ASPETTI GENERALI

La scelta del trattamento nel malato con oligometastasi: criteri di selezione e valutazione dei risultati

E. Maranzano, *Terni* - F. Trippa, *Terni*

ASPETTI GENERALI

- OLIGOMETASTASES definition
- Patient selection
- Evaluation of therapeutic results

ASPETTI GENERALI

- **OLIGOMETASTASES definition**
- Patient selection
- Evaluation of therapeutic results

Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago
Chicago, IL

EDITORIAL **1995**

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

Oligometastases

•The ***Halsted*** **theory (T → N → M)** proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatic to the lymph nodes and then to distant sites (***1907***).

• A subsequent ***Hellman*** **theory of systemic disease hypothesis (T → M)** proposed that clinically apparent cancer is already a systemic disease (***1980***).

• A third ***Hellman & Weichselbaum'*** **theory of spectrum hypothesis**: cancer range between disease that remains localized and disease that is systemic at time of diagnosis → multistep nature of cancer progression (***1995***).

The occasional success of surgical excision of one or a small number of pulmonary mets, brain mets or hepatic mets (*e.g., 25% of cure after hepatic resections for metastatic colorectal cancer*) lets to hypothesize the theory of *oligometastases*

Samuel Hellman
Ralph R. Weichselbaum
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EDITORIAL **1995**

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Oligometastases

Hellman & Weichselbaum suggested that

for many cancers a few metastases exist at first, before the malignant cells acquire widespread metastatic potential.

Consequently,

if radical intervention (Surgery or Stereotactic Body Radiotherapy - SBRT) could be delivered during an oligometastatic phase, the intervention could change disease progression in pts who would otherwise have been treated palliatively in most settings (the hierarchy theory)

ELSEVIER

16:120-130 © 2006

Seminars in
RADIATION
ONCOLOGY

Solitary Metastases: Illusion Versus Reality

Philip Rubin, MD, Ralph Brasacchio, MD, and Alan Katz MD, MPH

"Suddenly a solitary horseman appeared on the horizon, then another, then another . . . in a few moments a whole crowd of horsemen swooped down upon him."—Leacock

M1: a solitary metastasis in a single organ

M2: oligometastases, designate number and **limited to 1 organ** (**5** nodules, **5** cm in total)

Serum molecular markers as follows:

S0: not detectable

S1: detectable, low level

S2: intermediate level

S3: high level

A. **no systemic signs**: minimal 5% weight loss, minimal lab abnormalities.

B. **systemic signs**: 100% weight loss, cachexia, fevers nexplained, lab abnormalities, (*i.e. altered lung function, abnormal liver enzymes*)

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THE MAJOR METASTATIC ORGAN SITES

- **Solitary lung mets**
- **Solitary liver mets**
- **Solitary brain mets**
- **Solitary bone mets**
- **Other solitary site mets:**

  H&N, eye & orbit, ovary & vagina, heart, intestines

VOLUME 31 · NUMBER 11 · APRIL 10 2013
JOURNAL OF CLINICAL ONCOLOGY

(SBRT)

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*

OLIGOMETASTASES

Definition

An intermediate state of cancer spread between localized disease and wide spread mets

the implication is that oligometastatic disease may be cured with metastasis-directed therapy

VOLUME 31 · NUMBER 11 · APRIL 10 2013

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

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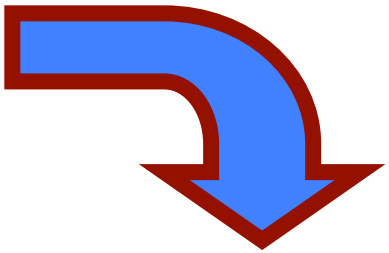
OLIGOMETASTASES



Stereotactic Body Radiotherapy (SBRT)

VOLUME 31 · NUMBER 11 · APRIL 10 2013

JOURNAL OF CLINICAL ONCOLOGY

(SBRT)

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OLIGOMETASTASES

- **Incidence** has not been well established
- **Prognosis** can be derived from surgical reports (***lung mets from sarcoma***, ***liver mets from colorectal cancer***, ***oligometastasis from breast cancer***)

→ this subset of patient can be cured in about 15-20% of cases

- **Diagnosis**

→ Potential **differential genetic signature** between samples isolated from pts with few or many mets (e.g., microRNA 200c expression or microRNA signature).

