

con il Patrocinio dell'Associazione Italiana di Oncologia Medica



Progetto **CANOA**

CARCINOMA MAMMARIO:

QUALI NOVITÀ PER IL 2014?

“Saper leggere” uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:

Stefania Gori

Giovanni L. Pappagallo

“IL TRATTAMENTO DELLA MALATTIA OLIGOMETASTATICA”

FILIPPO ALONGI

Direttore UOC Radioterapia Oncologica



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BREAST OLIGOMETASTASES PATIENTS: LOCAL THERAPIES ARE A REASONABLE OPTION?

BreastCare 2011

Does Radiotherapy Have Curative Potential in Metastatic Patients? The Concept of Local Therapy in Oligometastatic Breast Cancer

	Early disease	Locally advanced disease	Oligometastatic disease	Metastatic disease
Disease extend	small primary tumor, no lymph node metastases	large primary tumor, lymph node metastases	solitary or few metastatic lesions	multiple organ involvement
Chance of cure	high (90%)	medium (50%)	zero?	zero
Treatment intent	curative	curative	curative?	palliative
Type of treatment	locoregional + adjuvant systemic	locoregional + adjuvant systemic	systemic + local?	systemic





OLIGOMETASTASES: DEFINITION

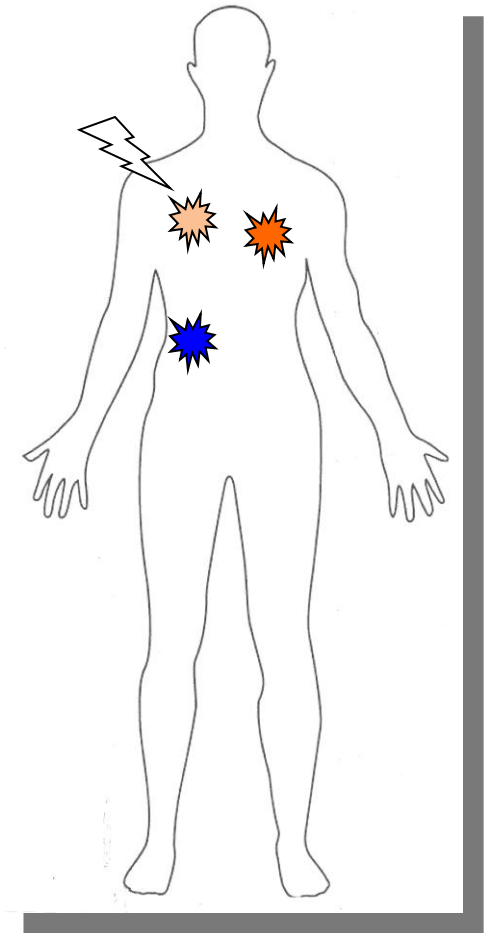
The term "***oligometastases***" was first described by Hellman and Weichselbaum in 1995 as "***...a less advanced state of metastatic disease amenable to and potentially curable with local therapy***".

Hellman S, Weichselbaum RR: JCO, 1995

The term "oligometastases" is usually used for five or fewer metastatic lesions .

Milano MT, et alJROBP, 2012.

Often, this clinical situation has a slow rate of progression, justifying focal treatments.





OLIGOMETASTASES: IMPACT OF SURGERY

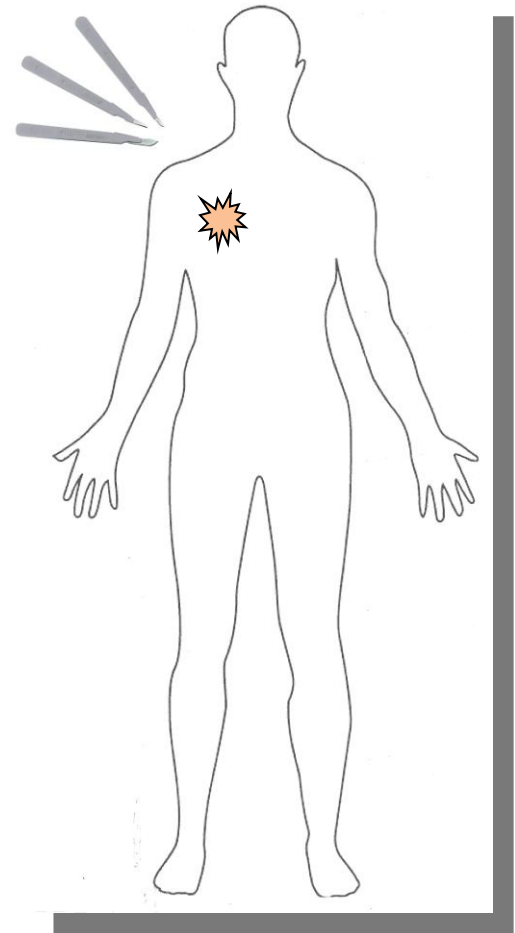
For several anatomical sites, ***surgical resection*** of metastases prolongs survival in selected patients.

Rubin P, et al. Semin Radiat Oncol, 2006

For example, *surgical resection* is the standard choice for patients with oligometastatic lung cancer.

Unfortunately the benefits of resection and appropriate *selection criteria* in patients who develop metastasis are still poorly defined.

Miller G, et al. J Am Coll Surg, 2007.





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OLIGOMETASTASES: THE NEW PARADIGMA FOR ABLATIVE DOSES WITH RT

H. Badakhshi · A. Grün · C. Stromberger · V. Budach · D. Boehmer
Department for Radiation Oncology, Charité University Medicine, Berlin

Oligometastases: the new paradigm and options for radiotherapy

A critical review

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Review and Uses of Stereotactic Body Radiation Therapy for
Oligometastases

FILIPPO ALONGI,^a STEFANO ARCANGELI,^a ANDREA RICCARDO FILIPPI,^b UMBERTO RICARDI,^b
MARTA SCORSETTI^a

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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*





OLIGOMETASTASES: RADIOSURGERY STEREOTACTIC BODY RT(SBRT)

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Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

