Decennale di

# HIGHLIGHTS in RADIOTERAPIA

*Update degli Studi Practice Changing 2024*

*Undicesima Edizione*

*In memoria di Renzo Corvò*

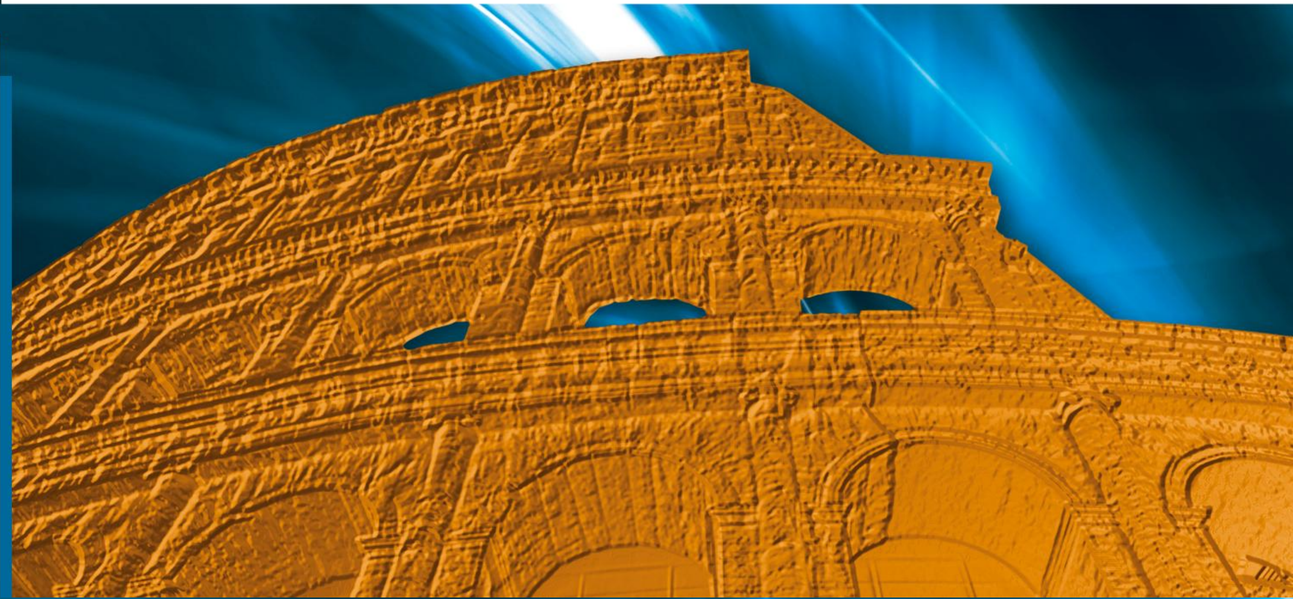
**ROMA**

30-31 gennaio 2025

Starhotels Metropole

# New evidence and practice changing **treatments in oligometastatic tumors**

*Prof.ssa Marta Scorsetti*



# Agenda

- **Oligometastatic disease: definitions and rationale**
- Oligometastatic disease in lower GI cancer
- Oligometastatic disease in upper GI cancer
- Oligometastatic disease in renal cancer
- Conclusions

# Oligometastatic disease: First definition

**EDITORIAL**

## Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding

An oligometastatic state is an “**intermediate state between purely localized lesions and those widely metastatic**”. The state was expounded to be “**amenable to a curative therapeutic strategy**” and “**amenable to localized therapy**”.

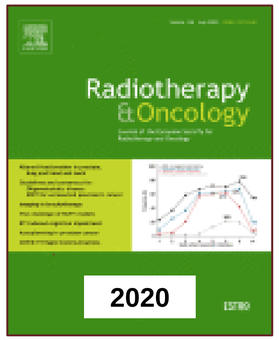
*Hellman S, Weichselbaum RR. JCO 1995*

# Oligometastatic disease: New definition

Consensus

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

Yolande Lievens [a,*], Matthias Guckenberger [b], Daniel Gomez [c], Morten Hoyer [d], Puneeth Iyengar [e], Isabelle Kindts [f], Alejandra Méndez Romero [g], Daan Nevens [h], David Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]





