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"PAZIENTE OLIGOMETASTATICO: OUTCOME A CONFRONTO

"SUCCESSIVI TRATTAMENTI RADIO-ONCOLOGICI?"

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XXII CONGRESSO NAZIONALE AIRO-18nov-ROMA

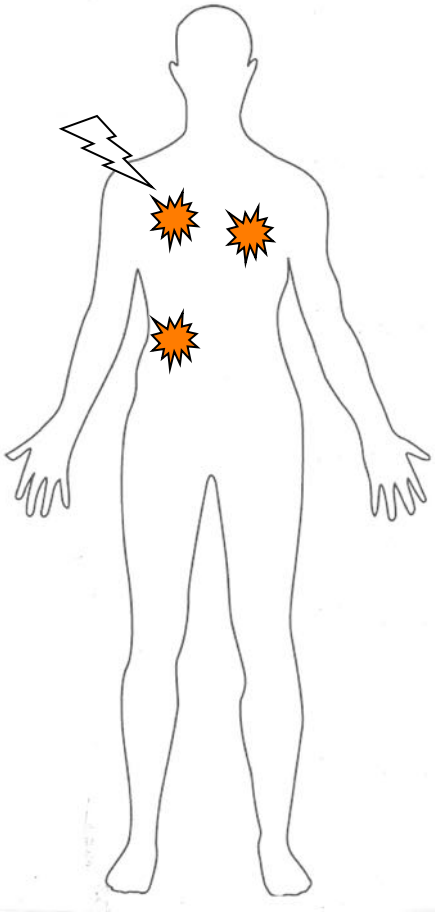
The term "***oligometastases***" was first described by Hellman and Weichselbaum in 1995 as ***"…a less advanced state of metastatic disease amenable to and potentially curable with local therapy".***

Hellman S, Weichselbaum RR: JCO, 1995

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

Milano MT, et alJROBP, 2012.

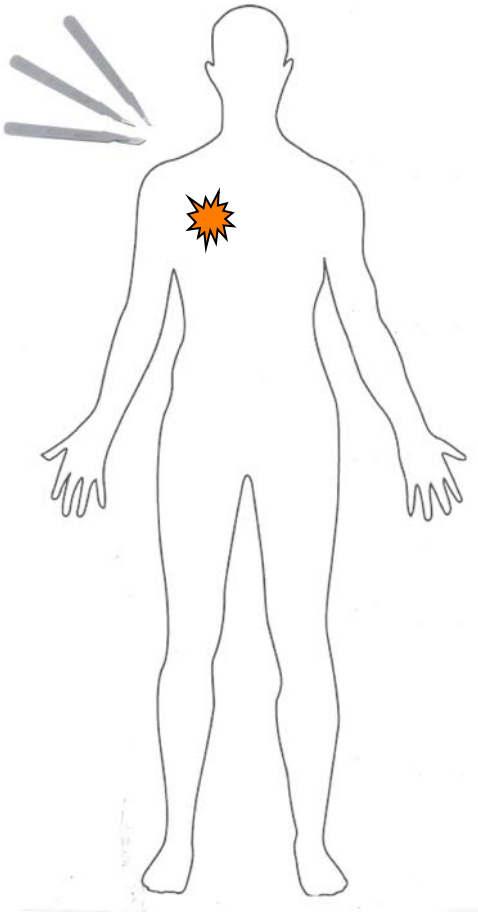
Often, this clinical situation has a slow rate of progression, justifying focal treatments.



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.



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

- In general SBRT for oligometastases should follow the same philosophy relating to indications for 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 on an outpatient basis.

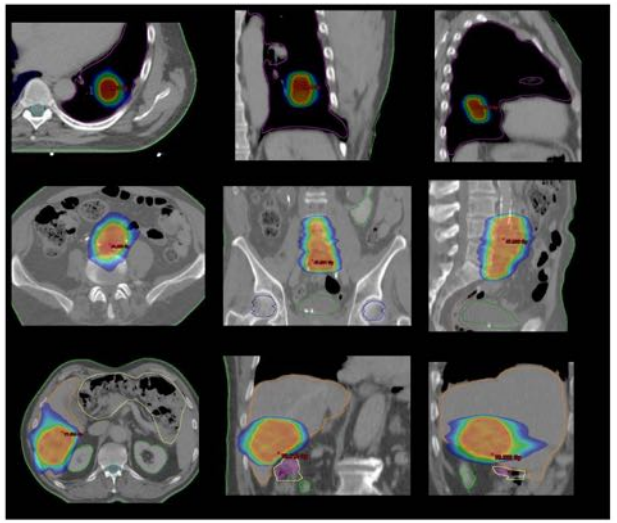
Alongi F et al. Critical Rev Oncol Hematol, 2012