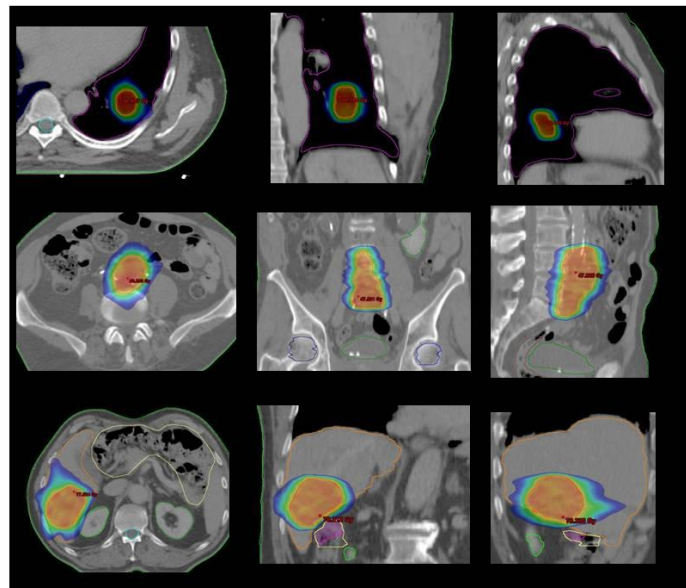
FILIPPO ALONGI,^a STEFANO ARCANGELI,^a ANDREA RICCARDO FILIPPI,^b UMBERTO RICARDI,^b
MARTA SCORSETTI^a

- The primary end point of **Radiosurgery and SBRT** is to achieve local control of targeted tumor deposits with *ablative* doses.

- In general SBRT for oligometastases should follow the same philosophy of surgical metastasectomy.

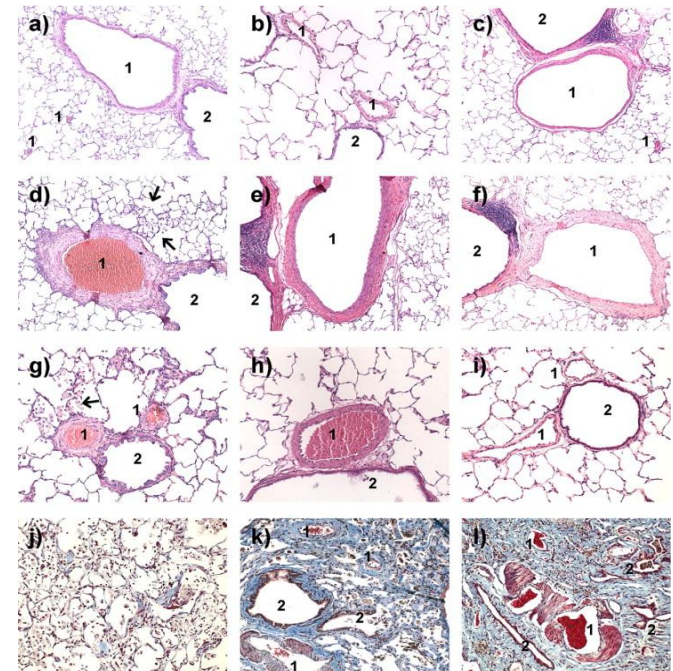
- As smaller foci of metastases are found, high conformal radiation may well prove *less invasive and more/equal effective* than surgery, decreasing morbidity and delivering ablative treatment more economically.

Alongi F et al. Critical Rev Oncol Hematol, 2012



OLIGOMETASTASES: RADIOSURGERY STEREOTACTIC BODY RT(SBRT)

- In terms of **Radiobiology, Radiosurgery and SBRT** may add a novel mechanism of radiation-induced damage.
 - At higher doses per fraction (**ablative doses**), emerging data suggest that a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill. **Garcia - Barros M., et al. Science, 2003**
- Targeting the tumor vasculature for obliteration with high-dose radiation may be beneficial for tumor control.
- Fuks and Kolesnick, Cancer Cell 2005 .**





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OLIGOMETASTASES:

BRAIN



BRAIN STEREOTACTIC RADIOSURGERY



Non-Invasive



Invasive





BRAIN STEREOTACTIC RADIOSURGERY

RADIOSURGERY FOR SINGLE/FEW BRAIN MTS

- NO randomized trials comparing surgical metastasectomy with SRS
- → Retrospective reports support comparable outcomes.
- The SELECTION of treatment should depend on patient- and disease-related factors (**SIR/RPA**).

Radiosurgery is intended to provide:

- > local tumor control,
- improve clinical symptomatology,
- enhance survival.

All of these radiosurgical goals are generally achieved with:

- low morbidity,
- low cost,
- essentially zero mortality

*Noyes et al, Radiosurgery 1996;
Rutigliano et al, Neurosurgery 1995*

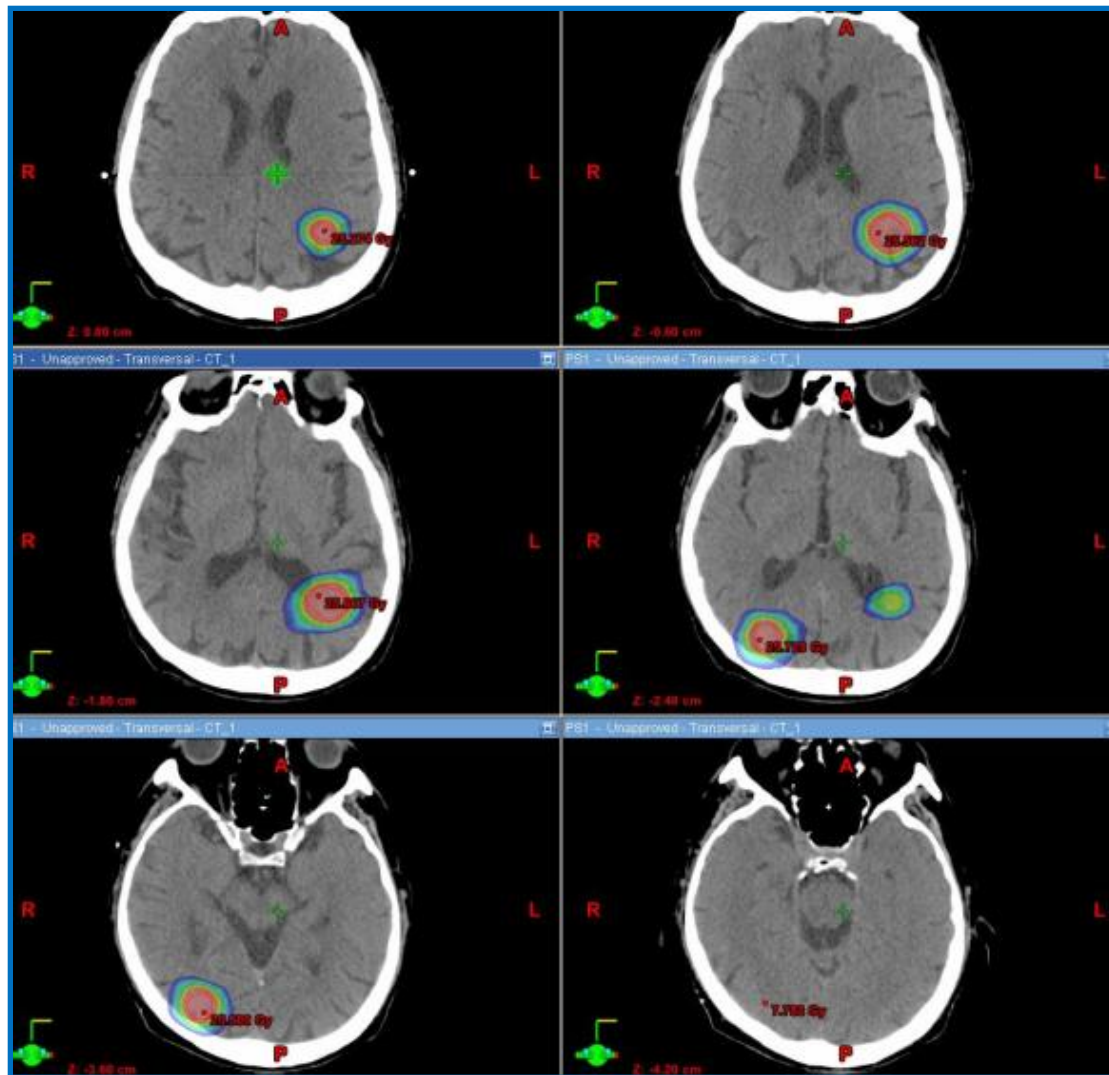


BRAIN STEREOTACTIC RADIOSURGERY

RADIOSURGERY FOR SINGLE/FEW BRAIN MTS

Patient with 2 brain metastases.

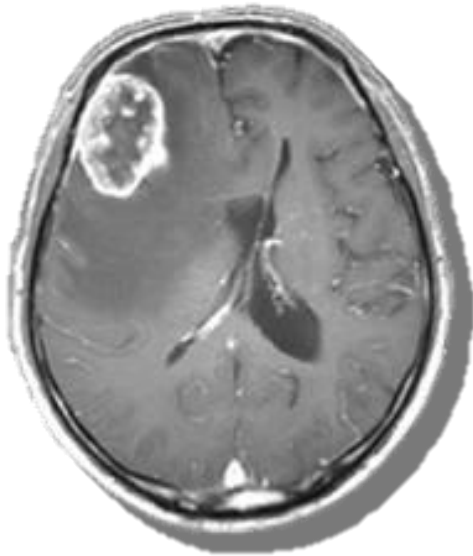
*RADIOSURGERY:
Dose prescription: 25 Gy in
single fraction.*





BRAIN STEREOTACTIC RADIOSURGERY

FRACTIONATED STEREOTACTIC RADIOSURGERY



Lesion diameter >3 cm

- 3 FRACTIONS (>8 Gy per fraction)
- 2 FRACTIONS (> 11.5 Gy per fraction)

Wiggenraad R, et al. A systematic review. Radiother Oncol 2011



Randomized phase III trials in brain metastases

SRS vs SRS + WBRT:

	# of patients	Intracranial progression free survival (months)	Overall survival (months)
<i>Aoyama 2006</i>	132 (67 SRS vs 65 SRS+WBRT)	Favour to SRS + WBRT	No difference
<i>Chang 2009</i>	58 (30 SRS vs 28 SRS+WBRT)		
<i>Kocher & Soffiatti 2010</i>	359 (179 SRS/Surg. vs 180 SRS/Surg + WBRT)		
<i>Mondschein 2010</i> (Abst ASTRO) MELANOMA	74 45 SRS vs 29 SRS+WBRT	2.1 vs 3 ($p = 0.815$)	



BRAIN STEREOTACTIC RADIOSURGERY

FRACTIONATED STEREOTACTIC RADIOSURGERY

Lancet Oncol 2009; 10: 1037-44

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

1. **WBRT causes a decline in learning and memory function by 4 months compared with the group that received SRS alone.**
 2. **In patients 1-3 brain metastases initial treatment should be SRS**
 3. **clinical close monitoring is recommended for early diagnosis of relapse**
 4. **WBRT should be reserved only as a salvage therapy**
-





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OLIGOMETASTASES: EXTRACRANIAL



STEREOTACTIC BODY RT(SBRT): A PARADIGM OF SUCCESS IN LOCAL CONTROL

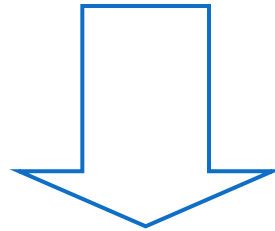
CLINICAL INVESTIGATION



2010

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON-SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

HIROSHI ONISHI, M.D.,* HIROKI SHIRATO, M.D.,† YASUSHI NAGATA, M.D.,‡ MASAHIRO HIRAOKA, M.D.,§



In **primary NSCLC**, when ablative doses are used,
the survival rate for SBRT is potentially
comparable to that for surgery.



STEREOTACTIC BODY RT(SBRT): LUNG

Lung metastases probably represent the paradigm of SBRT: produce high rates of tumor control with very limited toxicity.

For isolated or a few lung metastases the **local control** probability at 1 year is in the range of **70%–100%**.

Ricardi et al, Lung cancer 2011; Okunieff, Acta oncologica 2006

In most series, the prescribed biologically *effective doses (BED) are 100 Gy*, with several fractionation schedules and different delivery techniques.