## 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, Daniel H Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost*

# Oligometastatic disease: New definition

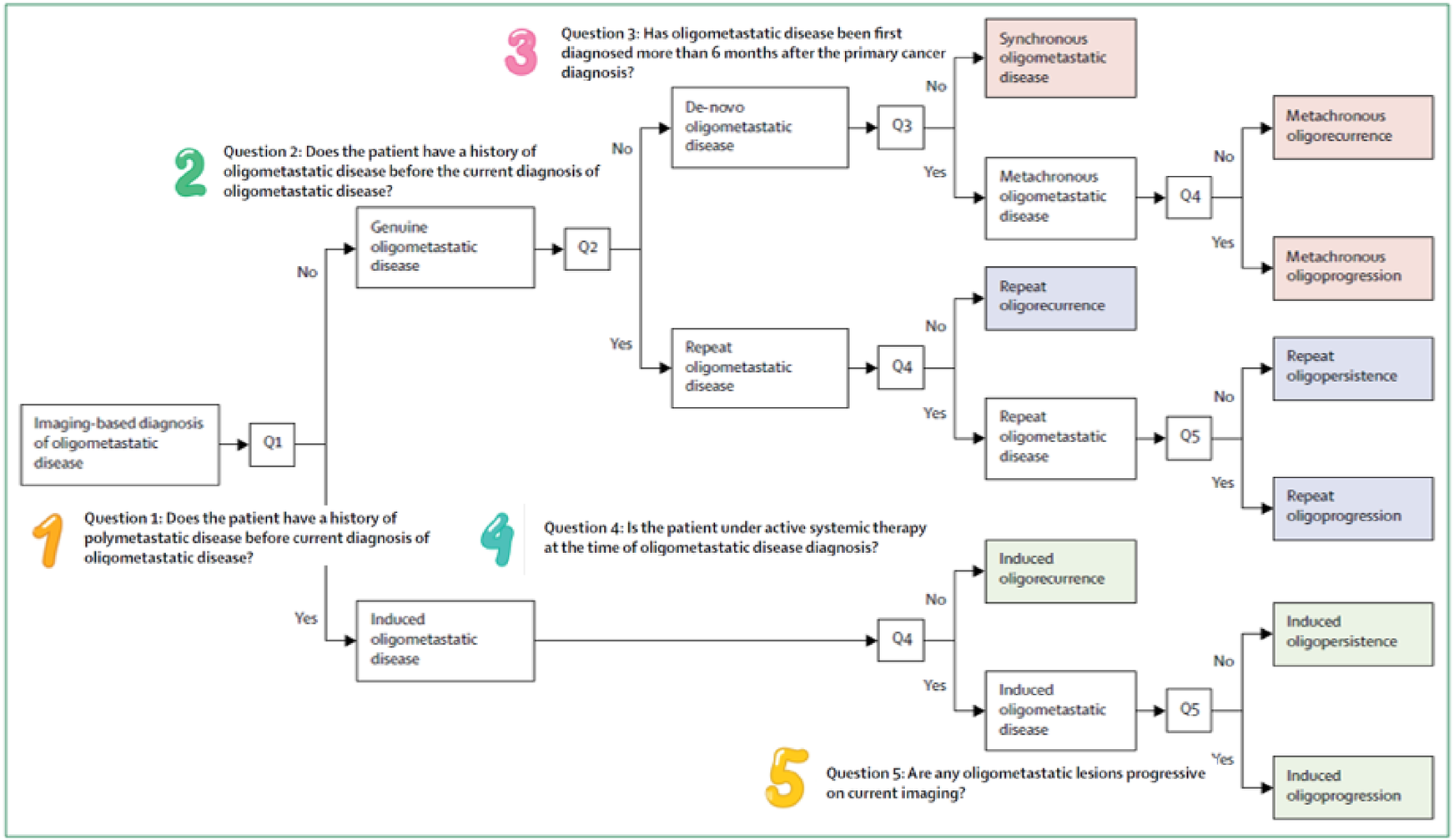



*Figure 3*: Decision tree for classification of oligometastatic disease

5 questions, several settings

Oligometastases are a **heterogeneous scenario**

*Guckenberger M et al. Lancet Oncol 2020*

# Oligometastatic disease: Rationale

» **Increase local control** to prevent symptoms and **maintain QoL**

» Ablate all visible metastases to **prolong PFS**

» Reduce tumor burden to **prolong OS**


» Ablate resistant clones to **prolong systemic therapy efficacy**

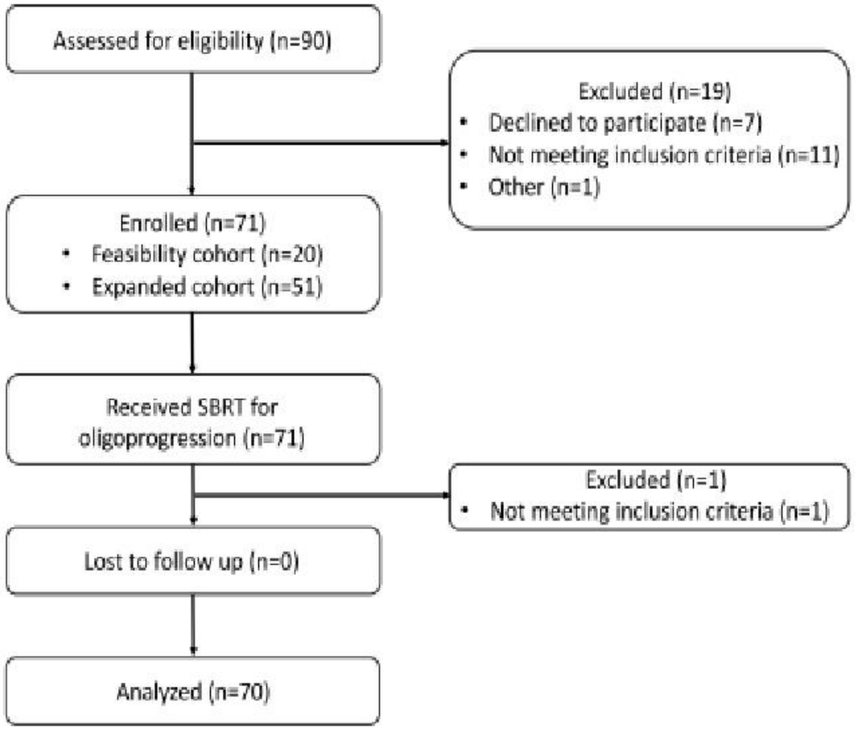
» **Delay** further **disease progression** to **delay** the need to **start systemic therapy**

» **Synergize** with systemic therapies to **improve outcomes**

