SBRT in Oligometastasis Lung / Liver: Available Evidences

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Flow of Presentation:

- Definition
- Biology of oligometastatic disease
- Best available evidence
- Role of stereotactic ablative radiotherapy (SABR)
- Future directions
- Take-home messages

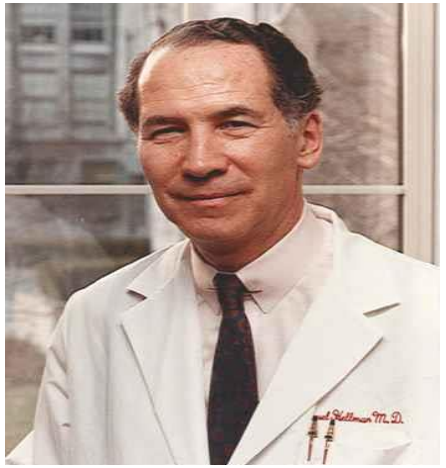
Definition:

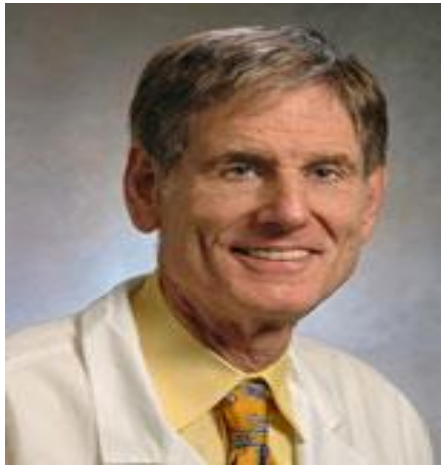
- No consensus.

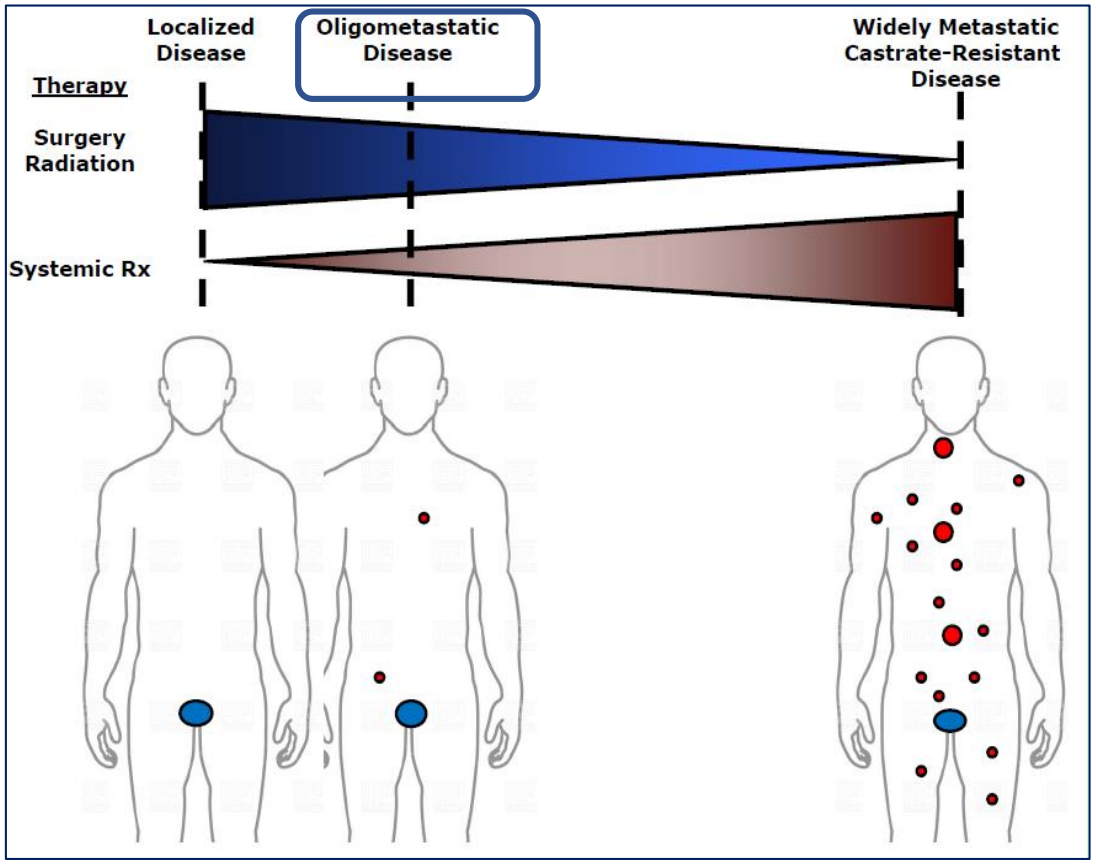
- 1995 - Hellman & Weichselbaum (JCO)
- Patients with a limited number of clinically detectable metastatic disease.
- Hypothetic transitional state between localised and widespread disease

Oligometastasis

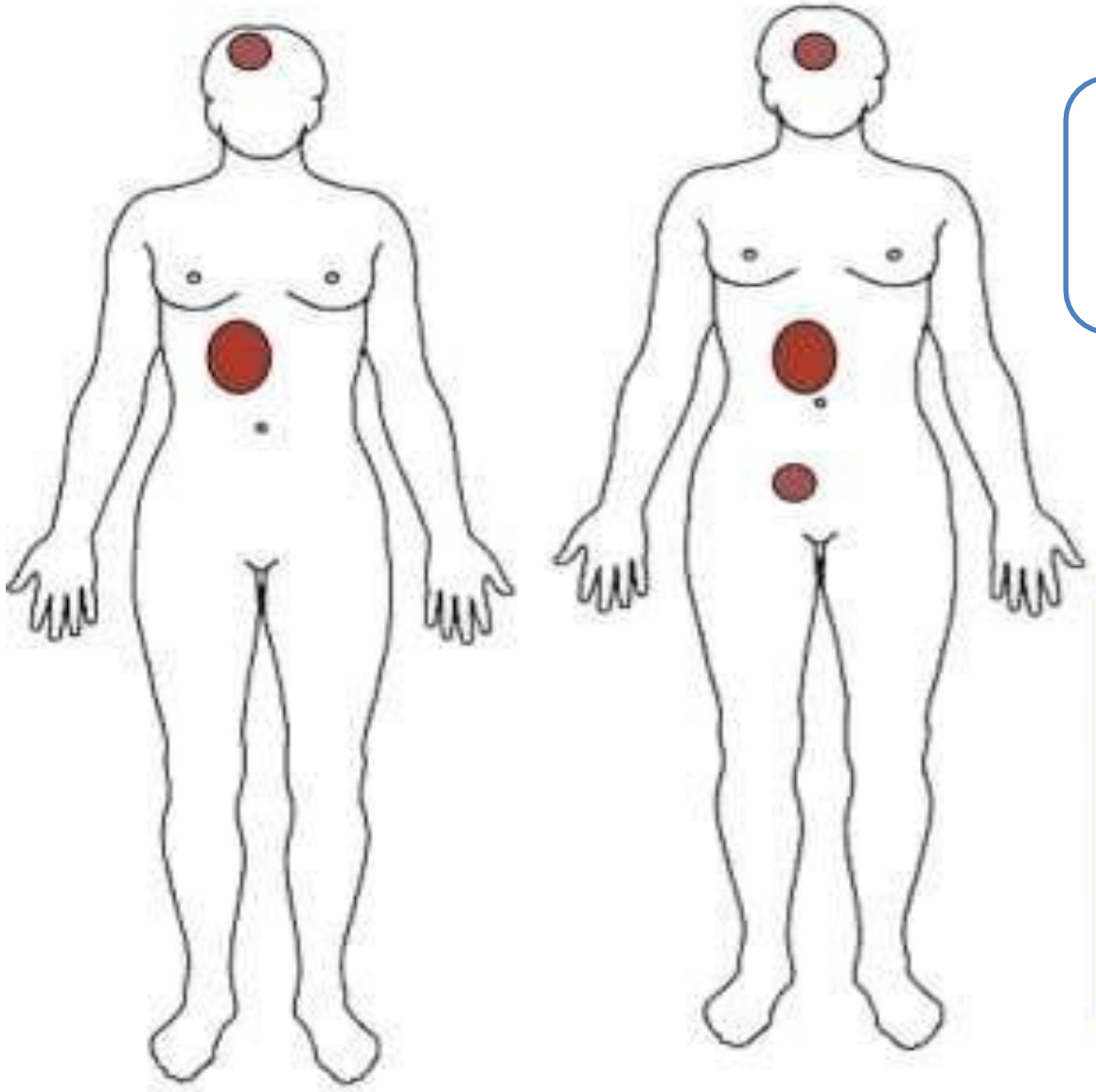
- Metastatic state with limited burden
- 1 to 5 metastasis