→ **Hierarchy** to the appearance of metastatic sites (i.e., early mets may be of limited nature and early therapy could prevent future spread)

→ Potential **increase of early identification** of oligometastasis with PET-CT (e.g., NSCLC with mets to adrenal gland at diagnosis)

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Potential **differential genetic signature** between samples isolated from pts with few or many mets (*e.g., microRNA 200c expression or microRNA signature*).

Incidence of oligometastases

Lung met from sarcoma — **19% one met**

Gadd MA et al: Ann Surg 1993

Liver-only mets from colorectal cancer — **49% one met**
38% ≤ 3 mets

Kienski et al: Ann Surg Oncol 2010

Distant failure from breast cancer — **16% (median 1,7)**

Dorn P et al: Int J Radiat Oncol 2011

Distant failure from lung cancer — **19%**

McManus MP et al: Int J Radiat Oncol Biol Phys 2001

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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*

SBRT treatment of limited metastases has shown promising local control rates for treated metastases, ranging from 67% to 95%.

Two- to 3-year survival rates have been reported in the range of 30% to 64%

SBRT results compare favorably with surgical results.

SBRT is less invasive than surgery and may be more broadly applicable to greater numbers of tumors in various organs

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→ **Potential differential genetic signature between phenotype isolated in oligometastatic pts (*e.g., microRNA 200c expression or microRNA signature*).**

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(2)107–111
doi:10.1093/jjco/hyp167
Advance Access Publication 4 January 2010

Review Article

Oligometastases and Oligo-recurrence: The New Era of Cancer Therapy

Yuzuru Niibe* and Kazushige Hayakawa

Department of Radiation Oncology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

