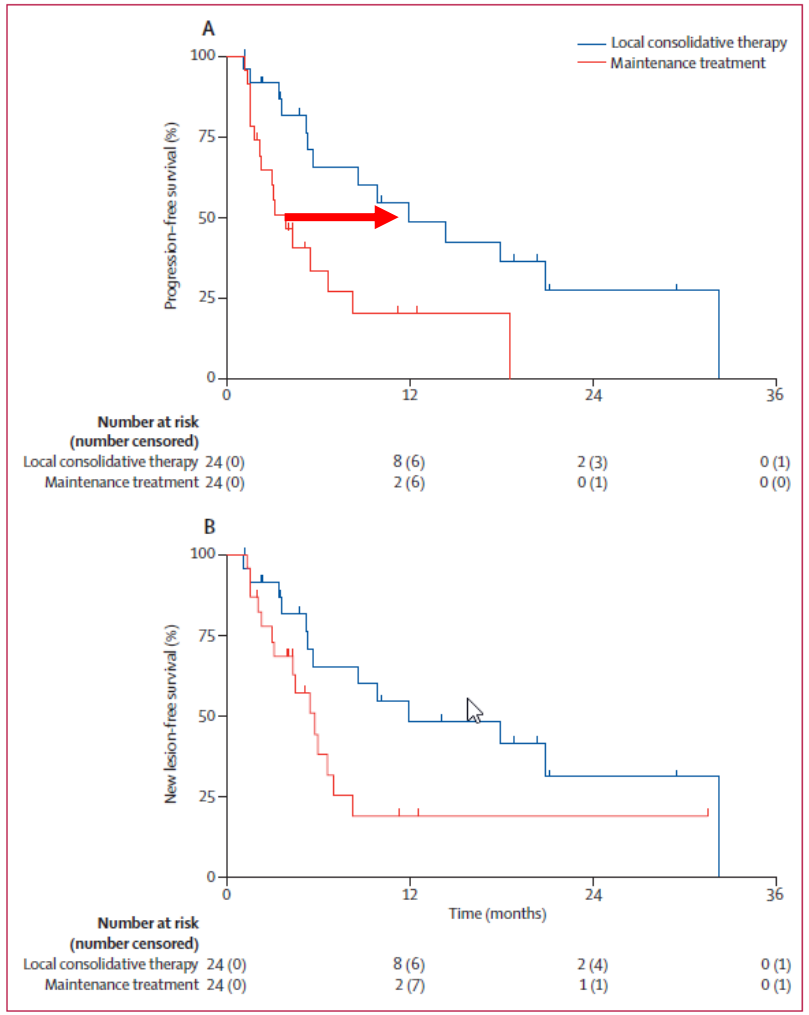
CANCER	# REFERENCES	EU / USA / Others	Tx ALGORITHM	OUTCOME End-p
Lung NSCLC	9	1 5 3	RT + Erlotinib TKI EGFR Pembrolizumab ***SBRT***	PFS OS Toxicity Response
Prostate	8	4 3 1	IMRT + HT ***SBRT***	BC; ADT-FS;Toxicity; Inmune effect
Breast	6	2 3 1	HD-CT + RT; RT + CT ***SBRT*** + MK-3475 ***SBRT*** +/- Trastuzumab	CTCs TTP PFS
Melanoma	3	- 3 -	***SBRT*** + Ipilimumab	PFS
Sarcoma	2	- 2 -	***SBRT***	Local C; OS
Colo-rectal	1	1 - -	RT + Beva + Cape	PFS
6 cancer types	**29 references**	**55% USA**	**SBRT/90% systemic**	**65% PFS**

Primeras evidencias clínicas prospectivas, aleatorizadas, controladas…

con rescate radioterápico (SBRT)

…2016

Lancet Oncol 2016; 17: 1672–82



Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

Findings Between Nov 28, 2012, and Jan 19, 2016, 74 patients were enrolled either during or at the completion of first-line systemic therapy. The study was terminated early after randomisation of 49 patients (25 in the local consolidative therapy group and 24 in the maintenance treatment group) as part of the annual analyses done by the Data Safety Monitoring Committee of all randomised trials at MD Anderson Cancer Center, and before a planned interim analysis of 44 events. At a median follow-up time for all randomised patients of 12·39 months (IQR 5·52–20·30), the median progression-free survival in the local consolidative therapy group was 11·9 months (90% CI 5·7–20·9) versus 3·9 months (2·3–6·6) in the maintenance treatment group (hazard ratio 0·35 [90% CI 0·18–0·66], log-rank p=0·0054). Adverse events were similar between groups, with no grade 4 adverse events or deaths due to treatment. Grade 3 adverse events in the maintenance therapy group were fatigue (n=1) and anaemia (n=1) and in the local consolidative therapy group were oesophagitis (n=2), anaemia (n=1), pneumothorax (n=1), and abdominal pain (n=1, unlikely related).