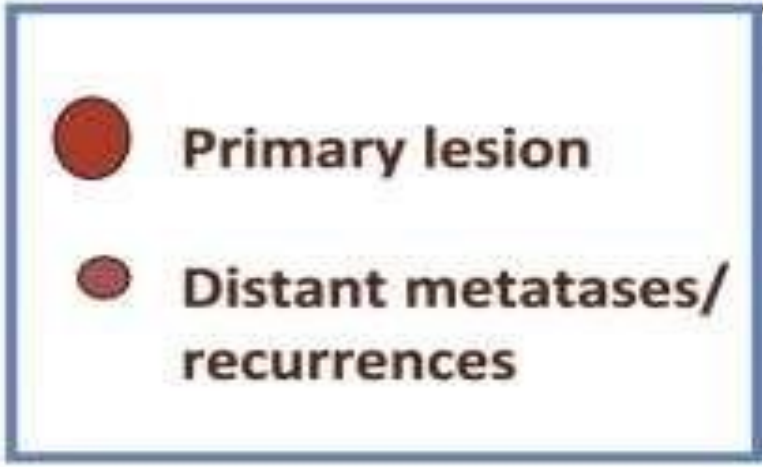




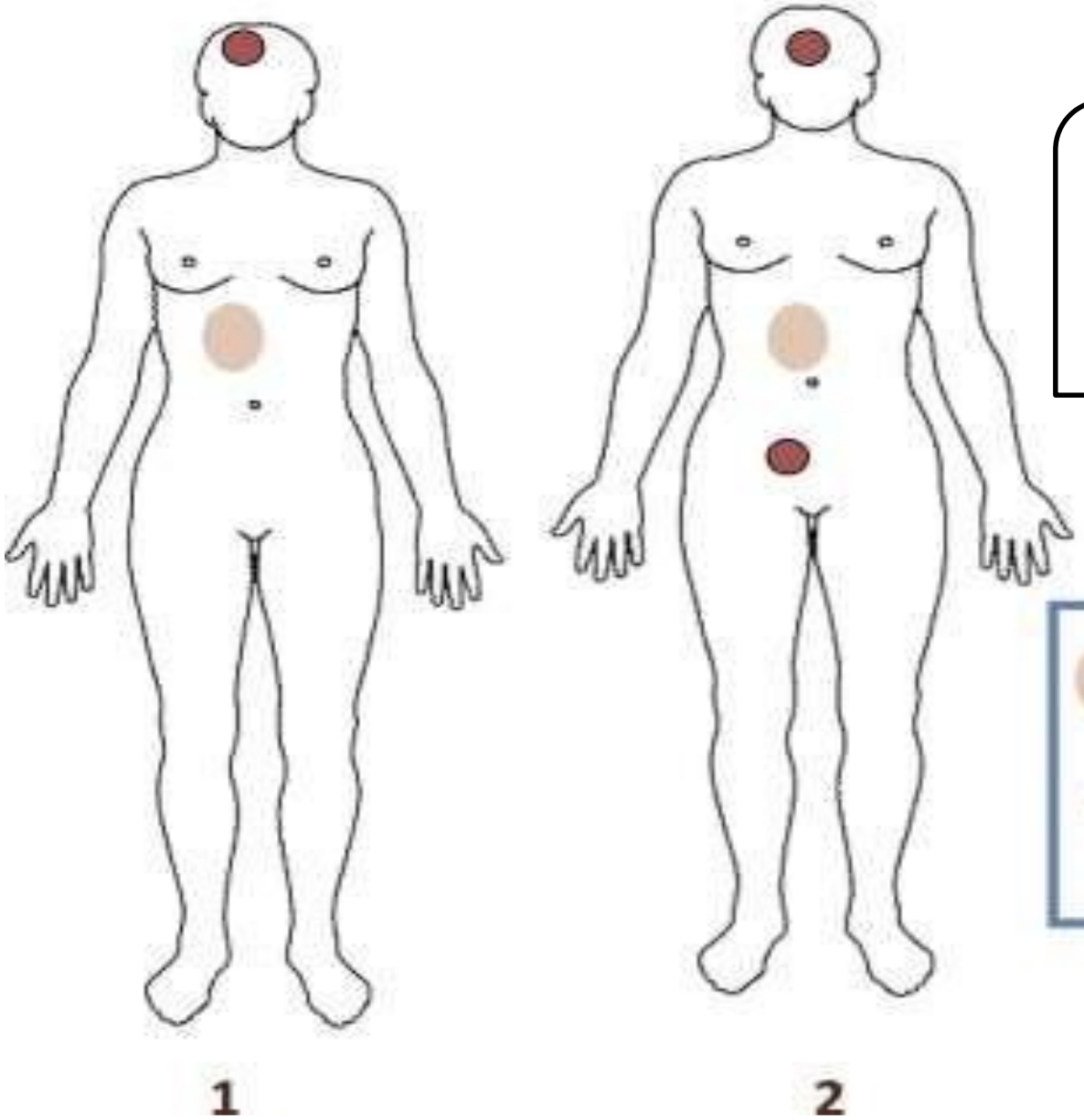
Schema of oligometastases



Oligometastases is the state in which the patient shows distant relapse in only a limited number of regions



Schema of oligo-recurrence

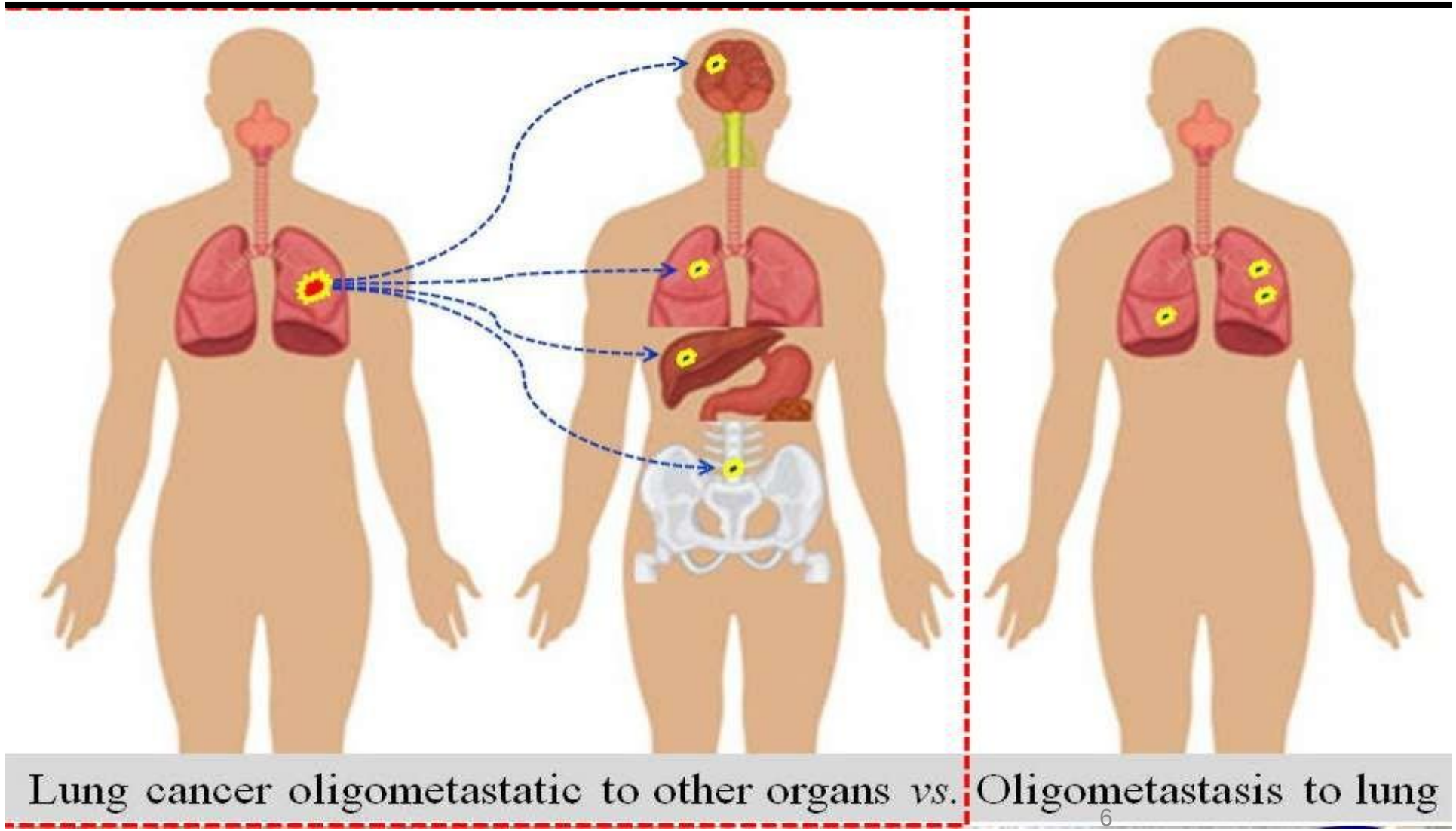


Oligo-recurrence has a primary site of the cancer controlled, meaning that all gross recurrent or metastatic sites could be treated using local therapy

Controlled primary lesion

Distant metatases/ recurrences

SAME ORGAN Vs DISTANT ORGAN



Synchronous oligometastasis

≤5 metastatic or recurrent lesions in the presence of active primary lesions

Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor

Metachronous oligometastaticdisease

Definition:

After period initial disease-free interval, new presentation of oligo-metastases

BIOLOGY OF OLIGOMETASTASIS

Oligometastatic *Versus* Systemic disease: Key-factors

	Oligometastatic disease	Systemic disease
Primary tumour	Favourable microenvironment	Poor conditions creating undifferentiated aggressive clones
Seed (migrating cells)	Sloughed cancer cells	Actively migrating cells
Soils (target organs)	Inhospitable target organs (trap)	Hospitable target organs

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

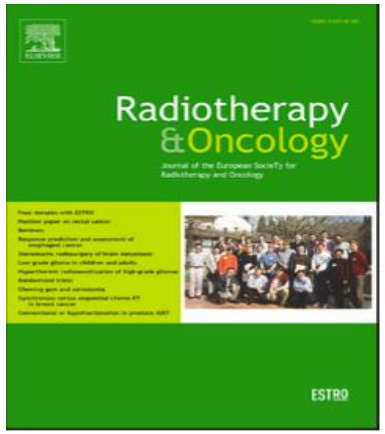
Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans, Beatrice Fournier, Coen Hurkmans, Frédéric E Lecouvet, Icro Meattini, Alejandra Méndez Romero, Umberto Ricardi, Nicola S Russell,

THE LANCET Oncology

2020

Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

Yolande Lievens • Matthias Guckenberger • Daniel Gomez • ... Marta Scorsetti • James Yu • Wendy A. Woodward • Show all authors



Conclusion:

- **OMD can be defined as 1–5 metastatic lesions.**
- **Controlled primary tumor is optional.**
- **All metastatic sites must be safely treatable**
- **Patient selection for SBRT/ curative intent MDRT hols the key.**

Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

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2020

- A systematic literature review focused on curative intent MDRT
- Common endpoints: PFS, OS, LC, QOL & Toxicity reported
- Uncommon endpoints as deferral of systemic therapy and cost were endorsed
- High-resolution imaging to assess and confirm OMD is crucial, including brain imaging when indicated

Conclusion:

- **Based on available data, OMD can be defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable**
- **More data are needed to define the optimal patient selection for SBRT/ curative intent MDRT for OMD**

Treatment for Oligometastatic disease:

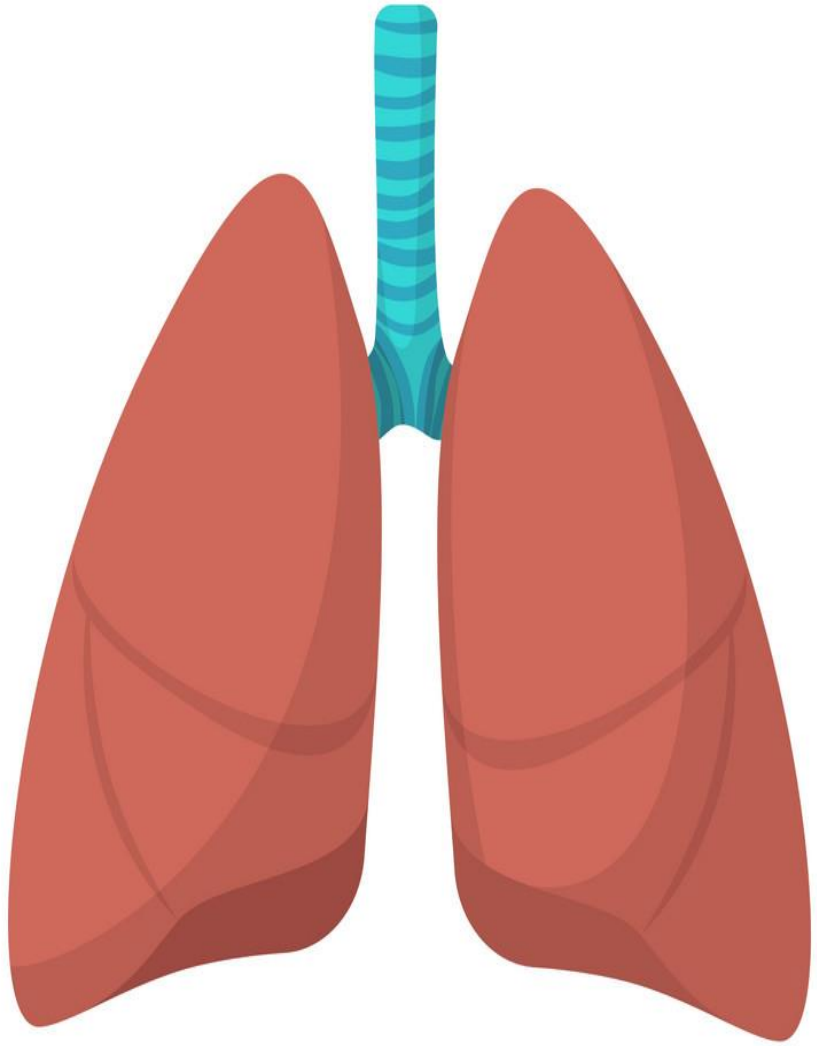
- Chemotherapy
- Targeted therapy
- Immunotherapy
- Radiotherapy
- Surgery

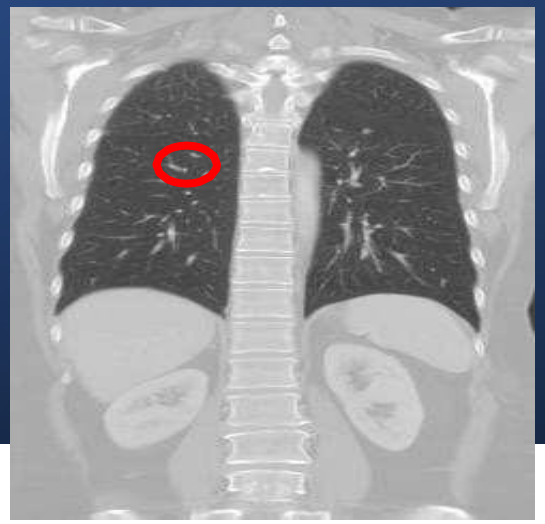
SABR is commonly used in:

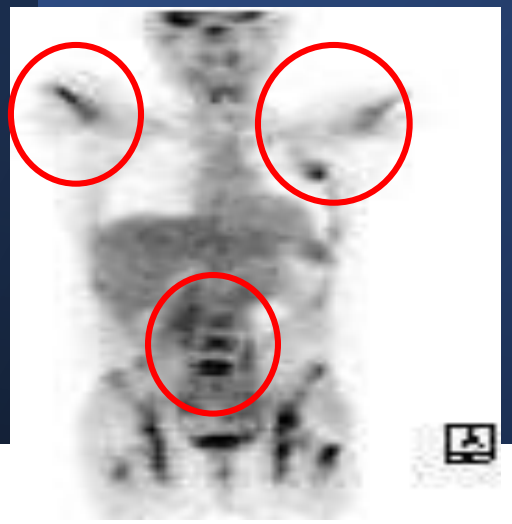
- Lung
- Liver
- Spine
- Prostate

LUNG

Prevalence of OMD in stage IV NSCLC has been estimated to range between 25% and 50%







Lung metastasis is most common in OMD

In OMD small number of metastatic lesions limited to an organ

Considered for curative treatment because long term survival can be expected

Aggressive local t/t to metastases in OMD increases the patients disease-free interval

In previous previous years for lung metastasis surgery is the primary of choice (Metastatectomy)

Surgery requires :

- Good PS
- Good CVS function
- Good Respiratory functions

Local Ablative Therapy in Oligometastatic NSCLC

Questions to be addressed before applying LAT?

Q-1: What defines OMD in NSCLC?

- OMD is defined by the presence of limited number of metastases (between 1 and 5) on appropriate imaging studies.
- As per, ESTRO-ASTRO consensus document proposed a definition of 1-5 metastases) with the primary tumor controlled and all metastatic sites amenable to safe t/t.

Q-2: Who is the appropriate patient for LAT?

- No biomarker to define OMD and to select appropriate NSCLC patients for LAT. (Nomograms and other predictive models have been proposed)

Local Ablative Therapy in Oligometastatic NSCLC

Q-3: Which is the most appropriate technique of Radiation therapy?

- **Most evidence supports an SABR.**
- **Other approaches:**
  - **Conventionally fractionated RT**
  - **Moderately hypofractionation**
  - **Lower dose regimens that may stimulate the immune system.**
  - **Most studies pre-immunotherapy, high-level evidence remains unavailable.**
  - **Patients with targetable mutations or in patients undergoing t/t with immune checkpoint inhibitors (ICIs). (When to give TAT?)**

Q- 4: What is the appropriate time to treat OMD by LAT?

- We don”t know the optimal timing of delivering LAT in relationship to systemic therapy.

How to treat OMD ?

What to treat in OMD?

- **TREAT PRIMARY**
- **TREAT MET SITES**
- **TREAT BOTH**

SBRT

RFA

SURGERY

BRACHYTHERAPY

INTRA ARTERIAL EMBOLIZATION

COMBINING WITH IMMUNOTHERAPY

Role of SABR in Oligometastatic NSCLC

Medical comorbidities & anatomical location decides the role of Surgery.

Local therapies like RT (SABR) evolved as a treatment for lung mets.