# Oligometastatic disease: RADIANT

**The Role of Stereotactic Body Radiotherapy in Oligoprogressive Malignant Disease (RADIANT): Oncologic Outcomes From a Phase 2 Nonrandomized Controlled Trial**

Rachel M. Glicksman, MD, MSc,[*] Srinivas Raman, MD,[*,†] Xiang Y. Ye, MSc,[†] Philippe L. Bedard, MD,[§,‖] Scott Bratman, MD,[*,†] Eric Chen, MD,[§,‖] Peter Chung, MBChB,[*,†] Laura A. Dawson, MD,[*,†] Andrew Hope, MD,[*,†] Ali Hosni, MBBCh,[*,†] Joanna Javor, CSRT,[*,¶] Patricia Lindsay, PhD,[*,#] Ciara O'Brien, MD,[**] Rebecca Wong, MD,[*,†] Aisling Barry, MD,[††] and Joelle Helou, MD[‡‡]


Single-center phase 2 study
70 patients with genitourinary, breast, and GI cancers
Systemic therapy for ≥3 months, then oligoprogression in ≤5 sites
SBRT to all OP disease maintaining the same therapy

**Primary endpoint**: cumulative incidence of change in ST
**Secondary endpoints**: PFS, OS and toxicity

# Oligometastatic disease: RADIANT

At 1 year, **change in ST occurred in 47%** (non statistically different between types):