2012 – 2016 NSCLC
74 pts estables o respondedores 1ra línea QT
< 3 mets (75% SBRT)
PFS 3.9 vs 11.9 meses (p= 0.005)

Interpretation Local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone. These findings suggest that aggressive local therapy should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake

Checkpoint blockade immunotherapy has received mainstream attention as a result of striking and durable clinical responses in some patients with metastatic disease and a reasonable response rate in many tumour types. The activity

Lancet Oncology 2015; 16: e498–509

"seed and soil"

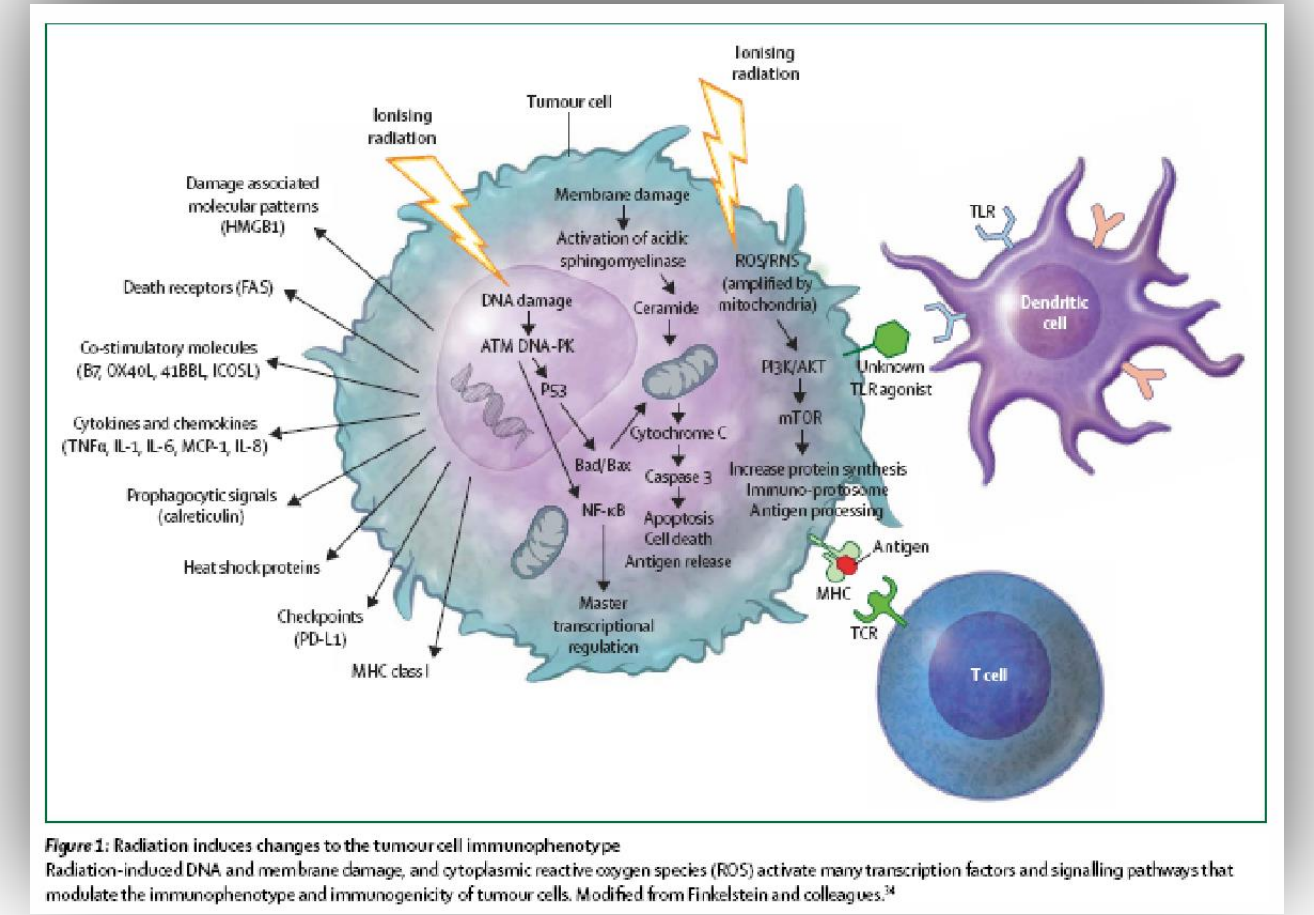


Figure 1: **Radiation induces changes to the tumour cell immunophenotype**