SBRT to be integrated in OMD when surgery not feasible

SBRT can offer curative treatment of OMD in Lungs

SBRT is non invasive.

Why SBRT:

- Non-invasive
- Precise
- Rapid dose fall off
- Maximum normal tissue sparing
- Potential reduction of the deleterious effect of tumor proliferation
- More lethal damage to DNA and less sublethal damage
- Ablative radiotherapy doses (i.e., those that destroy all living tissue in an area) need to have a higher biologically effective dose (BED)

Radiobiological advantages of SBRT

- Greater potential cell kill
- Engaging of sphingomyelin based endothelial mechanism of tumor control related to the high dose per fraction.
- Higher radiation doses overcomes hypoxic microenvironments found in metastases

Role of Sphingolipids:

Structural molecules of cell membrane

Maintains barrier function & fluidity

Also regulates biological processes

- **Growth**
- **Proliferation**
- **Migration**
- **Invasion or metastases by controlling signaling functions in cancer cell signal transduction network**

Sphingolipids are responsible for tumor proliferation, progression, and metastasis.

SBRT action on Sphingolipids:

↓

High-dose per fraction radiotherapy

↓

Endothelial membrane alterations

↓

Inducing sphingomyelin mediated endothelial apoptosis

↓

Microvasculature dysfunction

Tumor cell death

Other actions:

1) Ionizing radiation induces ceramide induced cytochrome C

Release into tumor cytoplasm

Apoptosis

2) High-dose per fraction radiotherapy

Induces antigen presentation within the tumor stroma

Facilitate cytotoxic T-cell therapy

Stromal targeting

Patient selection for SABR to Lung in OMD:

- Primary Tumor Histology
- Node negative
- Female
- KPS
- Control of primary tumor
- Size of largest metastasis
- Number of metastasis

Prognostic factors:

- Number of metastases
- Response to first-line systemic therapy
- CNS mets
- Intrathoracic nodal status
- EGFR/ALK mutation status.

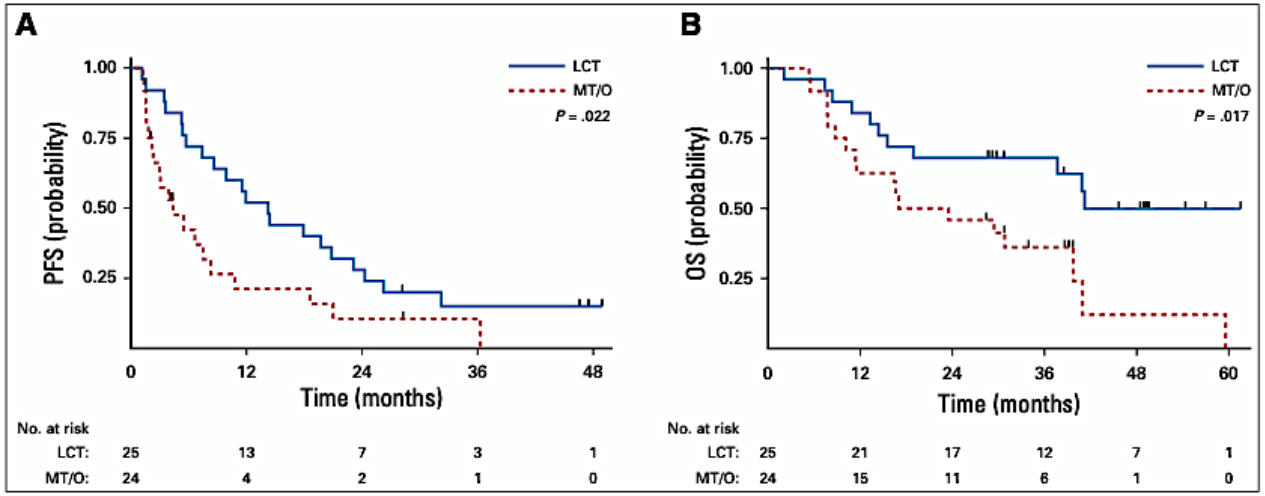
Lets’s see the Evidence

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

Lancet Oncology 2016

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**

- Phase II & Randomized study
- ≤3 metastases who did not progress on standard frontline systemic therapy with maintenance therapy/observation
- 49 Patients
- OS & PFS evaluated
- 2 arms



Conclusion:

In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

ASCO Journal of Clinical Oncology®

Update in 2019

Check for updates

Daniel R. Gomez, MD[1]; Chad Tang, MD[1]; Jianjun Zhang, MD, PhD[1]; George R. Blumenschein Jr, MD[1]; Mike Hernandez, MS[1]; J. Jack Lee, PhD[1]; ...

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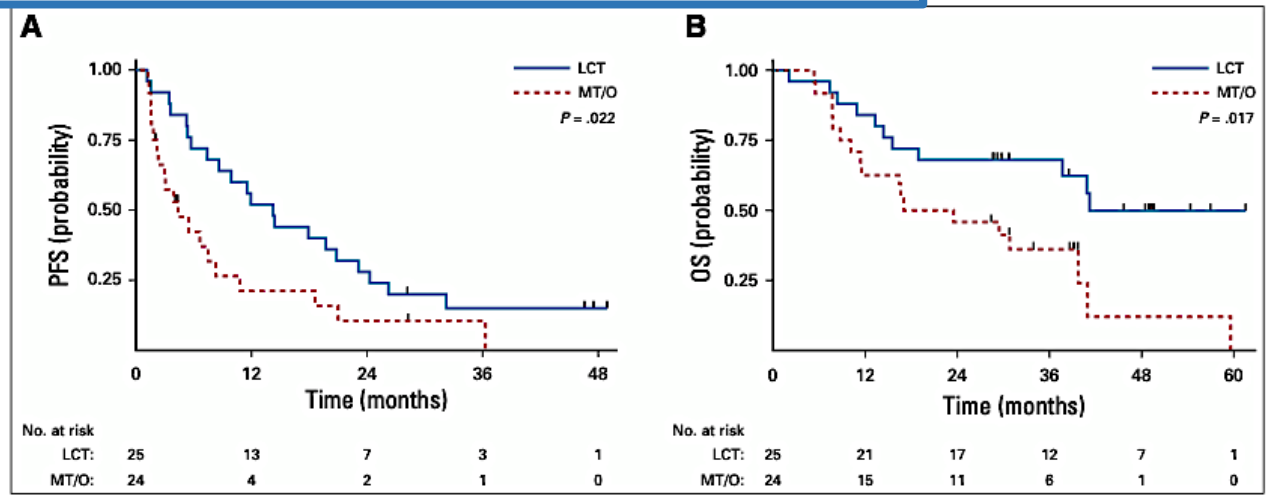

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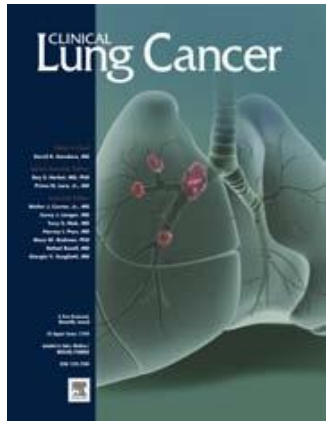
Original Study

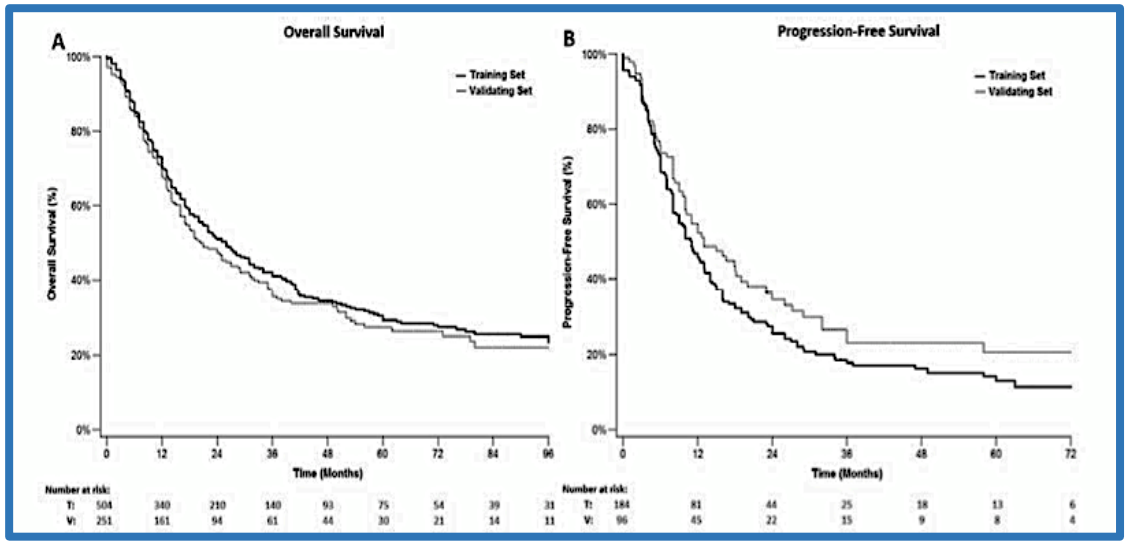
An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer

2015

Allison B. Ashworth [1], Suresh Senan [2], David A. Palma [1], Marc Riquet [3], Yong Chan Ahn [4], Umberto Ricardi [5], Maria T. Congedo [6], Daniel R. Gomez [7], Gavin M. Wright [8], Giulio Melloni [9], Michael T. Milano [10], Claudio V. Sole [11], Tommaso M. De Pas [12], Dennis L. Carter [13], Andrew J. Warner [1], George B. Rodrigues [1]



- Meta analysis
- 757 Patients
- 1 to 5 synchronous or metachronous metastases treated with surgical metastectomy, SRS/EBRT
- OS & PFS evaluated
- 38% of patients received RT



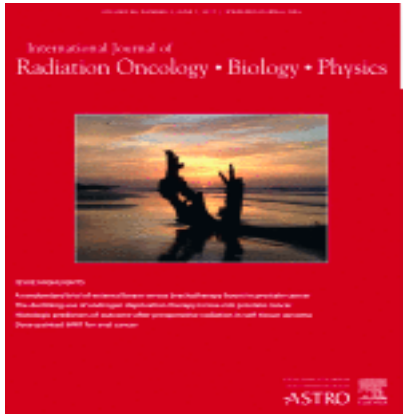
Conclusion:

- Significant OS / PFS benefits were observed in metastasis directed local therapy in NSCLC patients with OMD.