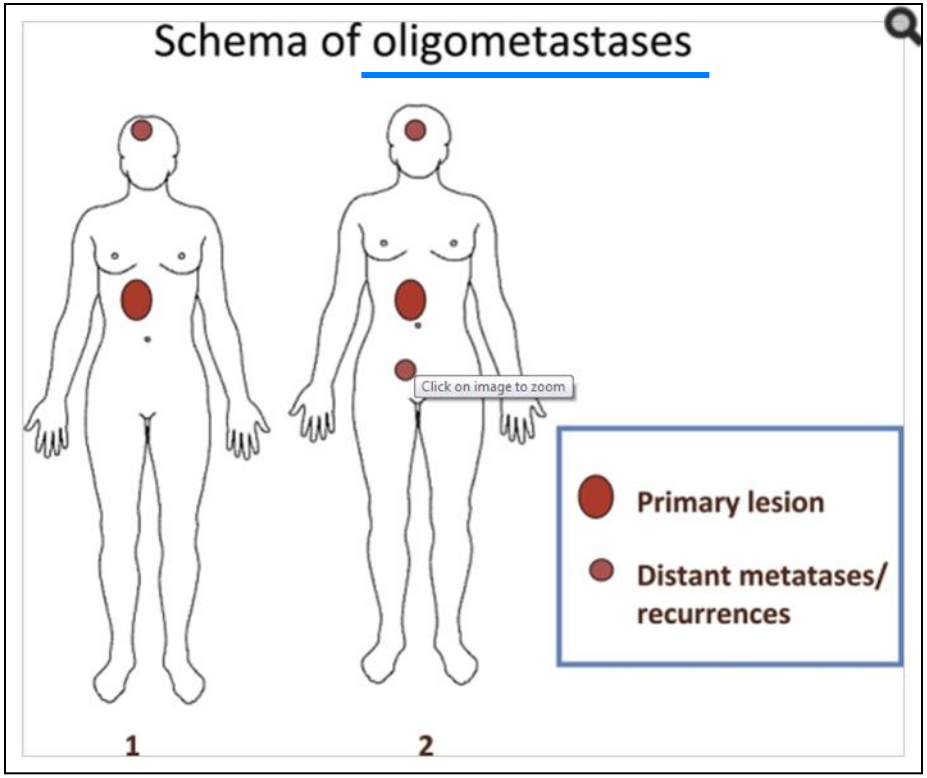
OLIGO-RECURRENCE

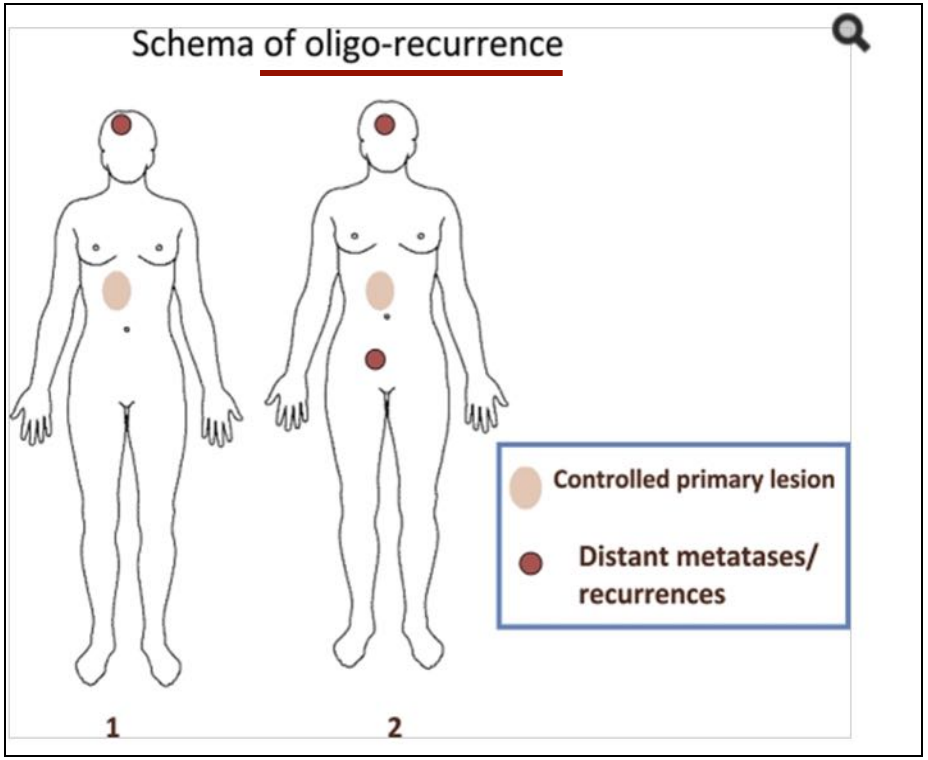
Patient with a limited number of metastases and controlled primary tumor

Table 1.

Oligometastases and oligo-recurrence

	Oligometastases	Oligo-recurrence
Reference	Hellman and Weichselbaum (1)	Niibe et al. (2,3,4)
Primary lesion	Uncontrolled/controlled	Controlled
No. of distant/metastases/recurrences	One to several	One to several (one is better)


Schema of oligometastases
Click on image to zoom
Primary lesion
Distant metatases/ recurrences
1
2


Schema of oligo-recurrence
Controlled primary lesion
Distant metatases/ recurrences
1
2

ASPETTI GENERALI

- OLIGOMETASTASES definition
- **Patient selection**
- Evaluation of therapeutic results