- Genitourinary 45%
- Breast 41%
- Gastrointestinal 60%

**1y-PFS was 32%** with **median PFS of 4.7 months** (statistically different between types):

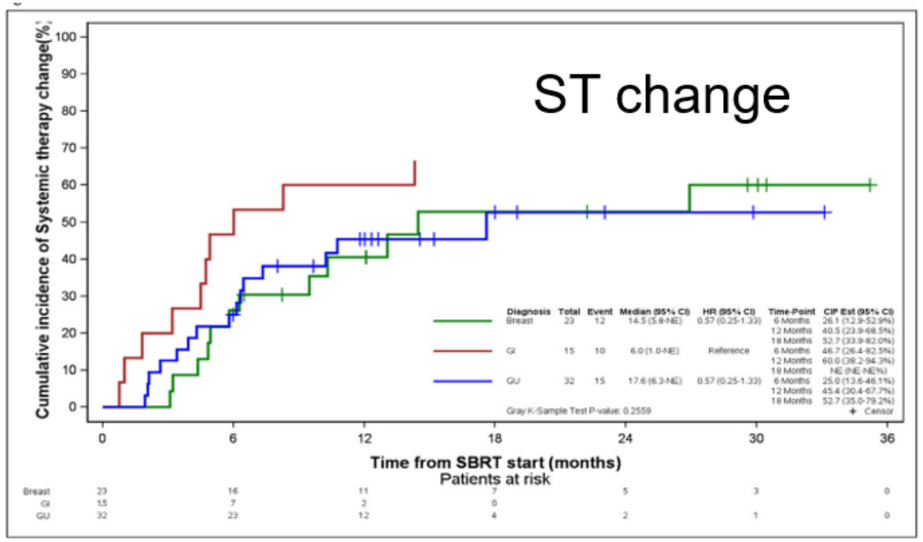
- Genitourinary 4.8 months
- Breast 6.5 months
- Gastrointestinal 3.2 months

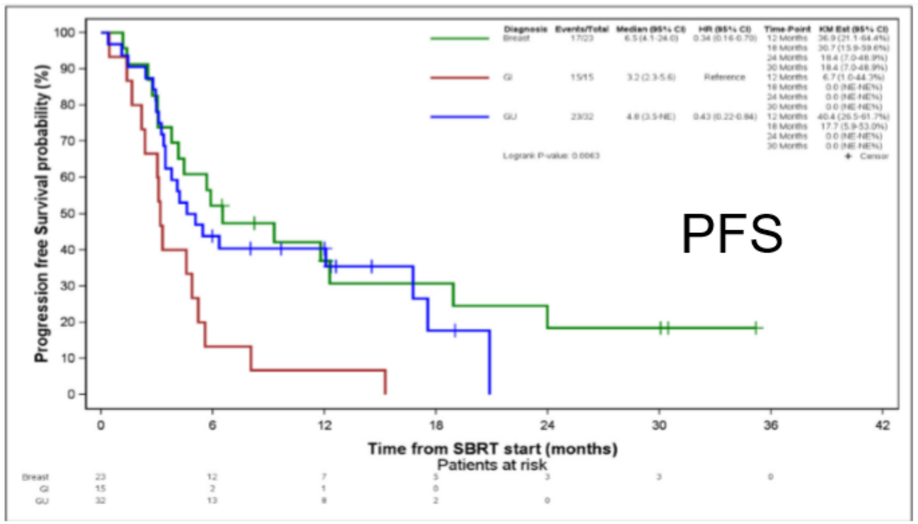
**1y-OS was 75%** (statistically different between types):