Radiation-induced DNA and membrane damage, and cytoplasmic reactive oxygen species (ROS) activate many transcription factors and signalling pathways that modulate the immunophenotype and immunogenicity of tumour cells. Modified from Finkelstein and colleagues.[34]

"…and soil"

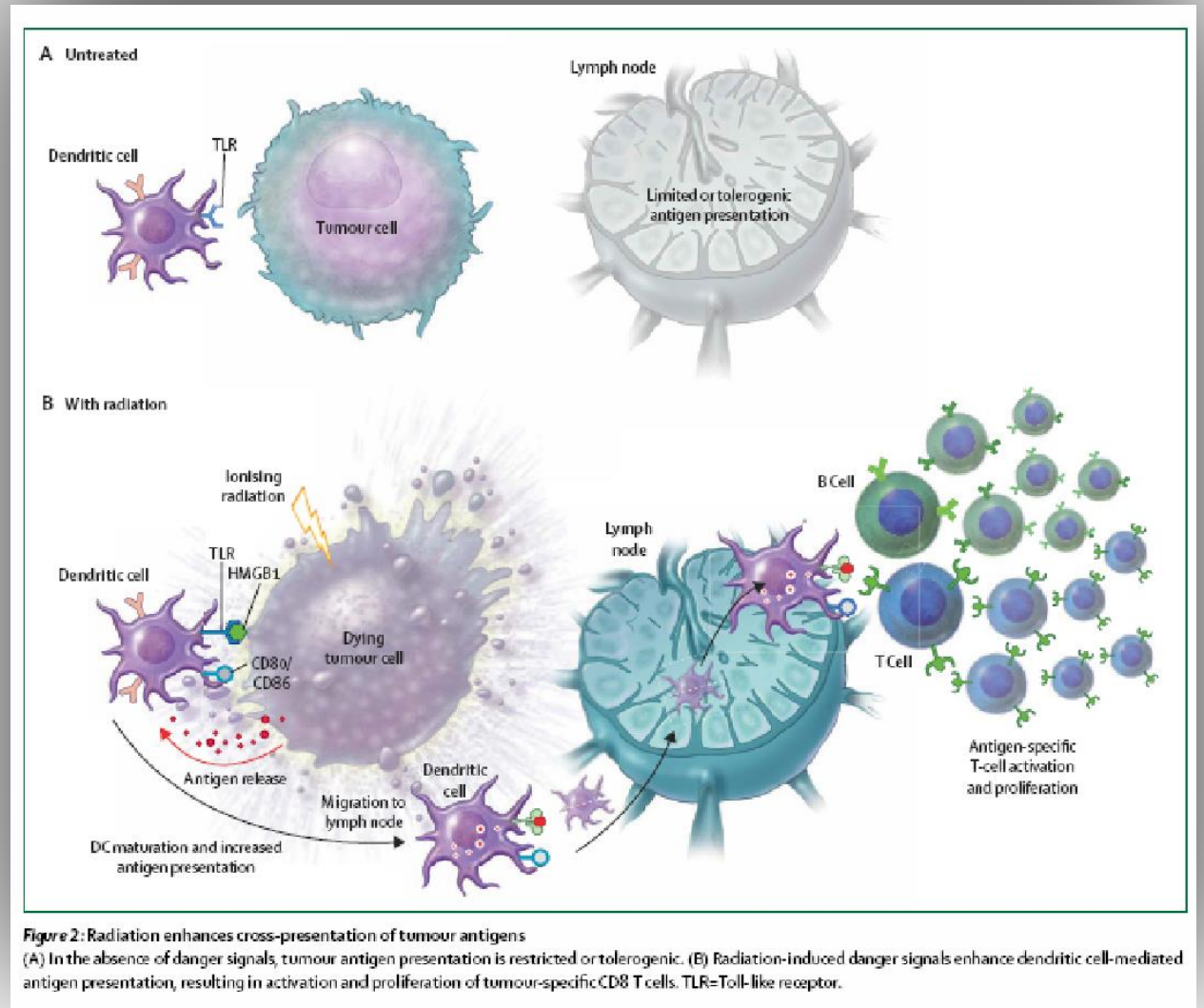


Figure 2: Radiation enhances cross-presentation of tumour antigens
(A) In the absence of danger signals, tumour antigen presentation is restricted or tolerogenic. (B) Radiation-induced danger signals enhance dendritic cell-mediated antigen presentation, resulting in activation and proliferation of tumour-specific CD8 T cells. TLR=Toll-like receptor.