PATIENT SELECTION

3 distinct cohorts of pts with oligometastases

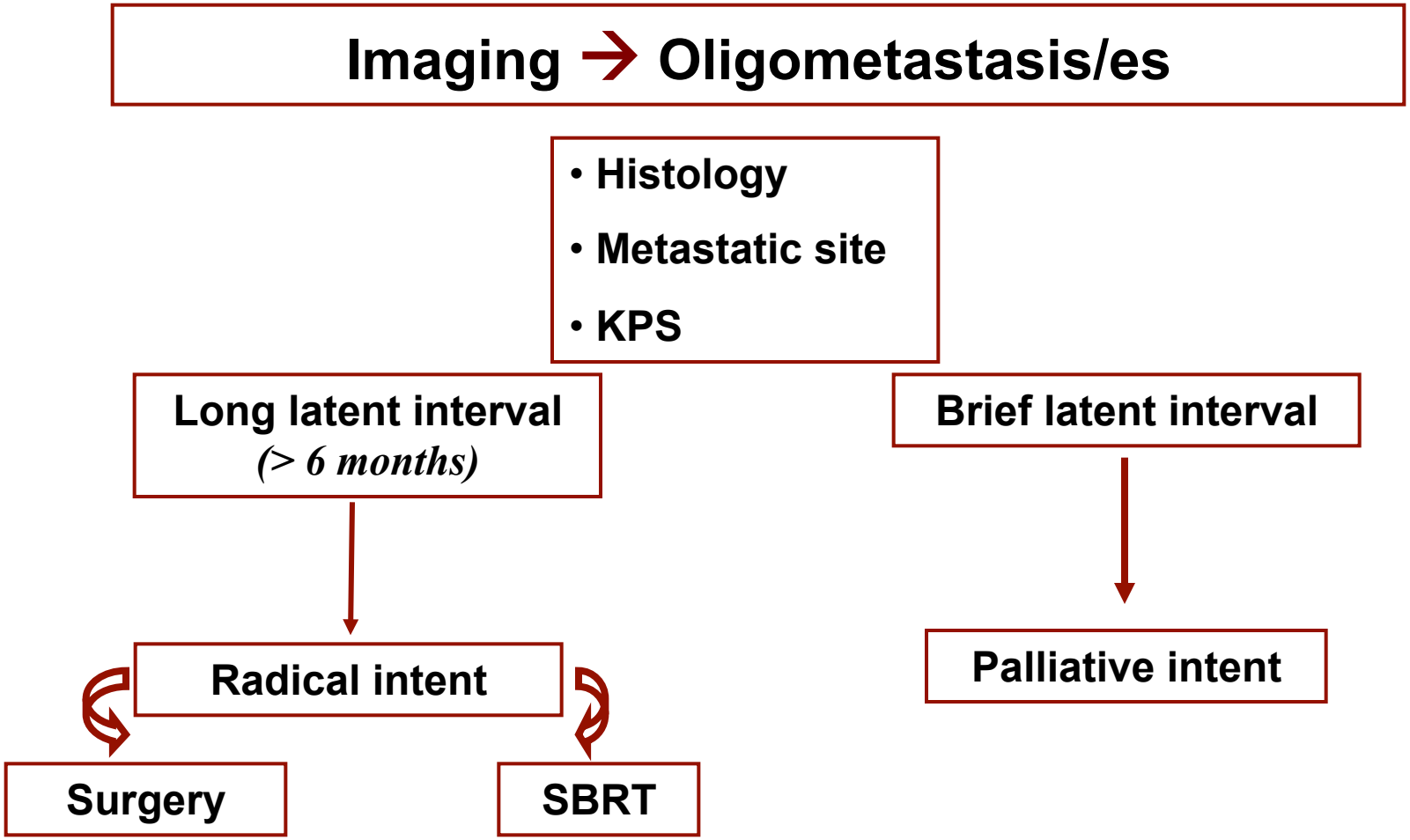
- **those who present with oligometastatic disease**
- **those with induced oligometastatic disease after cytoreductive therapy**
- **those with relapsed oligometastatic disease after curative locoregional therapy**

These different groups probably have different prognoses,

so therapeutic approaches might differ

AC Tree, Lancet Oncol 2013;14:e28-37

PATIENT SELECTION



AC Tree, Lancet Oncol 2013;14:e28-37

PATIENT SELECTION

Imaging → Oligometastasis/es

- **Histology**
- **Metastatic site**
- **KPS**

Brief latent interval

Palliative intent

Long latent interval
(> 6 months)

Radical intent

Surgery

SBRT

AC Tree, Lancet Oncol 2013;14:e28-37

PATIENT SELECTION

Imaging → Oligometastasis/es

- **Histology**
- Metastatic site
- KPS

Long latent interval

Radical intent

Surgery ?

SBRT ?

Brief latent interval

Palliative intent

PATIENT SELECTION

On the basis of HISTOLOGY

→ Better survival for breast cancer with respect to colorectal & lung
→ Radioresponsive vs radioresistant histologies

Surgery for **(?)***

- **kidney clear cell tumor,**
- **melanomas, or**
- **sarcomas**

---

* **Please note the ablative radiation effect that is not necessary related to radiosensibility!**

PATIENT SELECTION

Imaging → Oligometastasis/es

- Histology
- **Metastatic site**
- KPS

Long latent interval

Radical intent

Surgery ?

SBRT ?

Brief latent interval

Palliative intent

PATIENT SELECTION

On the basis of METASTATIC SITE

Surgery

- for peripheral lung mets →
- for easy accessible liver masses →
- when spinal stabilization is necessary →
- to remove bone impingement to the spine →

Radiation therapy

- in other cases

PATIENT SELECTION

Imaging → Oligometastasis/es

- Histology
- Metastatic site
- **KPS**

Long latent interval

Brief latent interval

Radical intent

Palliative intent

Surgery ?

SBRT ?

PATIENT SELECTION

On the basis of PERFORMANCE STATUS

Surgery

- for **good PSK pts**?