Rubin P, et al. Semin Radiat Oncol 2006.





STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS

Alongi, Arcangeli, Filippi et al.

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Table 1. Outcomes of stereotactic body radiation therapy for lung metastases from selected trials

Study	n of patients	Median dose/n of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 48% 2-yr, 21%	Grade 3, 1 (3.7%) Grade 5, 1 (3.7%)
Yoon et al. [71]	53	30 Gy/3; 40 Gy/4; 48 Gy/4	14 (4–56)	70% for 30 Gy, 77% for 40 Gy, 100% for 48 Gy	1-yr, 89%; 2-yr, 51%	Grade ≥2, 0%
Okunieff et al. [18]	50	50 Gy/10; 48 Gy/6; 57 Gy/3	18.7 (3.7–60.9)	3-yr, 91%	2-yr, 50%	Grade 2, 6.1% Grade 3, 2%
Norihisa et al. [6]	34	48 Gy/4; 60 Gy/5	27 (10–80)	2-yr, 90%	2-yr, 84%	Grade 2, 4 (12%) Grade 3, 1 (3%)
Brown et al. [72]	35	5 Gy/1 to 60 Gy/4	18 (2–41)	Crude, 77%	2-yr, 72.5%	Grade 3–4, 1 (2.8%)
Rusthoven et al. [14]	38	60 Gy/3	15.4 (6–48)	2-yr, 96%	2-yr, 39%	No grade 4 Grade 3, 3 (8%)
Ricardi et al. [17]	61	45 Gy/3; 26 Gy/1	20.4 (3–77)	2-yr, 89%	2-yr, 66.5	Grade 3, 1 (1.6%)

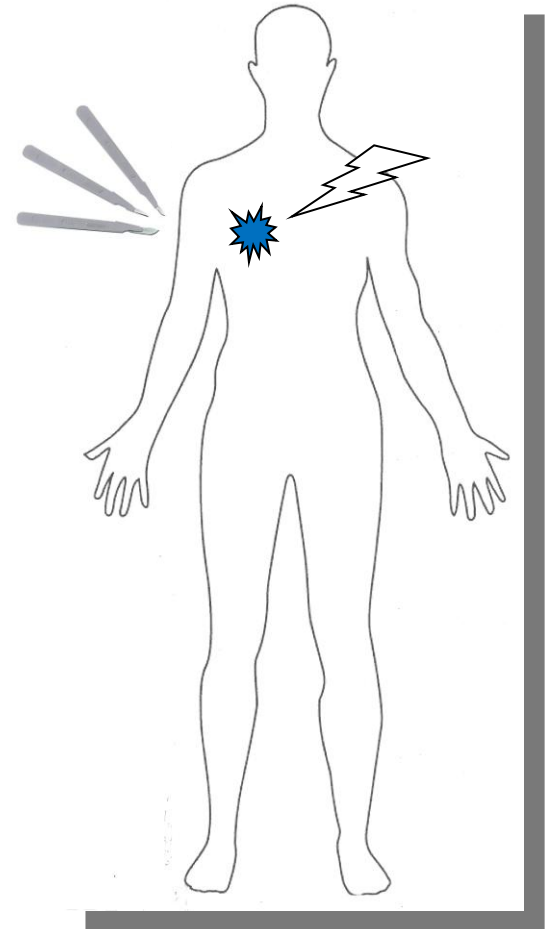


STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS

- It is difficult to properly evaluate **survival** using **SBRT** for lung metastases and compare with metastasectomy because there is:
 - an absence of randomized trials and because most of the phase I–II studies included patients with widely variable clinical characteristics.
 - a bias in selection: most patients referred for SBRT are judged to be inoperable because of medical comorbidities that are able to significantly affect their OS outcome.

Alongi F et al. Critical Rev Oncol Hematol, 2012

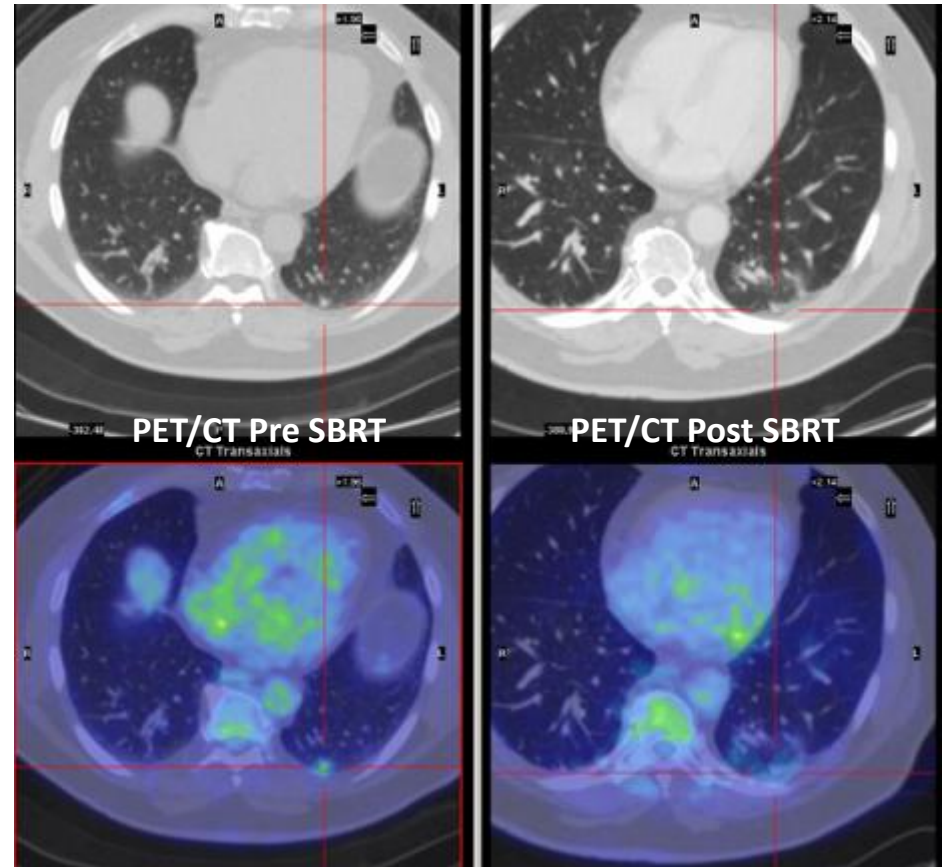
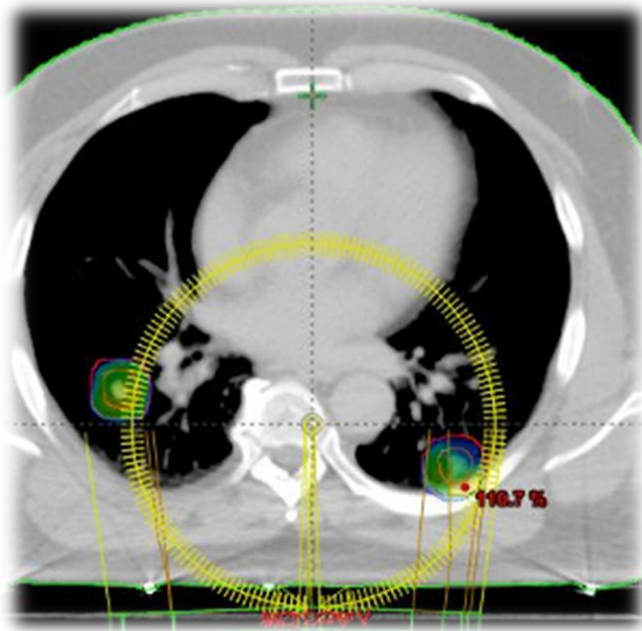
- **RFA(radiofrequency ablation)** could be a reasonable competitor but data are few and preliminary.