The Oncologist®

Radiation Oncology

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]



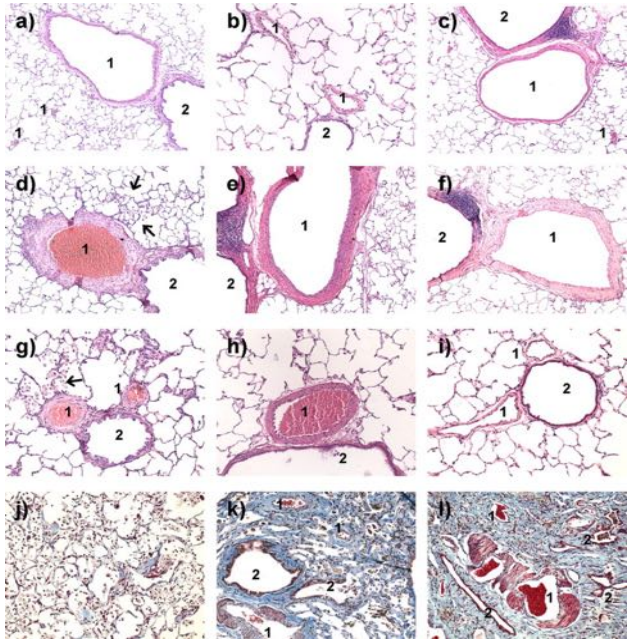
•In terms of ***Radiobiology, SBRT*** may add a novel mechanism of radiation-induced damage.

•At higher doses per fraction (***ablative doses***), emerging data suggest that, in addition to direct cytotoxicity, 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 .



CLINICAL INVESTIGATION

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

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

LUNG

Lung metastases probably represent the paradigm of the potential benefit achievable by SBRT, which is able to 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.

Alongi, Arcangeli, Filippi et al.

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

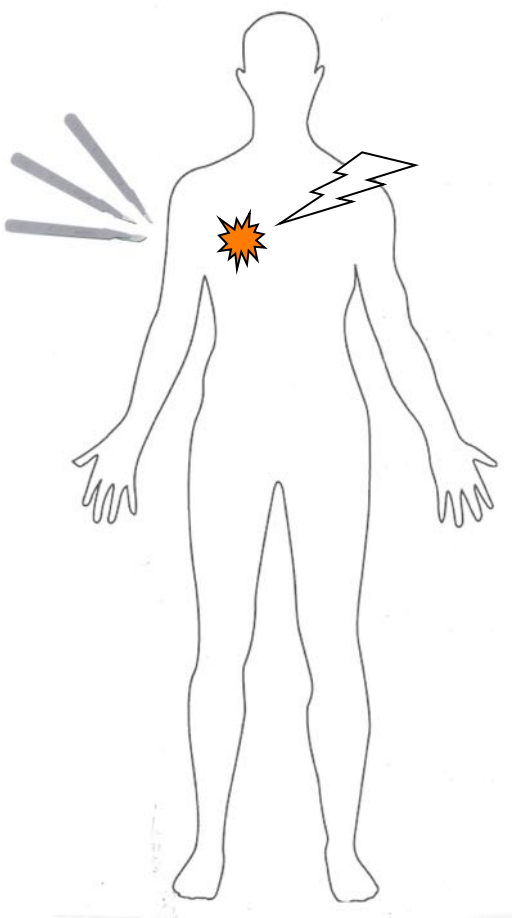
Study	*n* of patients	Median dose/*n* of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 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%)

•It is difficult to properly evaluate ***survival*** estimates using ***SBRT*** for lung metastases and compare with metastasectomy hystorical data 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 an preliminary.