Radiation therapy

- **in the other cases ?!**

ASPETTI GENERALI

- OLIGOMETASTASES definition
- Patient selection
- **Evaluation of therapeutic results**

EVALUATION OF THERAPEUTIC RESULTS

- **Local control**
- **Disease-free survival** ***(& Freedom from widespread distant metastasis*****!)**
- **Toxicity rate**
- **QoL**

EVALUATION OF THERAPEUTIC RESULTS

- **Local control rate: 67-95%**

Note that: ***most in-field recurrence occur(!)***

→ ***2-year in-field control rate (i.e., duration of response) ~ 20%***

- Disease-free survival (& Freedom from widespread distant metastasis?)
- Toxicity rate
- QoL

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.,*

Int J Radiation Oncol Biol Phys,
Vol. 83, No. 3, pp. 878–886, 2012

LOCAL CONTROL (LC)

The breast cancer patients had a 2-, 4-, and 6-year lesion LC rate of 87%;

the nonbreast cancer patients had a 2-, 4-, and 6-year lesion LC rate of 74%, 68%, and 65%, respectively.

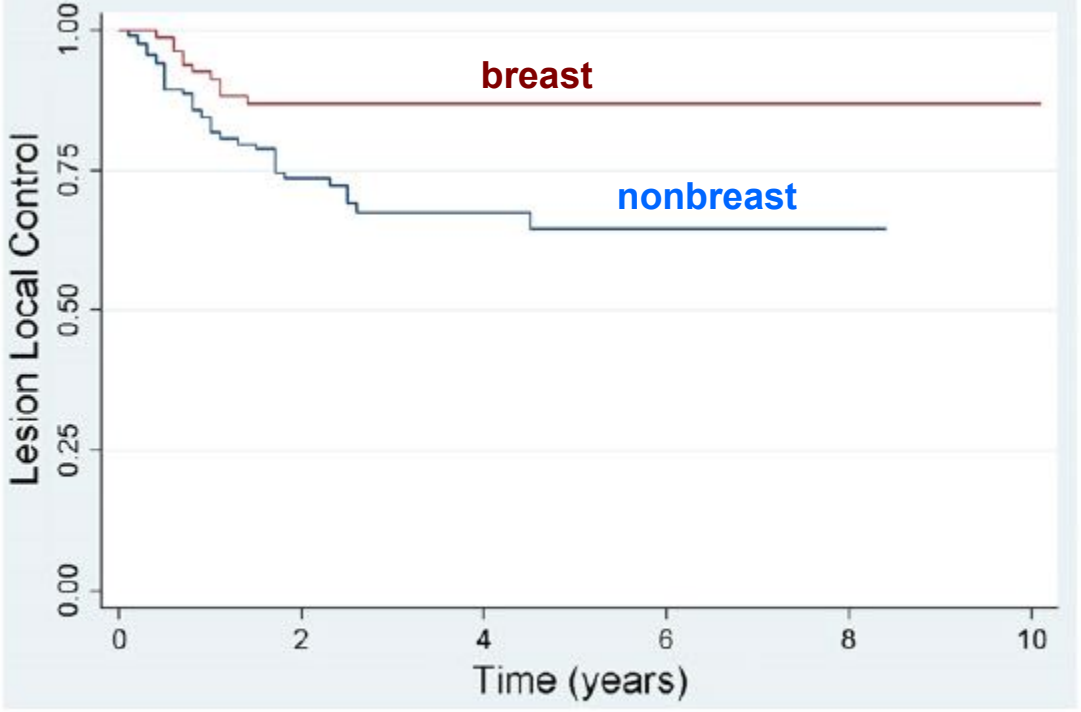


Fig. 2. Kaplan-Meier actuarial lesion local control for breast cancer (red line) and nonbreast cancer (blue line) patients. A color

- **CT and MRI are routinely used to evaluate response to therapy, with RECIST criteria.**

- **Postsurgical and postradiotherapy fibrosis and necrosis of both malignant tissue as well as surrounding normal tissue, often making it difficult to differentiate between malignant and non-malignant tissues in surveillance CT and MRI imaging**

Solanki *et al. Radiation Oncology* 2012, **7**:216
http://www.ro-journal.com/content/7/1/216

RADIATION ONCOLOGY

RESEARCH Open Access

The utility of FDG-PET for assessing outcomes in oligometastatic cancer patients treated with stereotactic body radiotherapy: a cohort study

EVALUATION OF THERAPEUTIC RESULTS

- Local control
- **Disease-free survival** (*& Freedom from widespread distant metastasis*!)
- Toxicity rate
- QoL