STEREOTACTIC BODY RT(SBRT): LUNG OLIGOMTS

**SBRT treatment for rectum bilateral
lung metastases :48 Gy /4 fract.
(TrueBeam FFF beams)**



CR @ PET/TC after 6 months



STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS

- The liver is one of the most common sites of metastatic spread from colorectal cancer (CRC).
- Surgical resection of limited ***liver metastases*** can result in long-term survival in selected patients.

Choti MA, et al. Ann Surg 2002





STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS



- Surgery is technically difficult and only 10–20% of metastatic colorectal cancer patients are candidates for surgical resection

Altendorf-Hofmann et al, Surg Oncol Clin N Am 2003

What kind of ablative options are available today for the remaining 80-90%?

- Cryotherapy, laser-induced thermotherapy, and high-intensity focal ultrasounds have some grade of invasiveness and are currently limited to smaller tumors (commonly <3 cm) and far away from critical structures.

de Meijer et al , Ann surg 2009



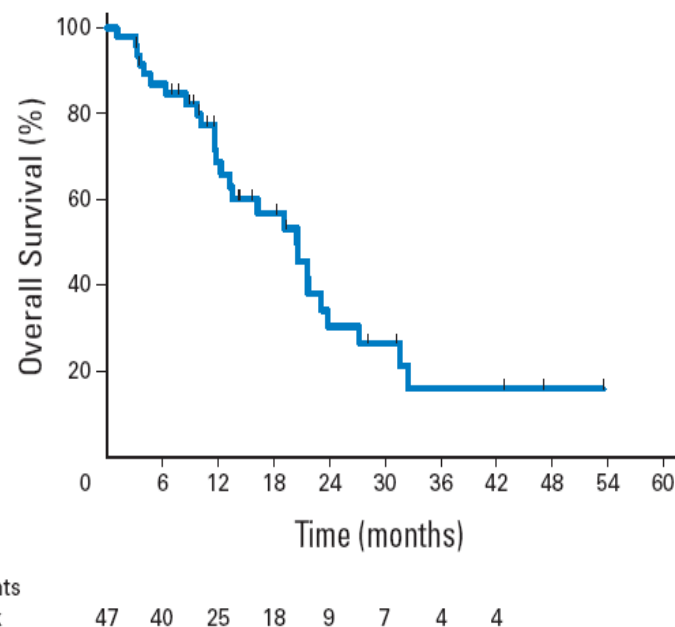
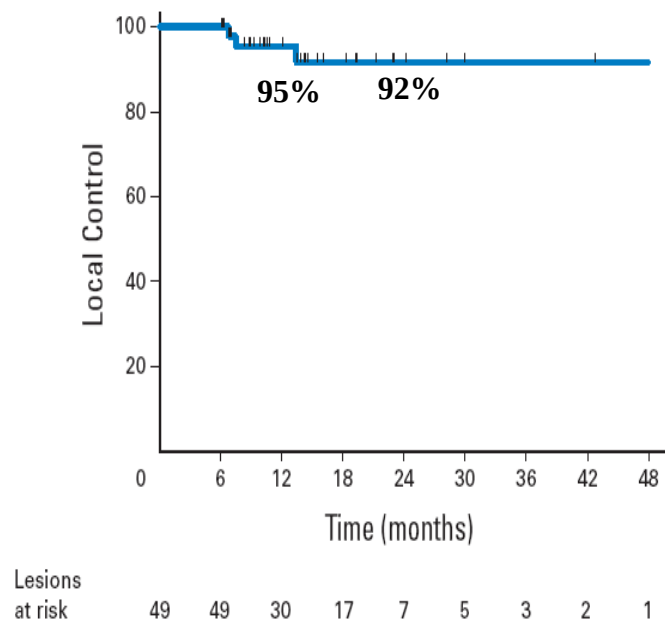
STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter



2009





STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS

Table 2. Summary of recent prospective trials with stereotactic body radiation therapy for liver metastases