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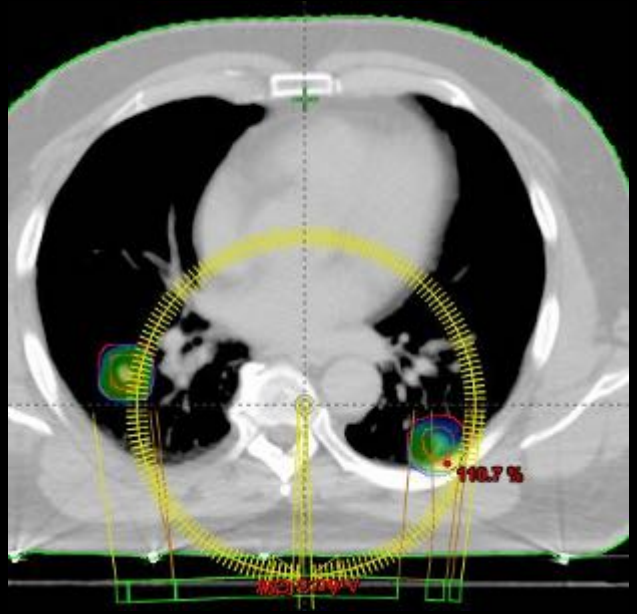
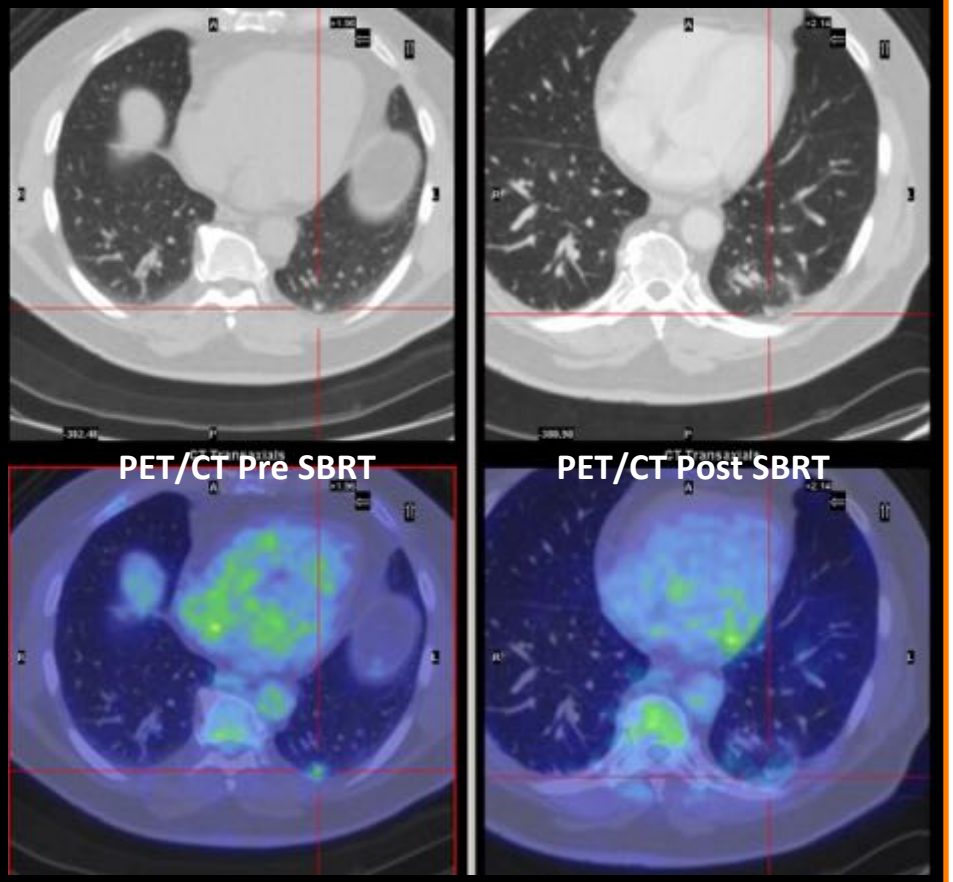
SBRT treatment for rectum bilateral lung metastases :**48 Gy /4 fract.**
(TrueBeam FFF beams)





CR @ PET/TC after 6 months

LIVER

- 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

•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 remaning 80-90%?