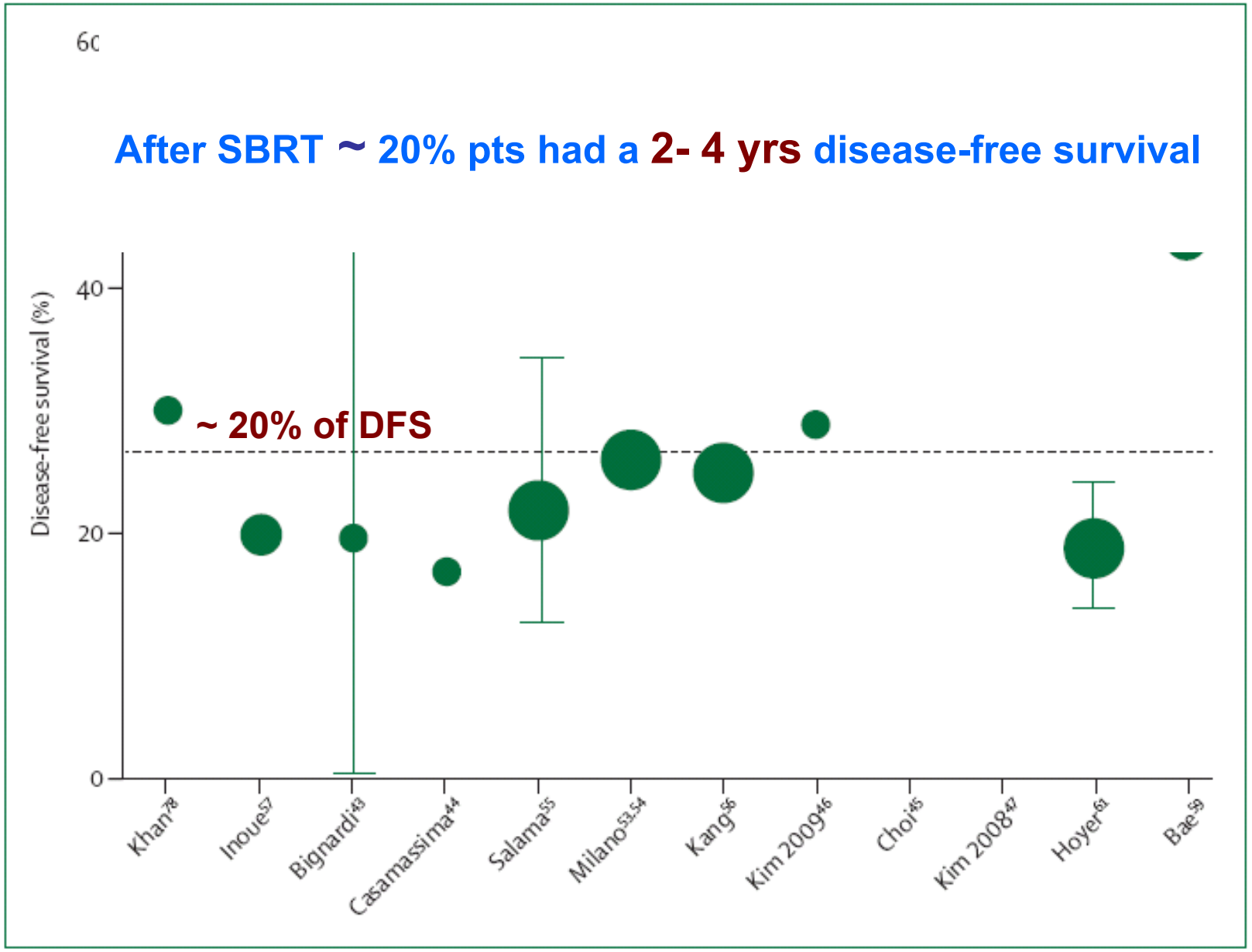


Figure 2: **Disease-free survival in patients with oligometastatic disease at 17–48 months' follow-up**
Dotted line represents mean proportion of patients who were disease free at the reported timepoint, weighted for number of patients in each cohort. Error bars represent 95% confidence intervals.

EVALUATION OF THERAPEUTIC RESULTS

- Local control
- **Disease-free survival (*& Freedom from widespread distant metastasis*!)**
- Toxicity rate
- QoL

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EVALUATION OF THERAPEUTIC RESULTS

Freedom from widespread distant metastasis survival

Widespread distant metastases are defined as ***distant progression not amenable to resection or locally ablative therapy***

(i.e., SBRT, stereotactic radiosurgery, radiofrequency ablation, embolization).