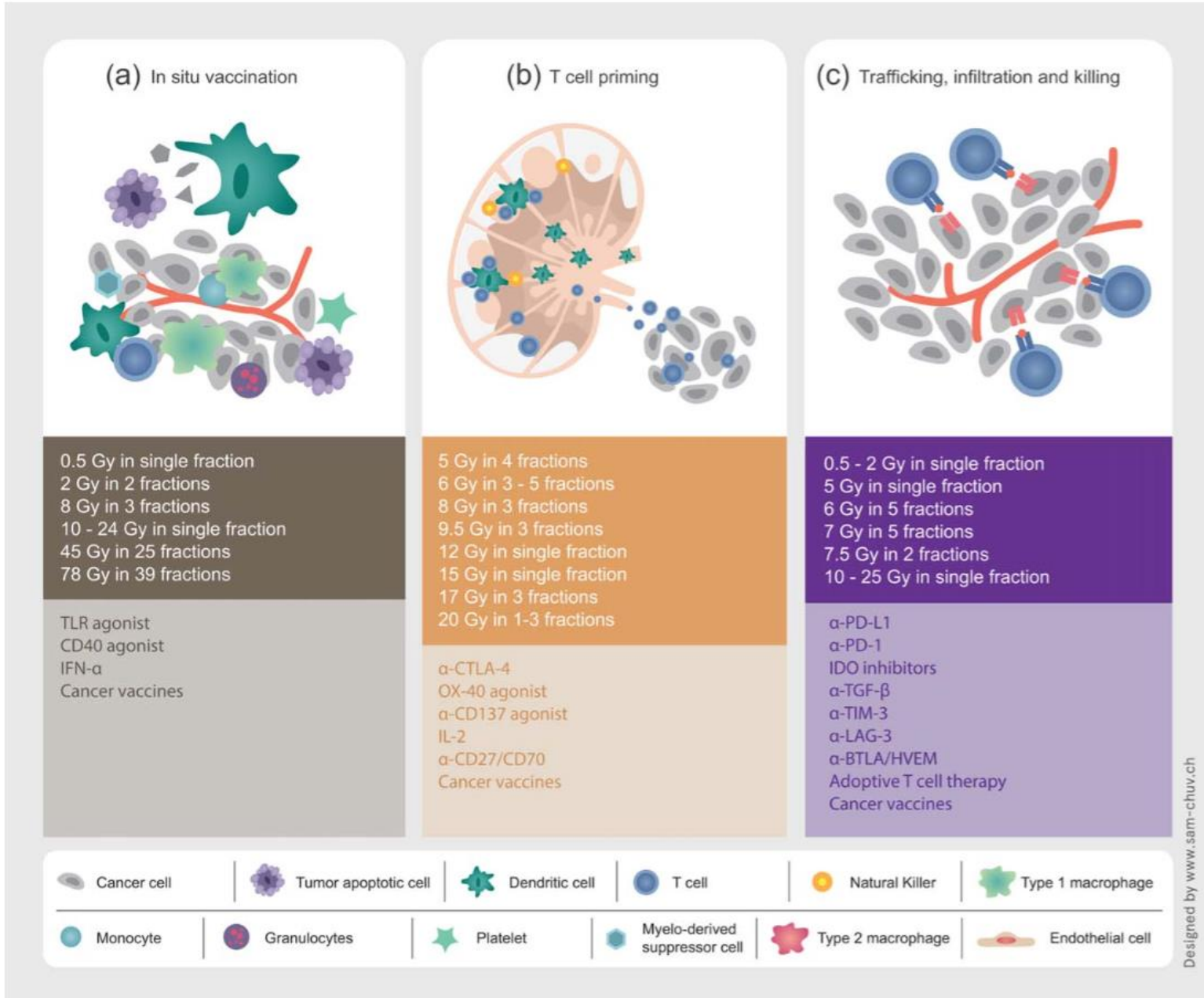
CA CANCER J CLIN 2017;67:65–85

Radiotherapy Combination Opportunities Leveraging Immunity for the Next Oncology Practice