Study	n of patients	Median dose/n of fractions	Median follow-up, mos	Local control rate	Overall survival	Toxicity
Herfarth et al. [37, 38]	33	14–26 Gy/1, prescribed to 80%	18	Crude, 78%; 6-mo, 75%; 12-mo, 71%; 18-mo, 67%	1-yr, 72%	Radiation-induced liver disease: 0%
Hoyer et al. [39]	44	45 Gy/3, prescribed to 95%	4.3 yrs	86%	24-mo, 38%	–
Kavanagh et al. [40]	36	60 Gy/3	19	18-mo, 93%	–	–
Lee et al. [42]	70	27.7–60.0 Gy/6, prescribed to isodose line covering PTV (median, 41.4 Gy)	10.8 for 68 assessable patients	1-yr, 71%	18-mo, 47%	Late grade 4 and 5 toxic effects, 2.9% and 1.5%, respectively
Méndez Romero et al. [43]	14	37.5 Gy/3, prescribed to 65%	12.9	Crude, 94%; 1-yr, 100%; 2-yr, 86%	1-yr, 85%; 2-yr, 62%	Grade ≥ 4 toxic effects, 0%
Rusthoven et al. [44]	47	12–20 Gy/3, prescribed to isodose line covering PTV	16	1-yr, 95%; 2-yr, 92%	2-yr, 30%	Grade 4 toxic effects, 0%
Goodman et al. [45]	26	18–30 Gy/1, prescribed to 80%	17.3	1-yr, 61.8%; 2-yr, 49.4%	1-yr, 61.8%; 2-yr, 49.4%	Late grade 2 gastrointestinal toxic effects, 2 of 26 patients
Rule et al. [46]	27	30–60 Gy/5	20	2-yr, 56%, 89%, and 100% for the 30-Gy, 50-Gy, and 60-Gy cohorts, respectively	–	Grade ≥ 3 toxic effects, 0%

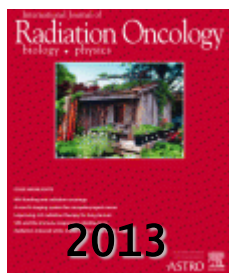
Abbreviation: PTV, planning target volume.



STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS

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Radiation Oncology
biology • physics

www.redjournal.org



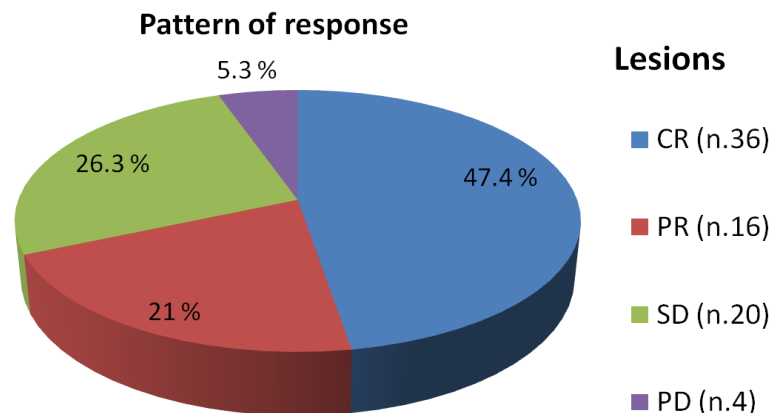
Clinical Investigation: Gastrointestinal Cancer

Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A Preliminary Report From a Phase 2 Trial

Marta Scorsetti, MD,* Stefano Arcangeli, MD,* Angelo Tozzi, MD,* Tiziana Comito, MD,* Filippo Alongi, MD,* Pierina Navarra, MD,* Pietro Mancosu, MSc,* Giacomo Reggiori, MSc,* Antonella Fogliata, MSc,† Guido Torzilli, MD,† Stefano Tomatis, MSc,* and Luca Cozzi, PhD‡

INCLUSION CRITERIA

- Inoperable or medically unsuitable for resection
- Maximum tumour diameter < 6cm
- ≤ 3 discrete lesions
- Performance status 0-2
- Good compliance to treatment



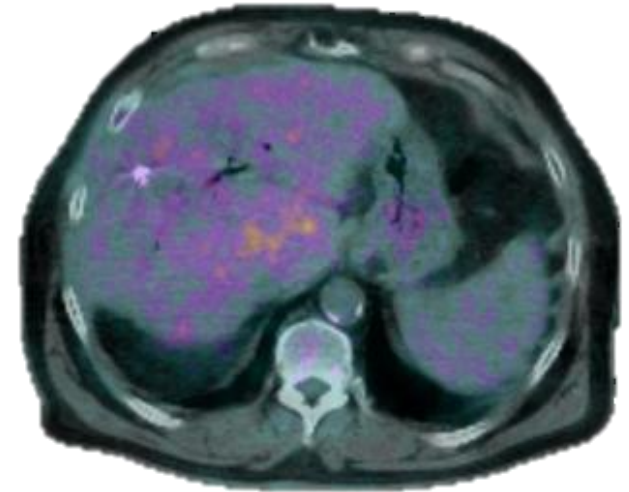
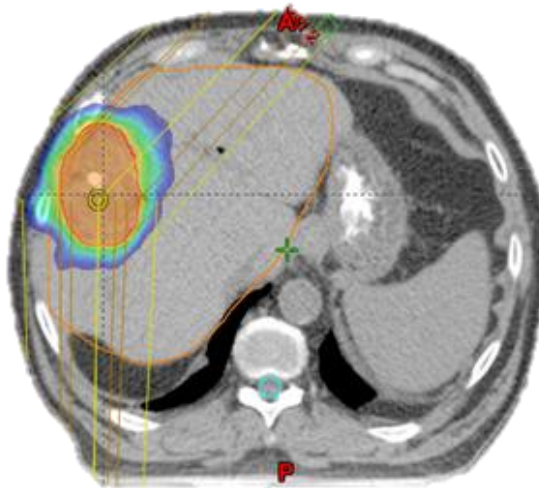
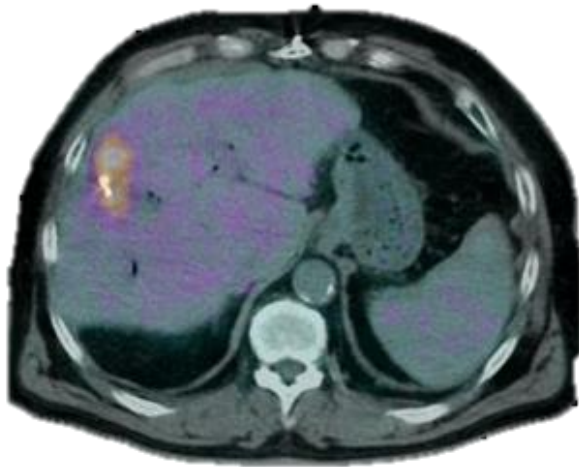
95% in field response rates