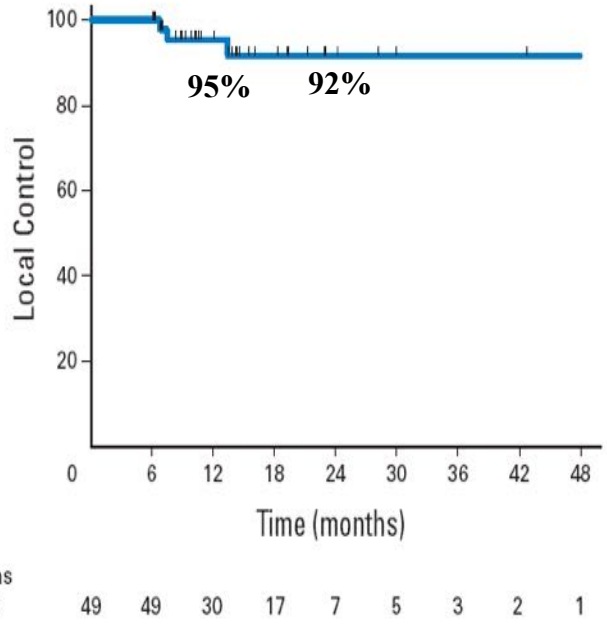
•Cryotherapy, laser-induced thermotherapy, and high-intensity focal ultrasounds have some grade of invasiveness and are currently limited to smaller tumors (commonly <3 cm) and far away from critical structures.

de Meijer et al , Ann surg 2009

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



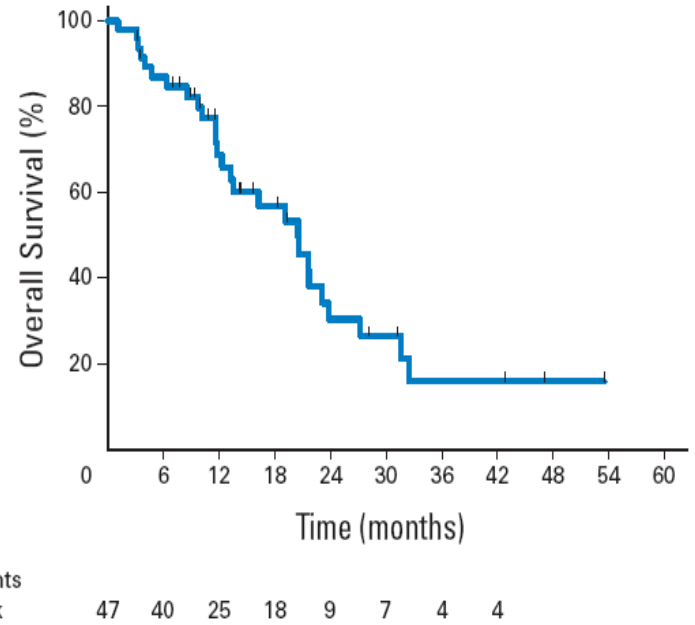


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Table 2. Summary of recent prospective trials with stereotactic body radiation therapy for liver metastases

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.

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Humanitas protocol in LIVER OLIGOMTS

INCLUSION CRITERIA

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

	Dose/fraction	Number fractions	Median dose
Standard dose	**25Gy**	**3**	**75 Gy**
Dose reduction 10%	**22.5 Gy**	**3**	**67.5 Gy**
Dose reduction 20%	**20. 63 Gy**	**3**	**61.89 Gy**
Dose reduction 30%	**18.75 Gy**	**3**	**56.25 Gy**

Scorsetti er al, ASTRO 2012 Annual meeting, Boston

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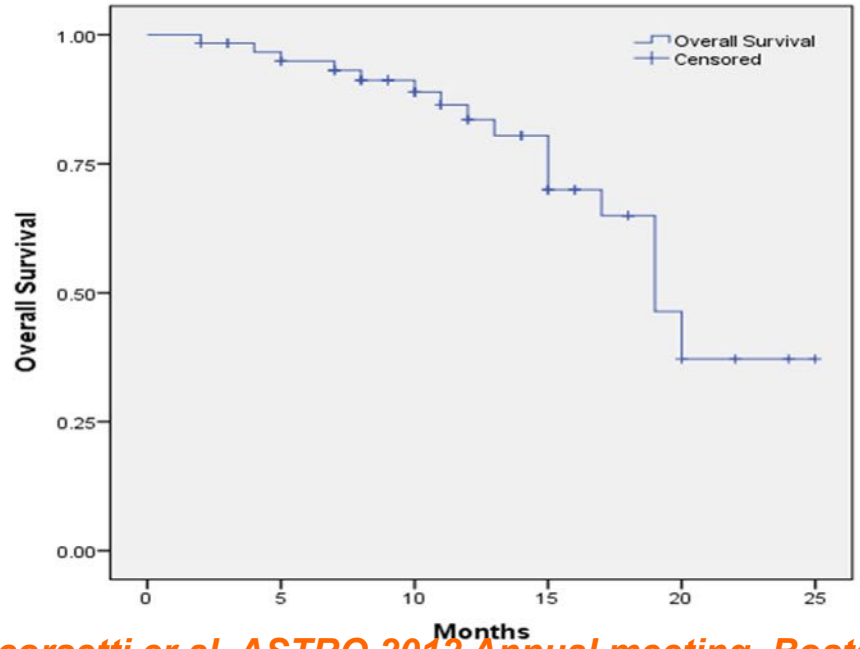
Humanitas protocol in LIVER OLIGOMTS