Fernanda G. Herrera, MD[1,2]; Jean Bourhis, MD, PhD[3]; George Coukos, MD, PhD[4,5]

[1]Radiation Oncologist, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [2]Instructor, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [3]Professor, Chief of Radiation Oncology Service, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [4]Professor, Director, Department of Oncology, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [5]Director, Ludwig Institute for Cancer Research, University of Lausanne Branch, Lausanne, Switzerland

ABSTRACT: Approximately one-half of patients with newly diagnosed cancer and many patients with persistent or recurrent tumors receive radiotherapy (RT), with the explicit goal of eliminating tumors through direct killing. The current RT dose and schedule regimens have been empirically developed. Although early clinical studies revealed that RT could provoke important responses not only at the site of treatment but also on remote, nonirradiated tumor deposits—the so-called "abscopal effect"—the underlying mechanisms were poorly understood and were not therapeutically exploited. Recent work has elucidated the immune mechanisms underlying these effects and has paved the way for developing combinations of RT with immune therapy. In the wake of recent therapeutic breakthroughs in the field of immunotherapy, rational combinations of immunotherapy with RT could profoundly change the stan-


(a) In situ vaccination
(b) T cell priming
(c) Trafficking, infiltration and killing
0.5 Gy in single fraction
2 Gy in 2 fractions
8 Gy in 3 fractions
10 - 24 Gy in single fraction
45 Gy in 25 fractions
78 Gy in 39 fractions
TLR agonist
CD40 agonist
IFN-α
Cancer vaccines
5 Gy in 4 fractions
6 Gy in 3 - 5 fractions
8 Gy in 3 fractions
9.5 Gy in 3 fractions
12 Gy in single fraction
15 Gy in single fraction
17 Gy in 3 fractions
20 Gy in 1-3 fractions
α-CTLA-4
OX-40 agonist
α-CD137 agonist
IL-2
α-CD27/CD70
Cancer vaccines
0.5 - 2 Gy in single fraction
5 Gy in single fraction
6 Gy in 5 fractions
7 Gy in 5 fractions
7.5 Gy in 2 fractions
10 - 25 Gy in single fraction
α-PD-L1
α-PD-1
IDO inhibitors
α-TGF-β
α-TIM-3
α-LAG-3
α-BTLA/HVEM
Adoptive T cell therapy
Cancer vaccines
Cancer cell
Tumor apoptotic cell
Dendritic cell
T cell
Natural Killer
Type 1 macrophage
Monocyte
Granulocytes
Platelet
Myelo-derived suppressor cell
Type 2 macrophage
Endothelial cell
Designed by www.sam-chuv.ch

1995

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 orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3,4] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

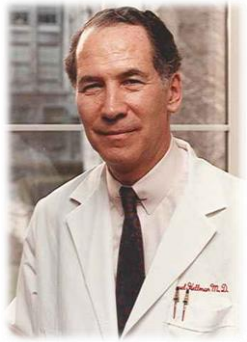
Both the contiguous and systemic theories of cancer pathogenesis are too restricting and do not consider what is now known about tumor progression during clinical evolution. A third paradigm, one that synthesizes the contiguous-systemic dialectic, has been suggested by one of us[5] to explain the natural history of breast cancer. This thesis argues that cancer comprises a biologic spectrum extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states. Metastases are a function of both tumor size and tumor progression.

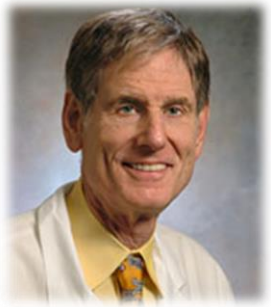
While much tumor evolution occurs during the preclinical period, we suggest that there is a progression of malignancy during the clinical evolution of a cancer. There is some evidence to support this progression of clinical cancer because pathologic grade usually correlates with tumor size, with smaller tumors being of lower grade than large ones.[6,7] Although this may be owing in part to the more rapid growth of high-grade tumors, it is also consistent with tumor progression during the clinical evolution of the tumor. Such possible tumor progression with increasing metastatic capacity during the clinically apparent period is receiving increasing support as we learn more about the multistep nature of the development of malignancy.[8-10] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[11] 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 lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous 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*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding tumor cell number and characteristics as well as the receptivity of the host organ. The importance of "seed and soil" have been considered elsewhere[12,13] and will not be discussed further. Tumors early in the chain of progression may have metastases limited in number and location because the facility for metastatic growth has not been fully developed and the site for such growth is restricted (this is in contrast to micrometastases, which, although small in size, are extensive in number). With further progression, the tumor seeding efficiency increases and becomes less fastidious with regard to the location of metastatic growth. In addition to this progression of malignancy, the increasing primary tumor size and therefore cell number should also be correlated with the increasing number of cells seeding. Tumor size is the principal basis of tumor staging and, with histologic grade, correlates with the likelihood of metastases.[6,14,15] This, we suggest, is due to the number of tumor cells, the tumor vascularity, and malignant progression as tumors grow.