Median OS rate was 19 months



STEREOTACTIC BODY RT(SBRT): LIVER OLIGOMTS

Patient treated with SBRT for local relapse after hepatic surgery for colorectal metastasis



**PET –CT pre-treatment,
CEA 72**

**PET –CT post-treatment
CEA 2.2**



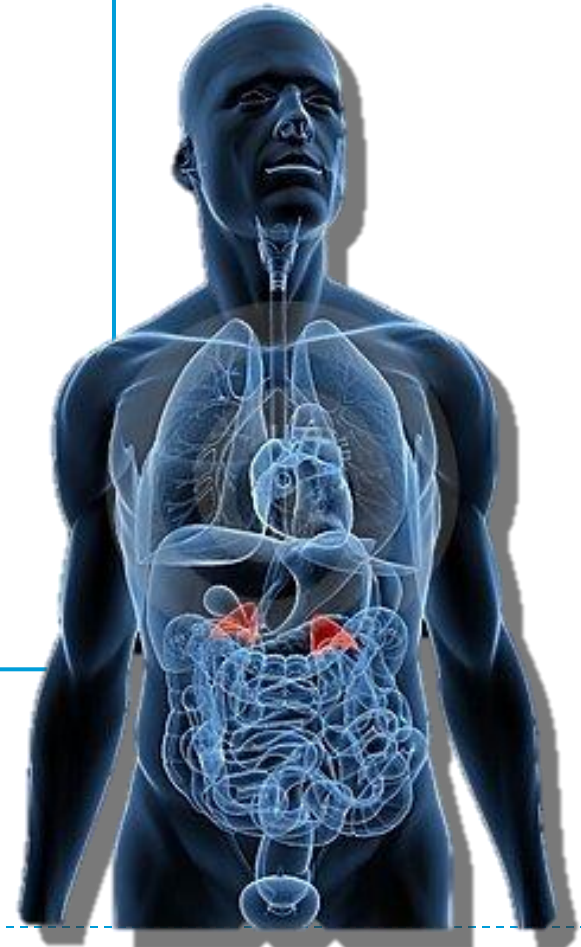


STEREOTACTIC BODY RT(SBRT): ADRENAL GLAND OLIGOMTS

- **Adrenal gland metastases** can occur as a result of various types of extra-adrenal primary cancers, although the most frequent primary tumor is non-small cell lung cancer (NSCLC).

- Longer median survival and OS times have been demonstrated with resection of clinically isolated adrenal metastases.

*Lam et al. Clinical Endocrinol 2002;
Duh et al, Ann Surg 2003.*





STEREOTACTIC BODY RT(SBRT): ADRENAL GLAND OLIGOMTS

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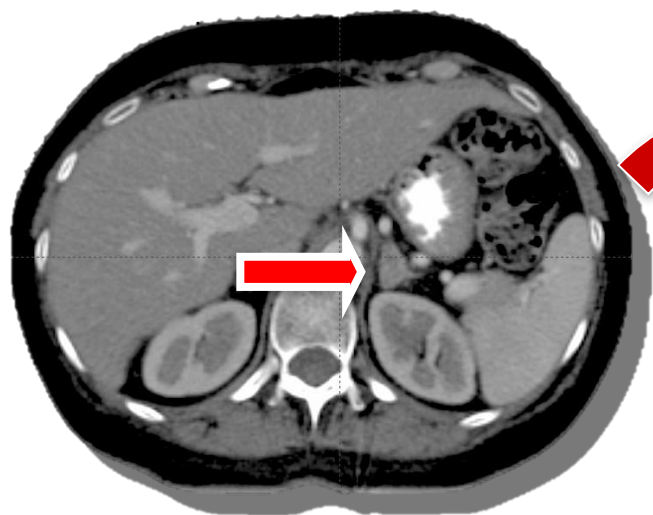
Table 4. Summary of published trials of stereotactic body radiation therapy for adrenal metastases

Study	n of patients	Median dose/n of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Casamassima et al. [26]	48	36 Gy/3	16.2 (3–63)	1–2 yrs, 90%	1-yr, 39.7%; 2-yr, 14.5%	1 case of grade II adrenal insufficiency
Chawla et al. [24]	30	40 Gy/10	9.8 (3.2–28.3)	1-yr, 55%	1-yr, 44%; 2-yr, 25%	Mild grade I fatigue and nausea, “common”
Oshiro et al. [25]	19	45 Gy/10	11.5 (5.4–87.8)	Objective response rate, 68%	1-yr, 56%; 2-yr, 33%; 3-yr, 22%	1 grade 2 duodenal ulcer
Holy et al. [54]	18	20 Gy/5 or 40 Gy/8	21	Objective response rate, 77%	Median, 23 mos	–
Torok et al. [55]	7	16 Gy/1 or 27/3	14 (1–60)	1-yr, 63%	Median, 8 mos	–

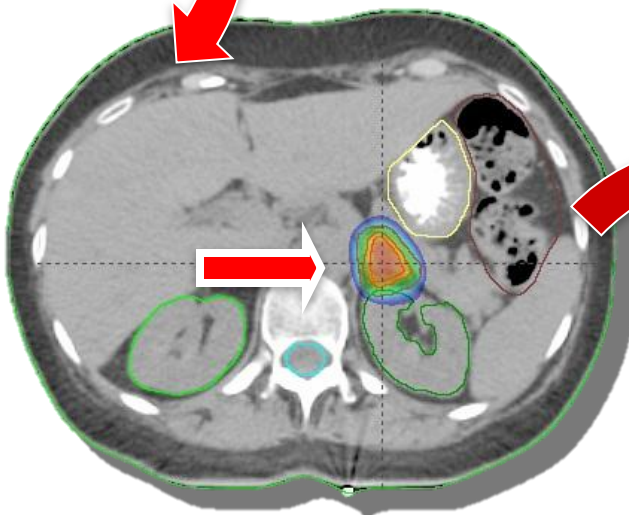
- Few studies have been published regarding the role of SBRT in adrenal glands metastases, and several criticisms could arise regarding the lack of clear data on local control and on dose fractionation.
- Nevertheless, the good tolerability and the promising clinical results should stimulate the scientific community to further design clinical studies with the aim of optimizing local control and evaluating a potential PFS benefit.