- From February 2010 and September 2011. ***61 patients (74 lesions)***
- Acute toxicity was limited: 26%G2 transient transaminase elevations definitively returned to baseline.
- No RILD. No major (grade 4 or 5) late toxicity.
- Median FU: 12 months(2-26)
- ***Actuarial LC at 6, 12 and 22 months were 100%, 94.0%% and 90.6%***
- ***Median OS rate was 19 months***

In field-response	Lesions (N= 76)
RC	**36 (47.4%)**
RP	**16 (21.0%)**
SD	**20 (26.3%)**
PD	**4 (5.3%)**

LOCAL CONTROL : 94.7% (72 of 76)



Scorsetti er al, ASTRO 2012 Annual meeting, Boston

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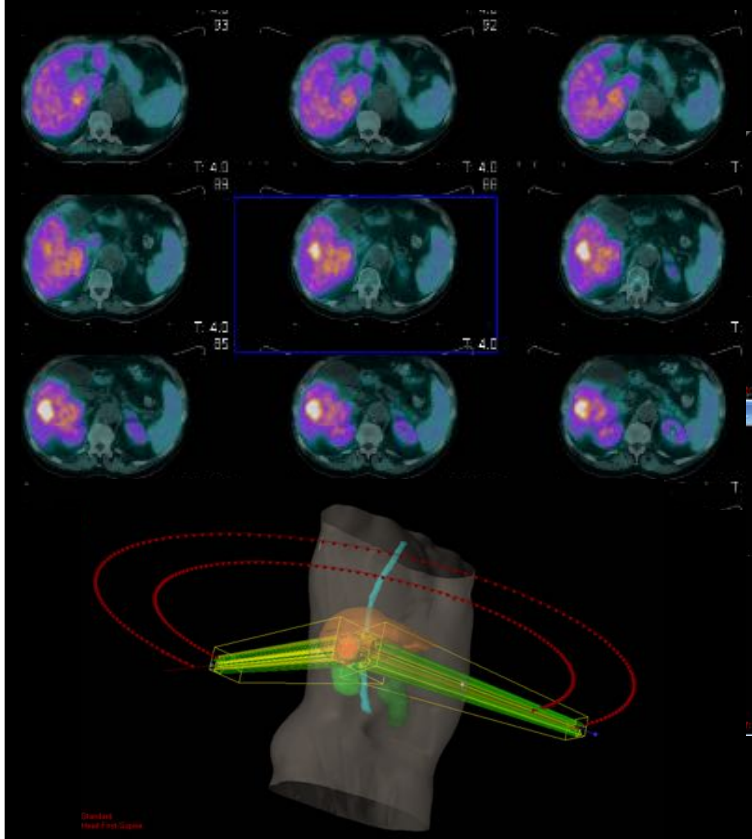
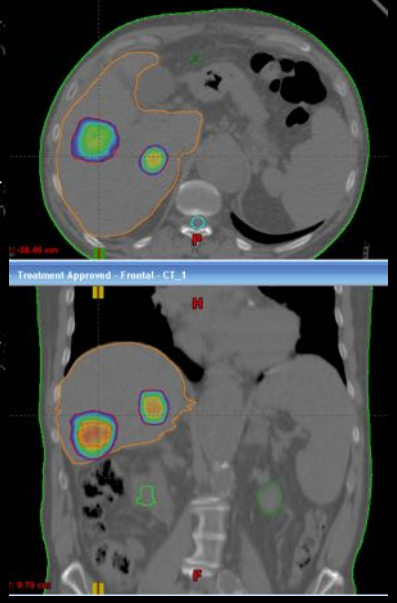
SBRT: Dose: 25 Gy x 3; 10FFF; DR 2400.