An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or

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





2011

OPINION

Oligometastases revisited

Ralph R. Weichselbaum and Samuel Hellman

Abstract | We previously proposed a clinical state of metastasis termed 'oligometastases' that refers to restricted tumor metastatic capacity. The implication of this concept is that local cancer treatments are curative in a proportion of patients with metastases. Here we review clinical and laboratory data that support the hypothesis that oligometastasis is a distinct clinical entity. Investigations of the prevalence, mechanism of occurrence, and position in the metastatic cascade, as well as the determination of molecular markers to distinguish oligometastatic from polymetastatic disease, are ongoing.

Weichselbaum, R. R. & Hellman, S. *Nat. Rev. Clin. Oncol.* **8**, 378–382 (2011); published online 22 March 2011; doi:10.1038/nrclinonc.2011.44

15 years after…

tribute to visionary clinical "eyes" in oncology

2017

REVIEWS

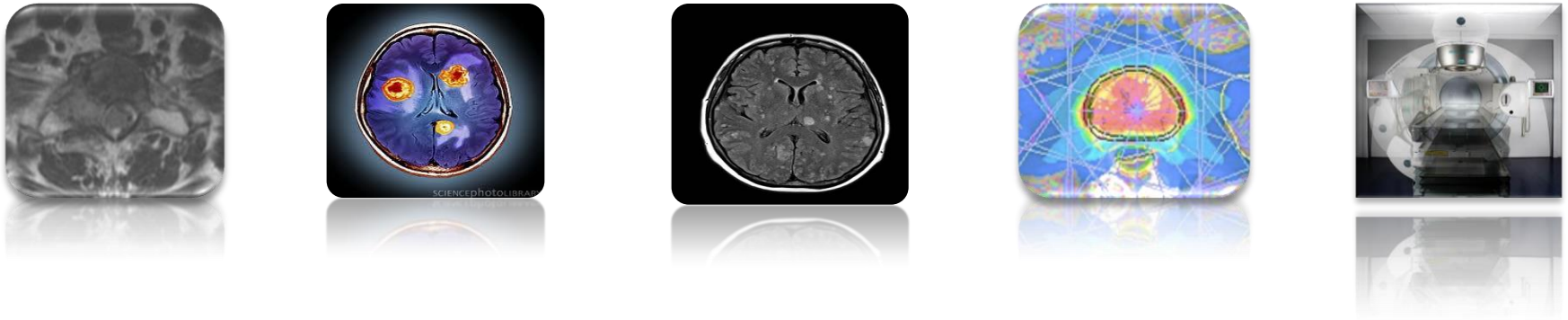
NATURE REVIEWS | CLINICAL ONCOLOGY

Radiotherapy and immunotherapy: a beneficial liaison?

Ralph R. Weichselbaum[1], Hua Liang[1], Liufu Deng[1] and Yang-Xin Fu[2]

Key points

- Radiotherapy not only exerts direct cytotoxic effects on tumour cells, but also re-programmes the tumour microenvironment to exert a potent antitumour immune response
- Tumour-cell proliferation and cell death due to T-cell cytotoxic killing coexist in irradiated tumours, resulting in stable disease that might provide a window of opportunity for immune-modulation
- Radiotherapy enhances antitumour immunity, but also induces immunosuppressive responses
- The combination of immunotherapy and radiotherapy presents a multimodal treatment approach that involves stimulating and suppressing various pathways



Super-precise RT context… Oligo-rectal cancer is a clinical reality

The change of paradigm: oligometastatic disease deserves radical local therapy

A radical RT contribution to the incurable = atoxic / fast / drug compatible

Radio-inmunogenesis + inmunotherapy: an unexpected opportunity…

SBRT for the non-surgical candidates?
SBRT for consolidation?

2017 practice-oriented paradigm components:

precision + hypofr + oligotopia + oligobiology + systemic Tx