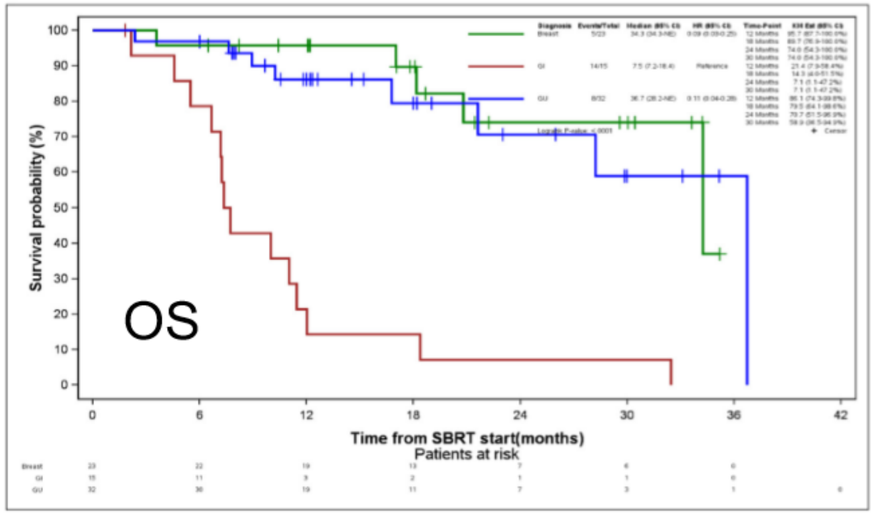
- Genitourinary 86%
- Breast 96%
- Gastrointestinal 22%

1.2% ≥G2 toxicities (No G4 or G5)
No difference in Quality of Life

# Oligometastatic disease: RADIANT




**Breast**
**Gastrointestinal**
**Genitourinary**

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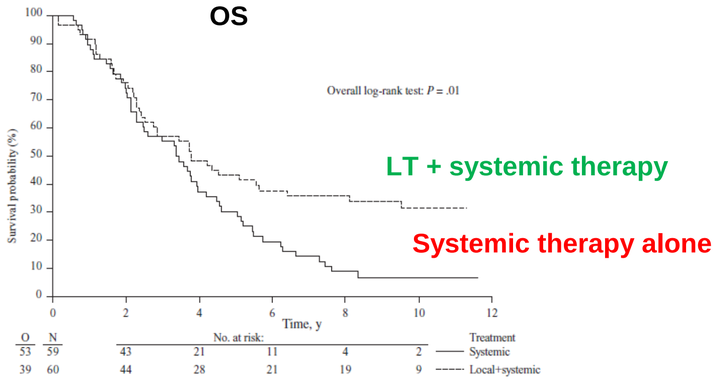
- Conclusions