PET pre

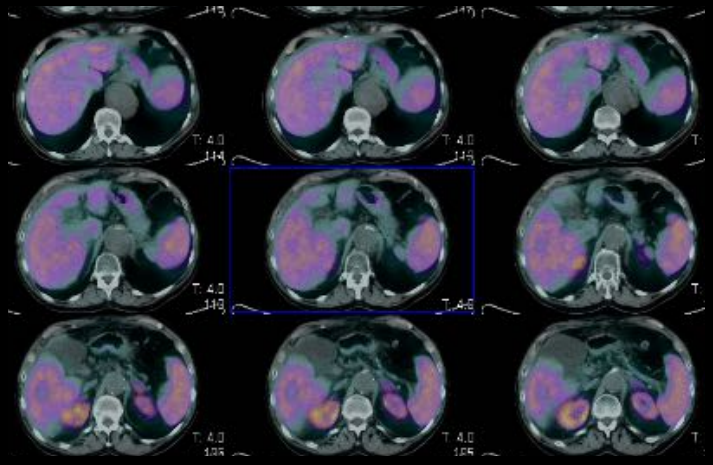


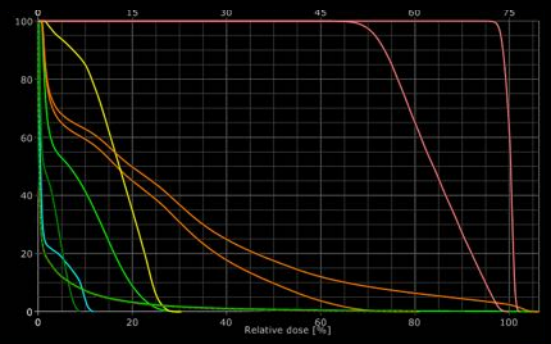
RapidArc
1 isocentre
2 arcs
Jaw tracking



MU:3174+3004
BOT:170s

PET after 6 months





LIMPH NODE

- Few published data exist on the local control rate using conventional RT in the context of ***isolated or limited lymph node metastases***.

- SBRT does not replace chemotherapy but rather can augment its effects on focal areas of gross disease as well as metastatic lymph nodes.

Choi et al. IJROBP 2009;
Jereczek-Fossaet al, Radiot and Oncol 2009.
Scorsetti et al, Acta Oncol 2011

- Because small volumes are irradiated for metastatic lymph nodes, dose escalation might result in better efficacy without prohibitive toxicity.

Kim et al World J Gastroneterol 2009.

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Table 3. Summary of published trials of stereotactic body radiation therapy for lymph node metastases

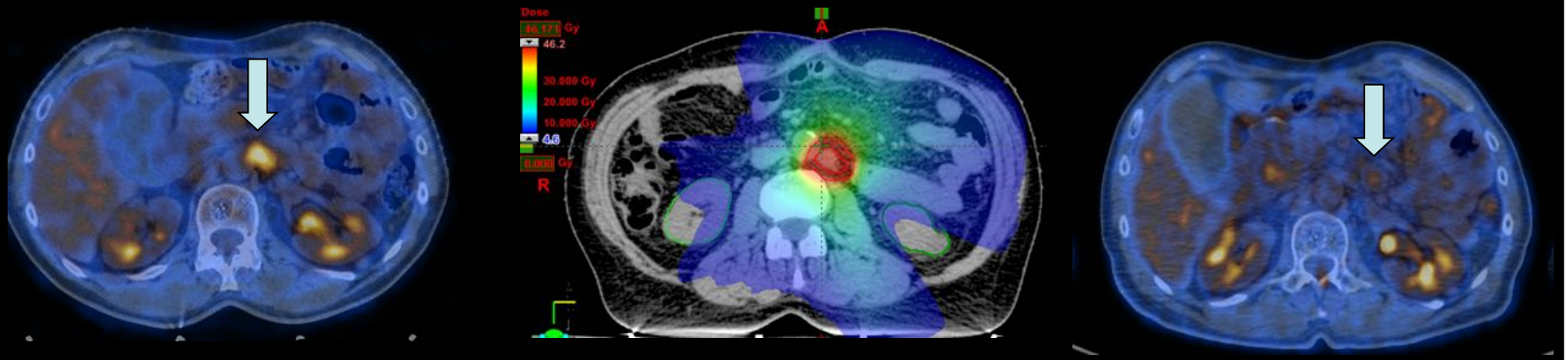
Study	Primary	*n* of patients	Median dose/ *n* fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Choy et al. [47]	Cervix	30	33–45 Gy/3 (n = 24); 4 patients also received 27–45 Gy external beam radiotherapy	15 (2–65)	4-yr, 67.4%	4-yr, 50.1 mos	Late grade 3 or 4 toxicity, 3%
Jereczek-Fossa et al. [48]	Prostate	34	30 Gy/4.5	16.9	17-mo, 91%	–	Late genitourinary grade 3, 5%
Kim et al. [49]	Stomach	7	45–51 Gy (median, 48 Gy)/3	26 (19–33)	–	3-yr, 43%	Late grade 3 or 4 toxicity, 0%
Kim et al. [50]	Colorectum	7	36–51 Gy/3	26 (15–70)	86 %	3-yr, 71.4%	Late grade 4 toxicity, 14%
Bignardi et al. [51]	Miscellaneous	19	45 Gy/6	12	12-mo, 77.8%	–	Late grade 3 or 4 toxicity, 0%