Stereotactic Body Radiotherapy for Oligometastatic Lung Tumors

2008

Yoshiki Norihisa M.D. *, Yasushi Nagata M.D., Ph.D. * ✉, Kenji Takayama M.D. *, Yukinori Matsuo M.D., Ph.D. *, Takashi Sakamoto M.D. †, Masato Sakamoto M.D. ‡, Takashi Mizowaki M.D., Ph.D. *, Shinsuke Yano B.S. *, Masahiro Hiraoka M.D., Ph.D. *



- **34 patients with 43 oligometastatic lung tumors**
- **Lung - 15, colorectum - 9, H & N - 5, Kidney - 3, Breast – 1 & Bone - 1**
- **Tumor diameter < 3 cm (91%), max – 4cm**
- **At 2 years:**
  - **OS – 84.3**
  - **Local Relapse free rate – 90%**
  - **PFS - 34.8%**
- **No local progression was observed in tumors irradiated with 60 Gy**

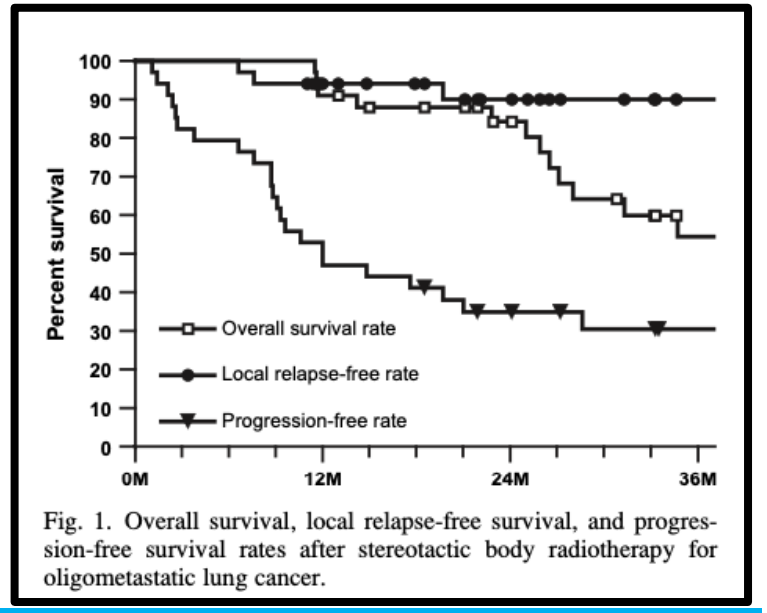


Fig. 1. Overall survival, local relapse-free survival, and progression-free survival rates after stereotactic body radiotherapy for oligometastatic lung cancer.

Conclusion:

- **SBRT for oligometastatic lung tumors was comparable to Surgical metastasectomy**
- **SBRT could be an effective treatment of pulmonary oligometastases.**

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer

A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD[1]; Zabi Wardak, MD[1]; David E. Gerber, MD[2]; et al

JAMA Oncology

2018

- 29 patients
- EGFR & ALK negative patients
- 1-5 synchronous oligometastasis
- Induction therapy given to all patients
- 2 arms: Control arm & SABR arm
- PFS: 9.7 vs 3.7 months

Doses:

- 21 -27 Gy in single fraction
- 26.5 – 33 Gy in 3 fraction schedule
- 30 – 37.5 Gy in 5 fraction schedule

Conclusion:

- Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone
- No difference in toxicity.

Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: role of local treatments

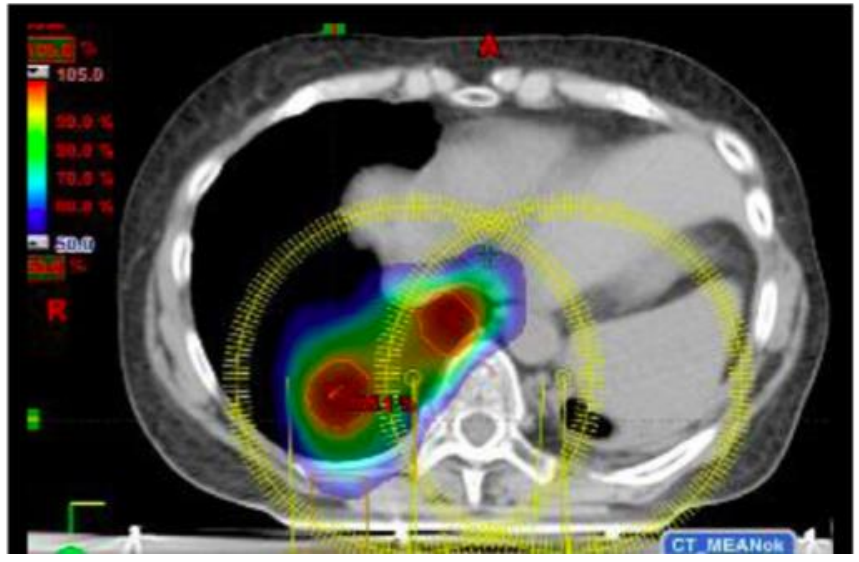
Pierina Navarria[1*], Anna Maria Ascolese[1], Stefano Tomatis[1], Luca Cozzi[2], Fiorenza De Rose[1], Pietro Mancosu[1], Filippo Alongi[1], Elena Clerici[1], Francesca Lobefalo[1], Angelo Tozzi[1], Giacomo Reggiori[1], Antonella Fogliata[2] and Marta Scorsetti[1]

RADIATION ONCOLOGY

2014

- 76 patients & 118 lung lesions treated
- SABR performed in
  - Controlled primary tumor
  - Long-term to disease progression.
  - Number of metastatic sites ≤ 5
- Dose: 48 Gy to 60 Gy.
- Median follow up – 20 months

	1 Year (%)	2 Years (%)	3 Years (%)
Local Control	95	89	89
OS	84.1	73	73



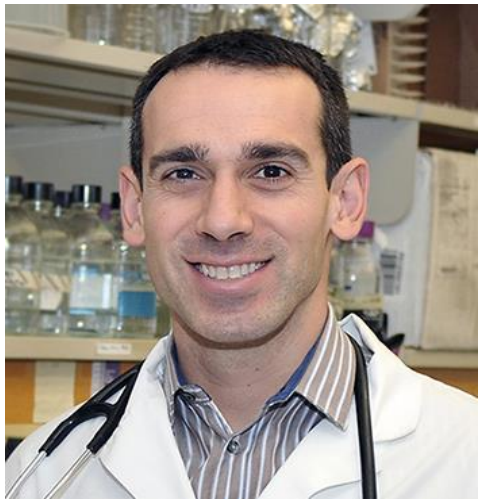
Conclusion:

SABR is feasible with promising results in terms of local control, survival and toxicity

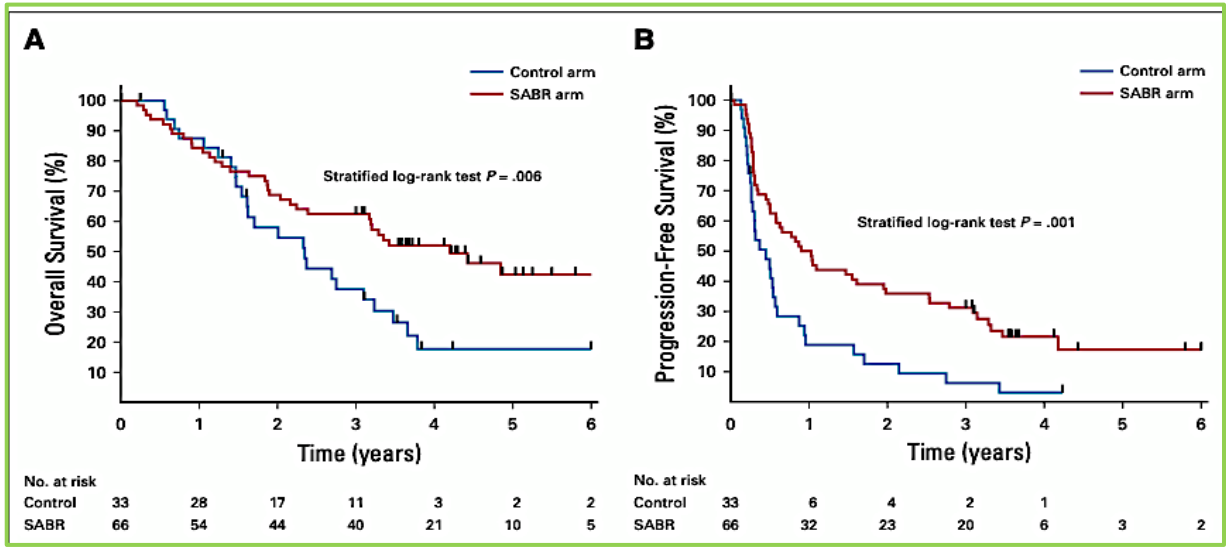
Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1];

Dr David Palma



Dr Suresh Senan



- Open-label, multi-centric (10 centres in Canada, Australia, Scotland and Netherlands).
- 2012-2016
- 1st trial to directly test the oligometasttic paradigm, i.e. OS after Ablative vs Palliative t/t
- Initial results- 13 month improvement of OS in test arm.