STEREOTACTIC BODY RT(SBRT): ADRENAL GLAND OLIGOMTS

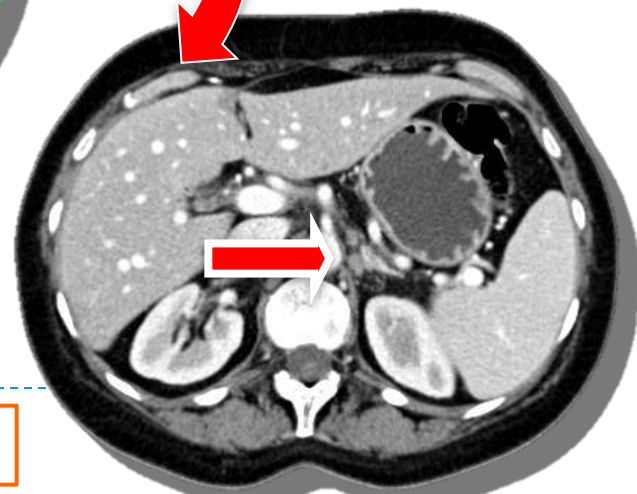


TC pre



SBRT:40Gy/4fr

TrueBeam FFF



TC post



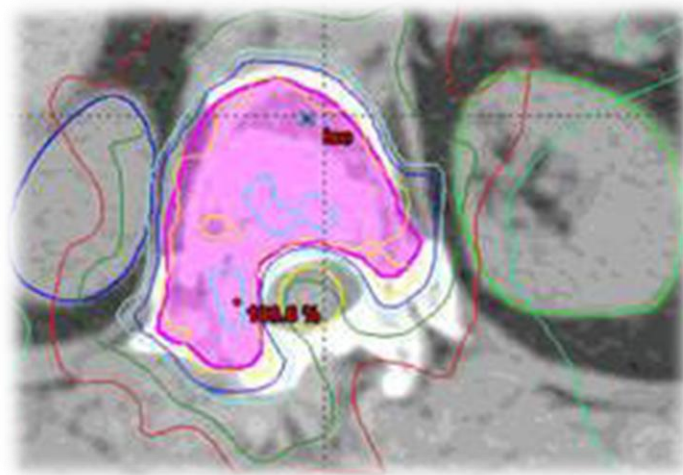
STEREOTACTIC BODY RT(SBRT): SPINAL OLIGOMTS

- **Spinal radiosurgery** has been proven to be an option in the treatment of spinal metastases in properly selected patients, even though only retrospective and phase I–II studies are available.

- Local control based on imaging and/or pain control is achieved in 80% of presentations.

- SBRT can also be safely applied in the postoperative setting, with the intent of reducing the extent of surgery (which can be limited to epidural decompression and fixation).

Sahgal et al J of Neursurg Spine, 2011.





STEREOTACTIC BODY RT(SBRT): SPINAL OLIGOMTS

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Table 5. Summary of published trials of stereotactic body radiation therapy for spinal metastases

Study	<i>n</i> of patients	Median dose/ <i>n</i> of fractions	Median follow-up, mos	Local control rate	Pain response
Yamada et al. [73]	93	24 Gy/1	15	15-mo, 90% (imaging)	NS
Ryu et al. [74]	49	10–16 Gy/1	6.4	93% (imaging and pain)	85%
Sahgal et al. [56]	14	24 Gy/3	9	78% (imaging and/or pain)	NS
	25	24 Gy/3	7	92% (imaging and/or pain)	NS
Nguyen et al. [75]	48	30 Gy/5	13.1	78% (imaging)	52%
		24 Gy/3			
Tsai et al. [76]	69	15.5 Gy/2	10	10-mo, 96.8% (imaging)	Improved pain control, 88%
Chang et al. [58]	63	30 Gy/5	21.3	77% (imaging)	Narcotic use declined 60% to 36%
		27 Gy/3			
Gibbs et al. [77]	74	14–25 Gy/1–5	9	NS	Clinical benefit, 84%
Gerstzen et al. [78]	393	20 Gy/1	21	88% (imaging)	Clinical benefit, 86%

Abbreviation: NS, not significant.

- There are several dose prescription schedules and total doses or doses per fraction, making direct comparison difficult, with a follow-up time globally of a few months.
- The predominant **pattern of failure** after SBRT for spinal metastases is characteristic of the procedure because the principle of SBRT is to treat only the target region, and areas close to the spinal cord are frequently underdosed.



STEREOTACTIC BODY RT(SBRT): TIMING??

A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases

Radiation Oncology 2012, 7:164 doi:10.1186/1748-717X-7-164

- The number of previous chemotherapy regimens administered or progression while receiving chemotherapy significantly correlates with a higher risk of failure after SBRT in 90 patients treated for oligometastases in Lung and Liver.
- One hypothesis that could explain this finding could be that the previous chemotherapy regimens, received by the patients, selected tumoral clones with a lower sensitivity to radiation, even if no study has been published to prove it.
- This suggests that SBRT should perhaps be used as a local treatment for metastases *before* the administration of several systemic therapies.

Lartigau et al, Radiation Oncology 2012.





CONCLUSIONS

•The role of radiation therapy **for selected breast metastatic disease** has evolved *from palliating symptoms to a potentially curative purpose*, as shown in specific settings, including oligometastases.

Thariat et al. Bull Cancer, 2010

Timmerman et al JCO, 2007

Lartigau Et al, Radiat oncol 2012

•For cases with more than one metastasis, the ***selection criteria* for radiosurgery and SBRT** should be evaluated with extreme attention to life expectancy and toxicity.





OPEN ISSUES

- what is the real cutoff between pure palliative and hypothetical curative **intent** therapy in oligometastatic patients,
- (b) what is the correct **timing with chemotherapy**,
- (c) what is the **optimal target** and how can the radiation oncologist define it as best as possible considering the risk for other potential microscopic foci of disease?
- Considering the high propensity for distant progression in these patients, the **combination of novel drugs and SBRT** needs to be deeply explored.

An international randomized phase II controlled trial called Comprehensive Treatment of Oligometastatic Tumors is currently accruing patients...





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