EVALUATION OF THERAPEUTIC RESULTS

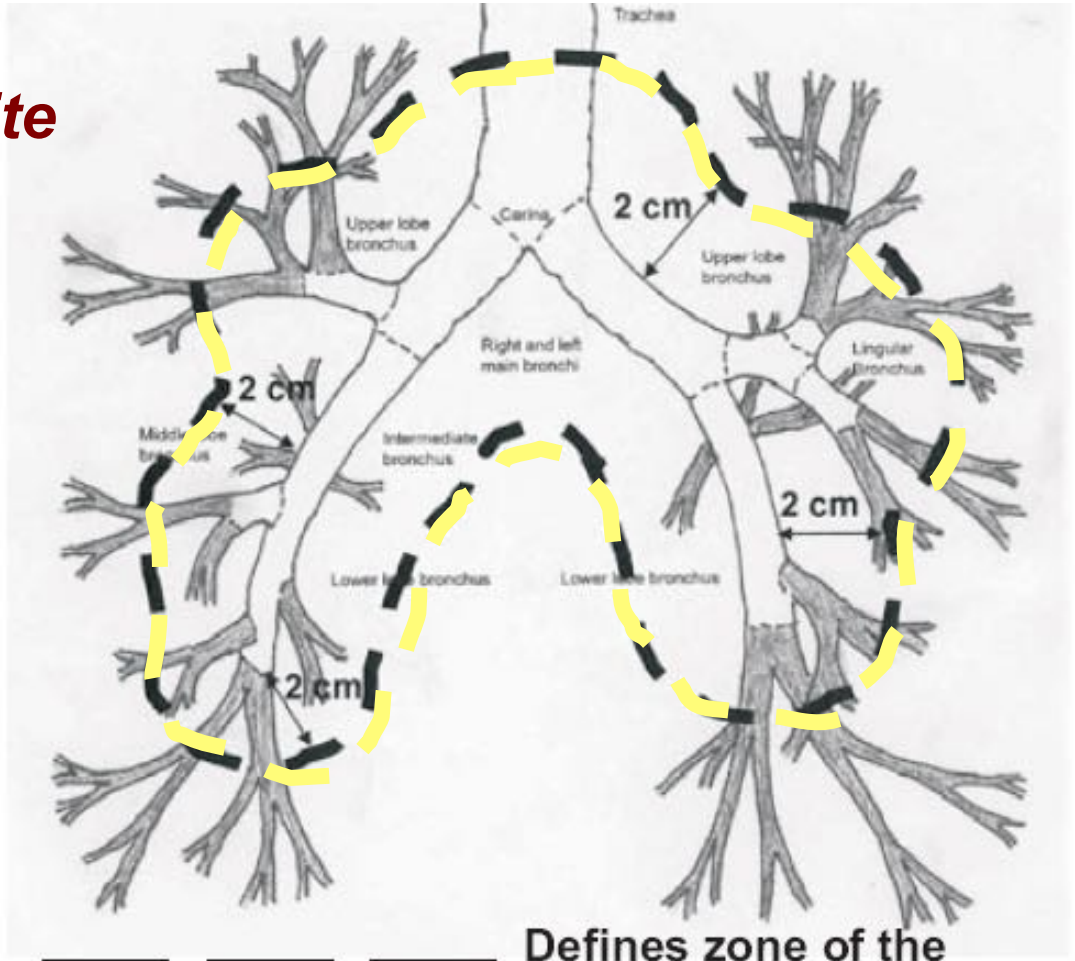
- Local control
- Disease-free survival *(& Freedom from widespread distant metastasis!)*
- **Toxicity rate**

→Toxicity is directly correlated to:

- ***administered dose,***
- ***tumor volume,***
- ***tumor site.***

- QoL

tumor site



EVALUATION OF THERAPEUTIC RESULTS

- Local control
- Disease-free survival *(& Freedom from widespread distant metastasis!)*
- **Toxicity rate**

→ **Toxicity is low if *radiation dose constraints* to normal tissues are respected**

- QoL

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Non-Small Cell Lung Cancer

Table 5. Normal Tissue Dose Volume Constraints for SBRT*

OAR	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great vessels	37 Gy	39 Gy 13 Gy/fx	49 Gy 12.25 Gy/fx	55 Gy 11 Gy/fx
Trachea/ Large Bronchus	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	40 Gy (8 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	31.2 Gy (7.8 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy 10 Gy/fx	36 Gy (9 Gy/fx)	40 Gy 8 Gy/fx
Stomach	12.4 Gy	27 Gy 9 Gy/fx	30 Gy (7.5 Gy/fx)	35 Gy 7 Gy/fx