Systematic Review

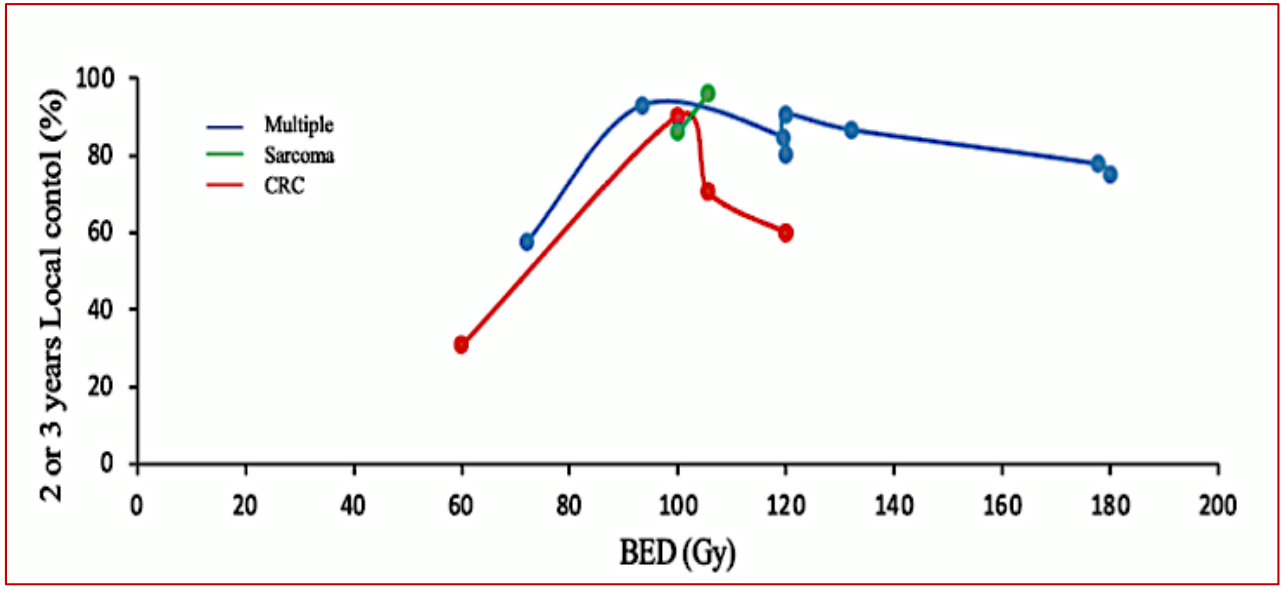
Stereotactic Body Radiotherapy for Patients with Lung Oligometastatic Disease: A Five-Year Systematic Review

Guillaume Virbel, Clara Le Fèvre, Georges Noël * and Delphine Antoni

cancers

2021

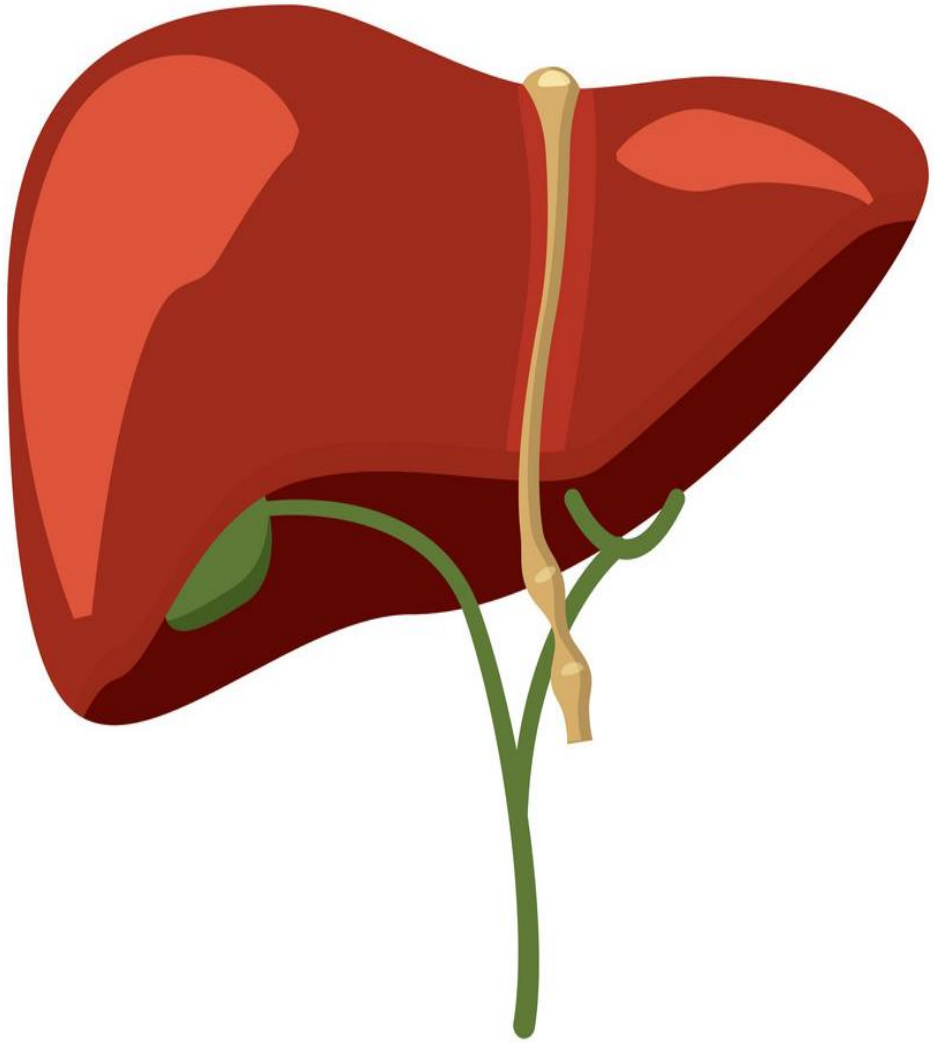
- 5 years systematic review
- 2015 to 2020 published data analyzed
- 18 studies included (Retrospective studies)
- 1191 patients
- 1705 metastases were irradiated
- Diameter of tumor – 7mm to 124mm



Conclusions:

- SBRT is an efficient and well-tolerated treatment for lung metastases in oligometastatis
- Optimal treatment schedule is not definite.
- BED > 100 Gy, appear to be appropriate to obtain a LC comparable with that of surgery.

LIVER



Metastases to the liver are common

Colorectal cancers commonly metastasize to the liver

Long-term survival is possible after metastatectomy.

Metastasectomy remains the gold standard for resectable liver metastases

Many patients are not candidates for surgical resection

Non-invasive techniques such as liver SBRT is am option.

SBRT is a recognized tool for ablation of liver metastases.