The poorer disease-free survival rates observed in several series may be explained by the substantial differences in the patient populations (primary tumor behavior; the burden of microscopic systemic disease outside the irradiated target, etc) .

Scorsetti et al , Acta Oncol 2011; Bignardi et al , IJROBP 2011

SBRT: Dose: 7.5 Gy x 6;10FFF;DR 2400.

Abdominal LN metastases
(primary gastric adenocarcinoma)



RC@PET after 60 days

ADRENAL GLAND

•***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.

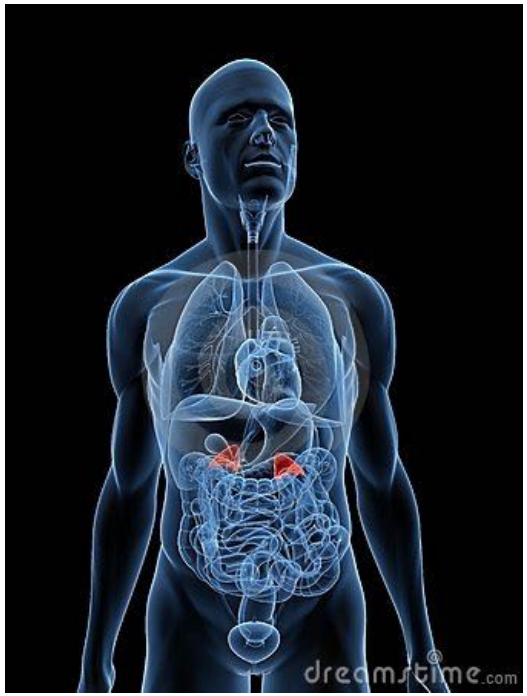


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Table 4. Summary of published trials of stereotactic body radiation therapy for adrenal metastases

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 1 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.