EVALUATION OF THERAPEUTIC RESULTS

- Local control
- Disease-free survival *(& Freedom from widespread distant metastasis!)*
- Toxicity rate
- **QoL**

EVALUATION OF THERAPEUTIC RESULTS

QoL

Since SBRT is associated with low toxicity rates with respect to surgery, the QoL benefit is probably greater

Tree AC et al Lancet Oncol 2013

Canadian-led International Development of a European Organization for Research and Treatment of Cancer Quality of Life Module for Malignant Spinal Cord Compression: Results of Phase I

Radiation Oncology UNIVERSITY OF TORONTO

Gunita Mitera[1], Andrew Loblaw[1], Arjun Sahgal[1], Brita Danielson[2]

Sunnybrook HEALTH SCIENCES CENTRE

[1]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada, [2]Cross Cancer Institute, Edmonton, AB, Canada

Objective

- To develop a relevant set of items assessing quality of life (QOL) issues in patients with malignant spinal cord compression (MSCC), not sufficiently covered by the European Organization for Research and Treatment of Cancer (EORTC) C15-PAL core questionnaire.

Table 1: Top 10 QOL issues ranked by patients (n=35)

Patients' Rank	QOL Issues	Freq (%)	HCPs' Rank
1	Have you had difficulty performing self-care (i.e. bathing, dressing)?	48.6	4
2	Did you have trouble controlling your bladder?	42.3	3
3	Did you have lower back pain?	42.3	7
4	**Difficulty in carrying out housework**	40.0	**N/A**
5	Have you worried about becoming dependent on others because of your illness?	40.0	6
6	Have you worried about becoming bed-bound because of your illness?	31.4	10
7	Did you have upper back pain?	28.6	N/A
8	Did you have to modify your daily activities because of your illness?	28.6	9
9	Have you worried about loss of mobility because of your illness?	28.6	7
10	Did you hope treatment would reduce pain as much as possible?	28.6	N/A

1 = Top priority issue for patients
Items included within the red box are items ranked by both groups to be in the top 10

Table 2: Top 10 QOL issues ranked by health care providers (n=62)

HCPs' Rank	QOL Issues	Freq (%)	Patients' Rank
1	Ability to walk without assistence	49.3	N/A
2		47.9	N/A
3	Did you have trouble controlling your bladder?	45.2	2
4	Have you had difficulty performing self-care (i.e. bathing, dressing)?	39.7	1
5	Did you experience leakage of bowels?	35.6	N/A
6	Have you worried about becoming dependent on others because of your illness?	28.8	5
7	Have you worried about loss of mobility because of your illness?	28.8	9
8	Did you have lower back pain?	27.4	3
9	Have you had to modify your daily activities because of your illness?	27.4	8
10	Have you worried about becoming bed-bound because of your illness?	27.4	6

1 = Top priority issue for health care providers
Items included within the red box are items ranked by both groups to be in the top 10

Patients suggestions for questions to add:

- Do you have **family support**?
- Do you worry about your **ability to drive** in the future?
- Were you able **to understand** your procedures, treatments, & medications?

Canadian-led International Development of a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Module for Malignant Spinal Cord Compression

~RESEARCH PROTOCOL~

ODETTE CANCER CENTRE, CANADA

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Indranil MALLICK

TATA MEMORIAL CENTRE, MUMBAI, INDIA

Ashwini Budrukkar

AUSTRALIA & NEW ZEALAND

To be determined at April meeting

GERMANY

Dirk RADES

ITALY

Ernesto MARANZANO

CONCLUSIONS

VOLUME 31 · NUMBER 11 · APRIL 10 2013

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*

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 RT vs SBRT**
UPCI 10-028	Phase II		
UPCI 10-027	Phase II		
NCT01565837	Phase II		
NCT01185639	Phase II		
PulMiCC	Randomized	Pulmonary metastases from colorectal cancer	**Active monitoring vs Surgery**

Ultimately, a randomized trial of ablative radiotherapy and/or surgery compared with the standard of care may be necessary to define the role of ablative modalities in oligometastases.

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

AC Tree, Lancet Oncol 2013;14:e28-37

Giotto - Scrovegni - Christ among the Doctors