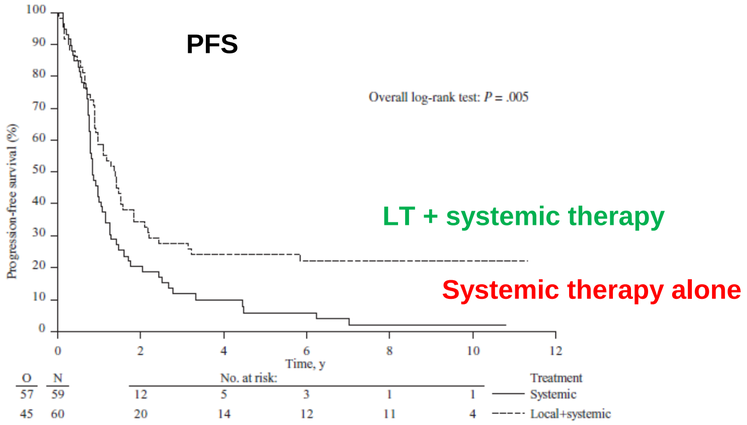
# COLORECTAL CANCER

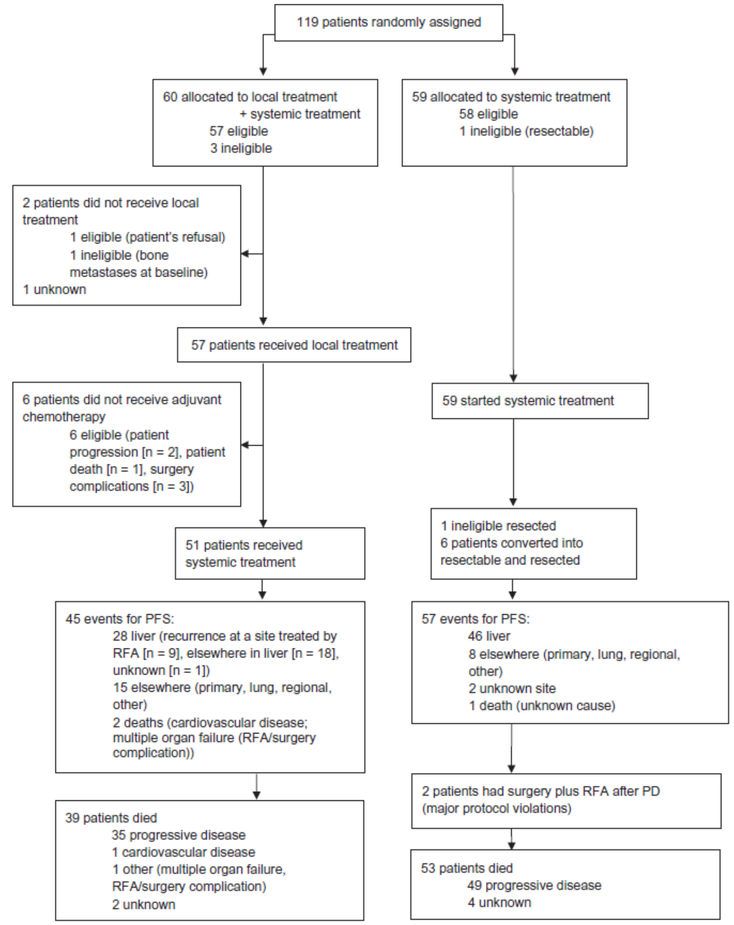
# Liver Oligomets from CRC

## Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial


Randomized phase II trial
119 patients with unresectable CRC liver mets
Patients randomized between CT alone vs CT + RFA +/- resection




8-year **OS** **35.9%** vs **8.9%**

Median **PFS** **16.8 mo** vs **9.9 mo**

**Both oligopersitent and oligoprogressive lesions**

# Lung Oligomets from CRC

cancers 2024 MDPI

*Article*

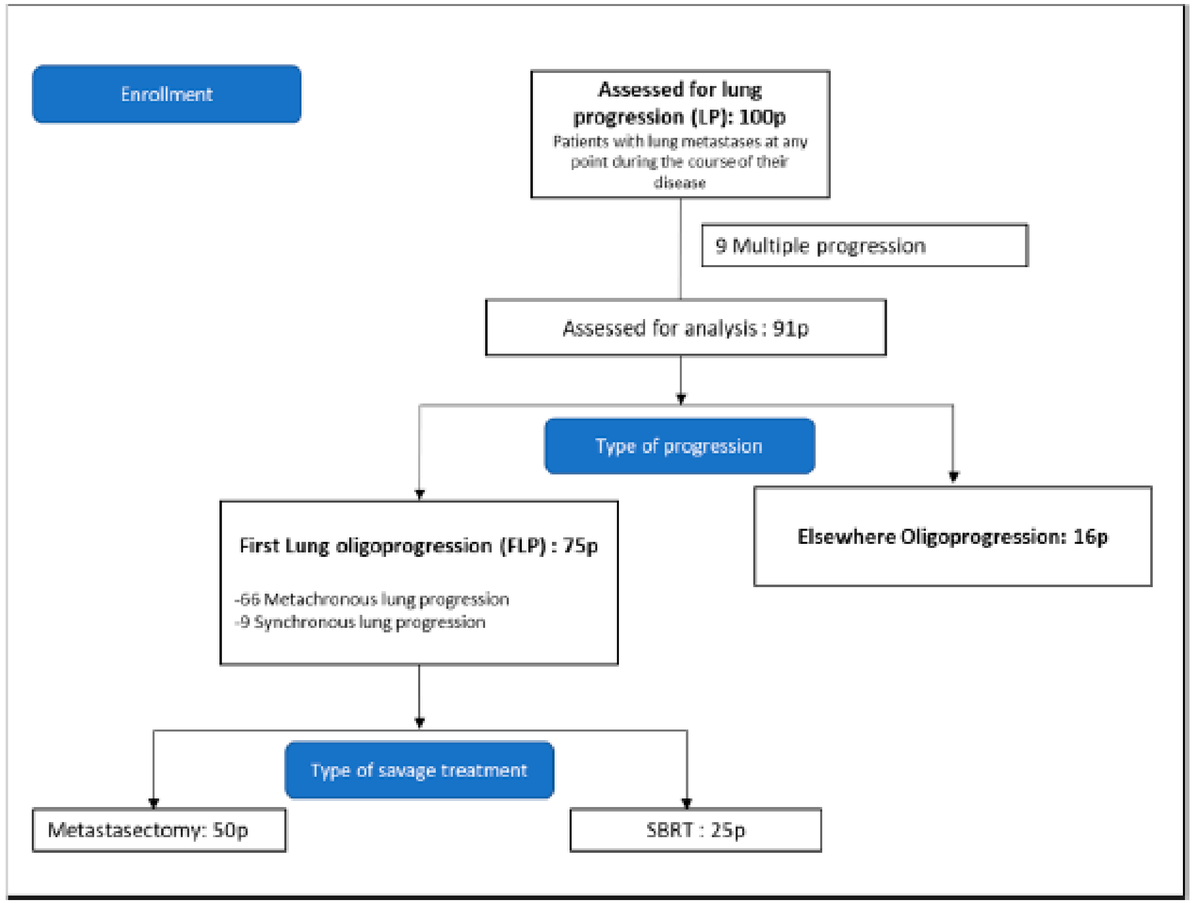
## Stereotactic Body Radiotherapy versus Surgery for Lung Metastases from Colorectal Cancer: Single-Institution Results