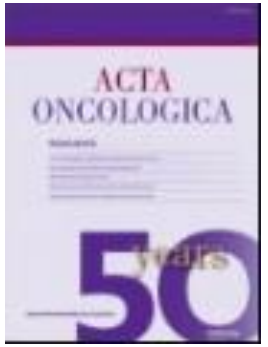
SBRT is an option for unresectable disease and for medically inoperable patients

Phase II study on stereotactic body radiotherapy of colorectal metastases

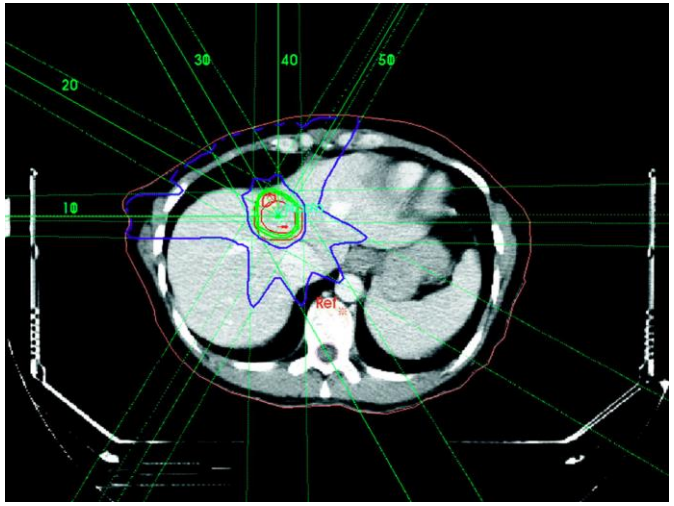
2009

Morten Hoyer ✉, Henrik Roed, Anders Traberg Hansen, Lars Ohlhuis, Jorgen Petersen, Hanne Nellemann, ...show all

Pages 823-830 | Received 15 Jun 2006, Published online: 08 Jul 2009

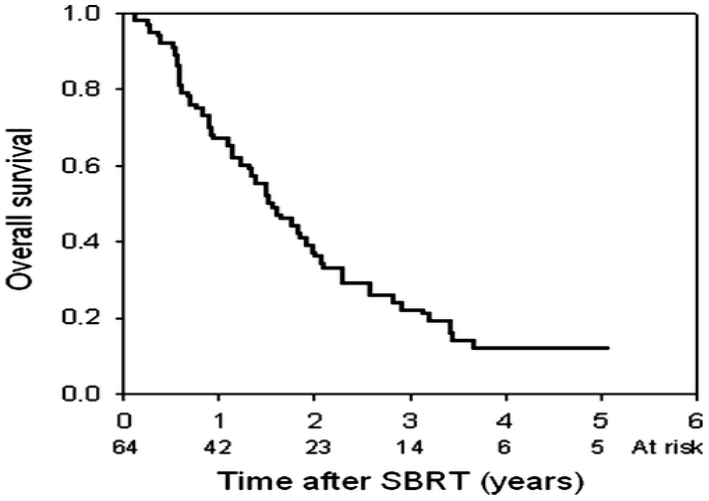


- 64 patients, 1999 - 2003
- 1-6 metastases (maximum diameter of the largest tumor <6 cm)
- Radical resection of the primary tumor & metastases had to be determined to be inoperable
- 141 metastases were treated (Liver mets 44)
- Dose: 15 Gy x 3fr within 5-8 days
- Tumor specific local control 79% at 2 years



Conclusion:

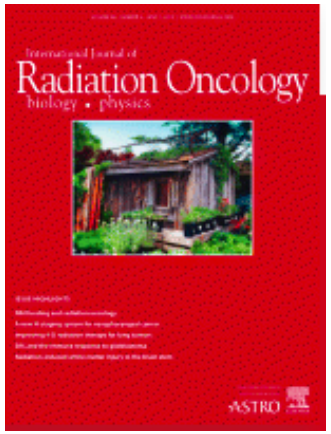
- Promising local control for patients with CRC metastases primarily in the liver and lungs treated with SBRT
- Re-treatment of new lesions was possible and in general, the toxicity of the treatment was moderate



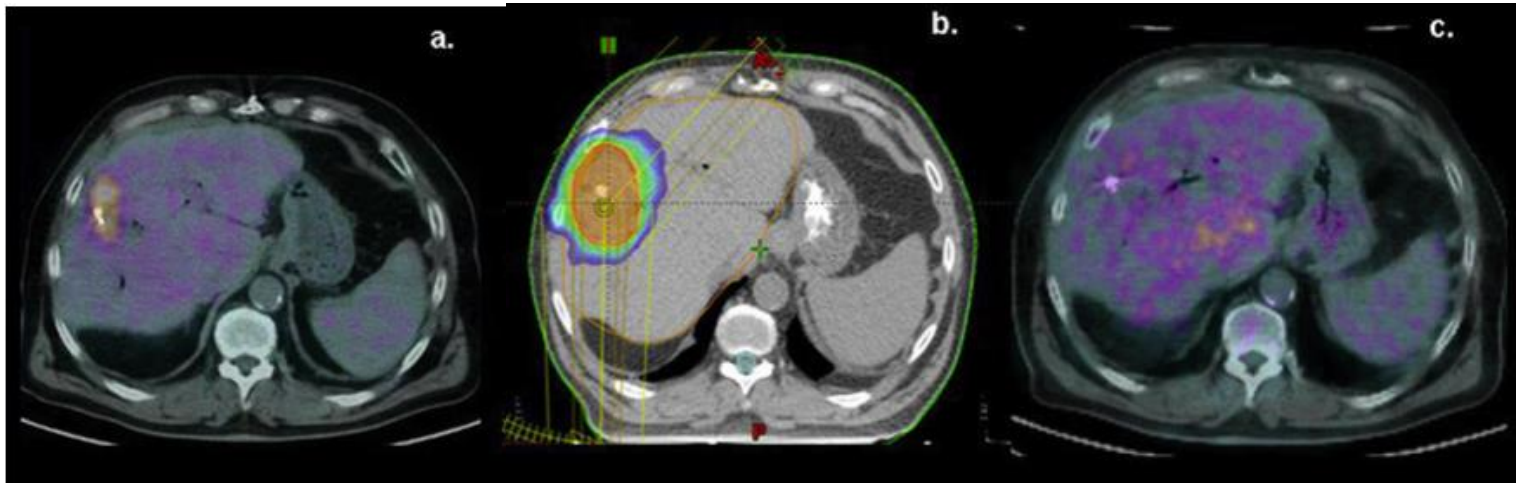
Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A Preliminary Report From a Phase 2 Trial

2013

Marta Scorsetti MD *, Stefano Arcangeli MD *, Angelo Tozzi MD *, Tiziana Comito MD *, Filippo Alongi MD *



- **61 patients were enrolled with 76 liver metastases**
- **1-3 unresectable liver metastases with max diameter < 6 cm**
- **34% of patients had stable extrahepatic disease**
- **Dose: 75 Gy in 3 fractions**
- **Primary end-point: In-field local control.**
- **Secondary end-points: Toxicity and survival**
- **1-year in-field LC was 94%**



Conclusion:

SBRT for unresectable liver metastases is an effective, safe, therapeutic option, with excellent local control and a low t/t toxicity.

DOSE:

- 15 Gy x 3 fractions given in 5-8 days
- 30-37.5 Gy in 3 fractions
- 36 Gy to 60 Gy in 3 fractions
- 75 Gy in 3 fractions

Stereotactic Body Radiotherapy for Colorectal Liver Metastases

Daniel T. Chang, MD[1]; Anand Swaminath, MD[2]; Margaret Kozak, BA[1]; Julie Weintraub, MD[3]; Albert C. Koong, MD, PhD[1];

Pooled analysis
65 patients with 102 lesions treated from August 2003 to May 2009
1 - 4 lesions & Received 1 - 6 fractions of SBRT
Radiological imaging 3 months post-treatment

Conclusion:

- **3-fraction regimen of SBRT of prescription dose of 48 Gy should be considered, if normal tissue constraints allow**
- **Patients without active extrahepatic disease have better OS than patients with active extrahepatic disease**

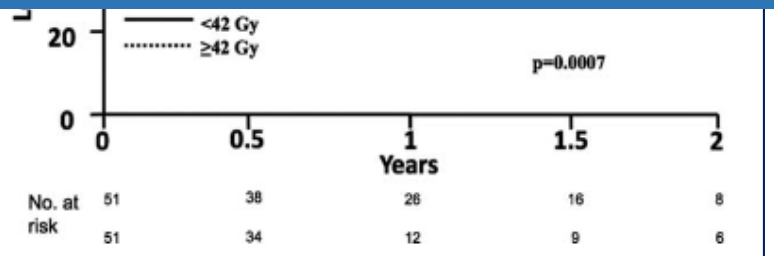


Figure 1. Actuarial local control by lesion stratified by total dose delivered is shown. Gy = gray.

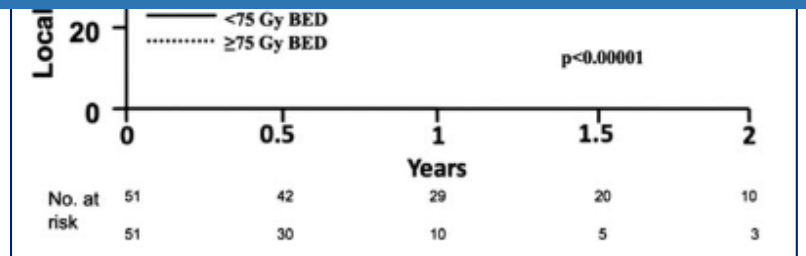
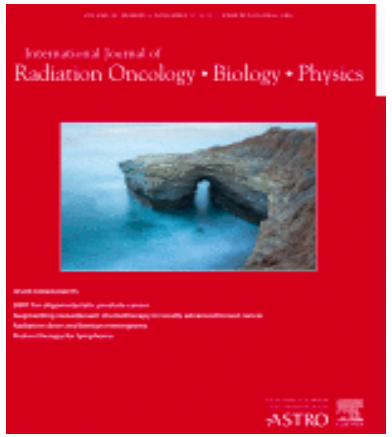


Figure 2. Actuarial local control by lesion stratified by biologically effective dose (BED) delivered is shown.

Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases From Colorectal Cancer

2017

Ji Hyeon Joo MD *, Jin-hong Park MD, PhD *, Jin Cheon Kim MD, PhD †, Chang Sik Yu MD, PhD †, Seok-Byung Lim



- 70 patients with 103 colorectal liver metastases
- 45 to 60 Gy in 3 to 4 fractions

Conclusion:

- **Longer local control can be expected if higher doses are used**
- **SBRT of liver metastases derived from colorectal cancer offers a locally effective treatment without significant complications**

Group 1	</= 80 Gy	52
Group 2	100 - 112	83
Group 3	>/= 132	89

Non colorectal Liver metastases

Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control

2011

Michelle A Stinauer, Brian D Kavanagh, Tracey E Schefter, Rene Gonzalez, Thomas Flaig, Karl Lewis,

- RCC – 13 patients, 25 lesions
- Melanoma – 17 patients, 28 lesions
- LC defined pathologically by negative biopsy or radiographically by lack of tumor

Conclusion:

An aggressive SBRT regimen with SFED ≥ 45 Gy is effective for controlling metastatic melanoma and RCC

model

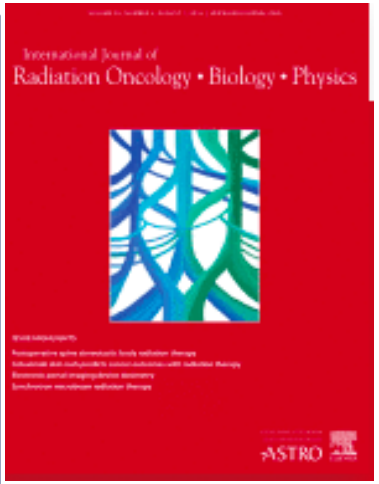
- The actuarial rate of LC at 24 months was 100% for SFED ≥45 Gy v 54% for SFED <45 Gy.
- TCP modeling indicated that to achieve ≥90% 2 yr LC in a 3 fraction regimen, a prescription dose of at least 48 Gy is required

Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy

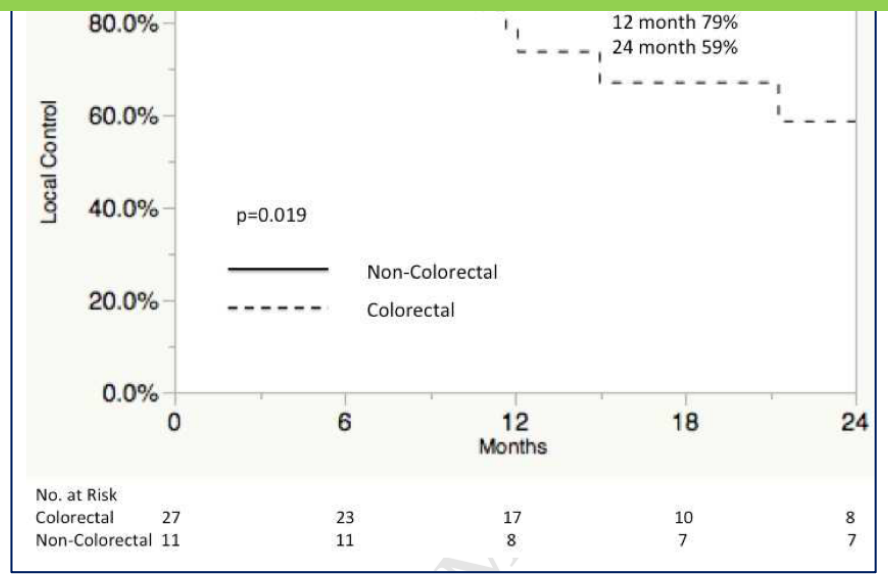
2015

Partially presented in oral form at the 57th Annual Meeting of the American Society for Radiation Oncology, San Antonio, Texas, Oct 21, 2015.

Kamran A. Ahmed MD *, Jimmy J. Caudell MD, PhD *, Ghassan El-Haddad MD †, Anders E. Berglund PhD ‡, Eric A.

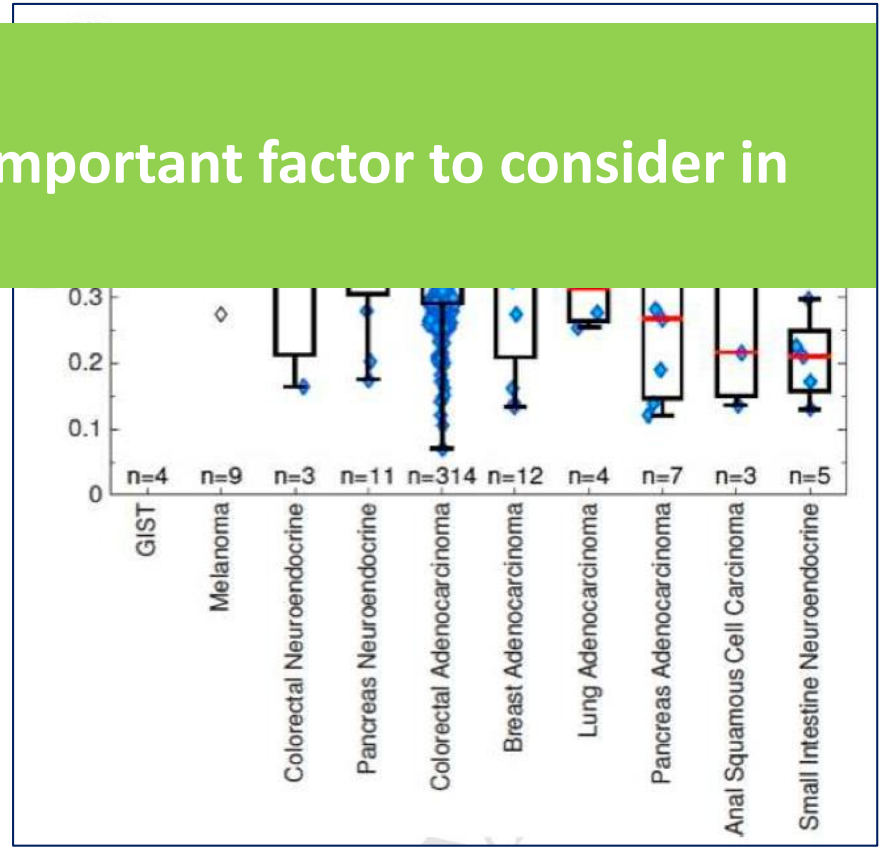


- **Conclusion:**
- **This study suggests that primary histology may be an important factor to consider in SBRT radiation dose selection**



Dose

50-60Gy / 5 fr



FUTURE DIRECTIONS

Immunotherapy with SBRT

- Anti-PD-1/PD-L1 therapy
- Anti-CTLA-4
- IFN- Gamma

Radiation therapy to convert cancers

↓

Into an “in situ tumor vaccine” by inducing release of antigens during cancer cell death

↓

promoting proinflammatory signals within and out of the radiation field

↓

creating positive microenvironmental changes

↓

Stimulate the innate immune system to activate tumor specific T cells and enhance cancer infiltrations

- This augments the effectiveness of Immunotherapy

ASCO
Journal of Clinical Oncology®

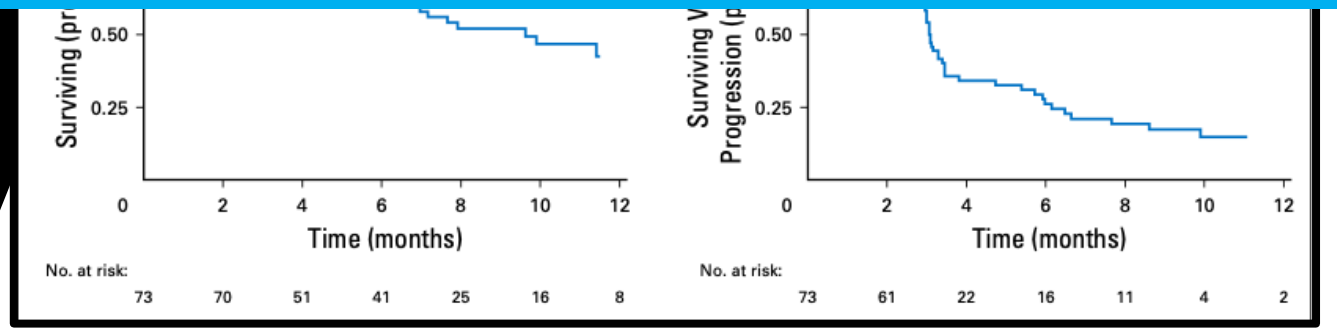
Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors

Jason J. Luke, Jeffrey M. Lemons, Theodore G. Karrison, Sean P. Pitroda, James M. Melotek, Yuanyuan Zha, ...

- 79 patients
- 3 patients only received SBRT
- Patients included in the analysis were
-
-
  SBRT to two metastases
- Median follow-up for toxicity was 5.5 months (interquartile range, 3.3 to 8.1 months)
- Median OS - 9.6 months & Median PFS - 3.1 months

Conclusion:

Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity.



Thank You