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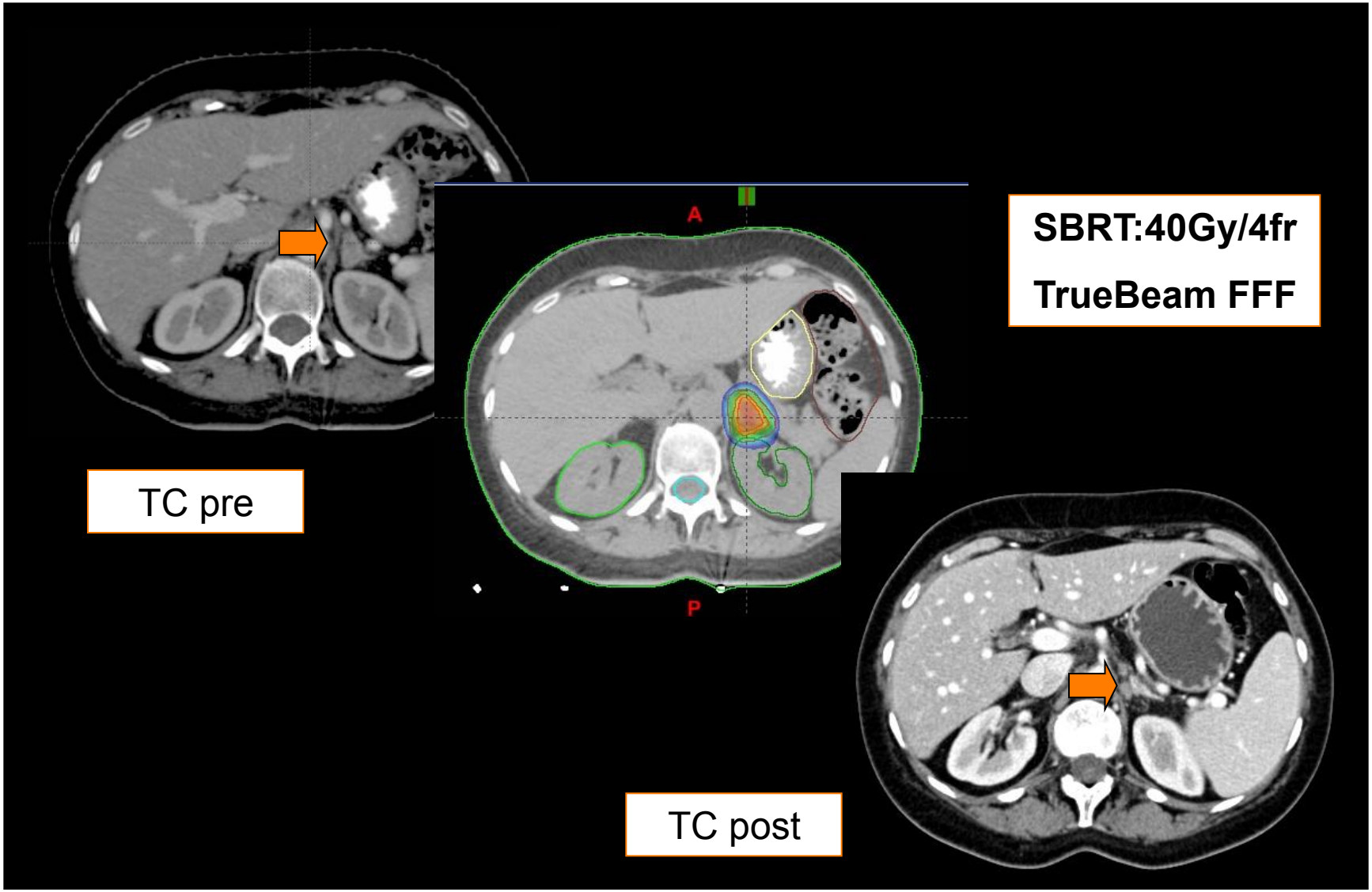

SPINE

- ***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.

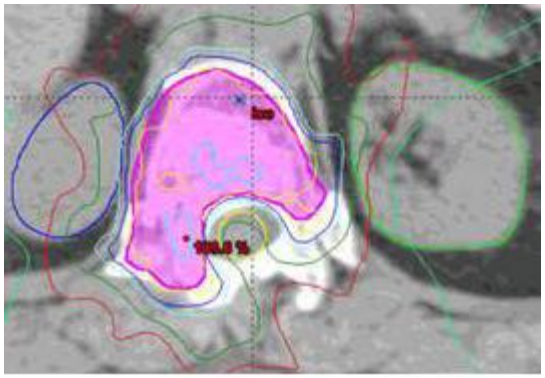

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Table 5. Summary of published trials of stereotactic body radiation therapy for spinal metastases

Study	*n* of patients	Median dose/ *n* 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 24 Gy/3	13.1	78% (imaging)	52%
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 27 Gy/3	21.3	77% (imaging)	Narcotic use declined 60% to 36%
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.

SBRT and Systemic Therapy: 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.

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CONCLUSIONS

•From preliminary published results, thanks to the more extensive prescription of SBRT and SABR, the role of radiation therapy for metastatic disease has evolved *from palliating symptoms to a potentially curative purpose*, as shown in specific patient settings, including promising data from oligometastases.

Thariat et al. Bull Cancer, 2010
Timmerman et al JCO, 2007
Lartigau Et al, Radiat oncol 2012

•In the subgroup of patients with a solitary metastasis, investigating SBRT dose escalation in order to optimize local control may be worthwhile.

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

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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.

•With this background and rationale, prospective trials of high-dose SBRT should be proposed to definitively assess its role in selected oligometastatic cancer patients.

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

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THANK YOU