Nagore Garcia-Exposito [1], Ricard Ramos [2], Valentin Navarro-Perez [3], Kevin Molina [4], Maria Dolores Arnaiz [1], Susana Padrones [5], Jose Carlos Ruffinelli [4], Cristina Santos [4], Ferran Guedea [1] and Arturo Navarro-Martin [1,*]

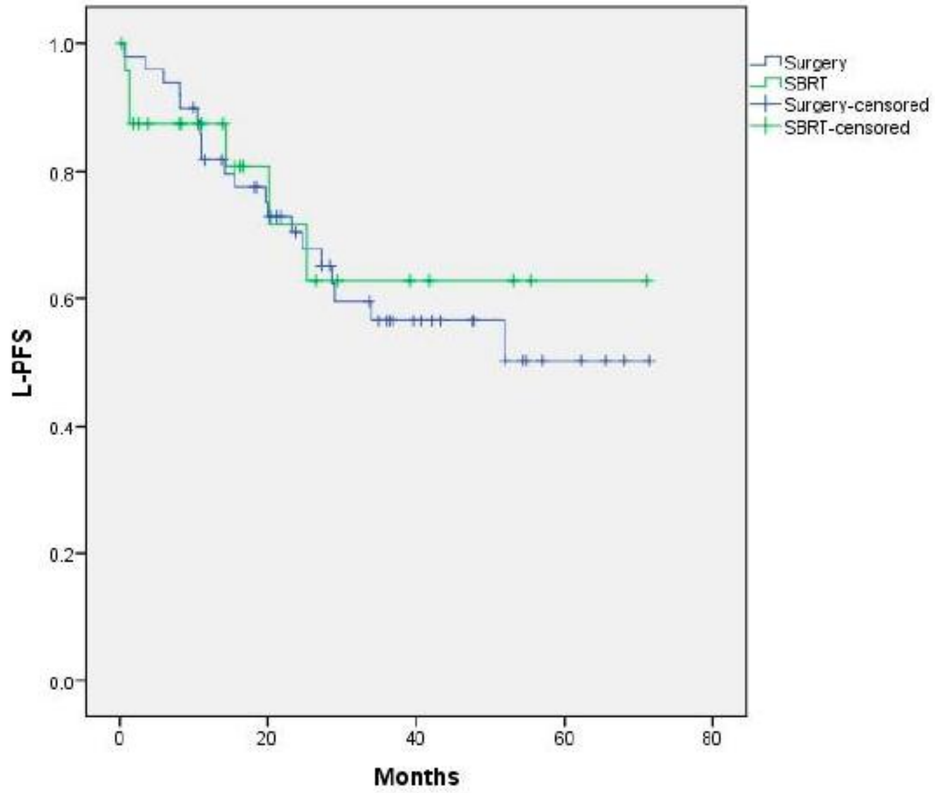
**Surgery group:**
- 1-year L-PFS: 85%
- 2-years L-PFS: 70%

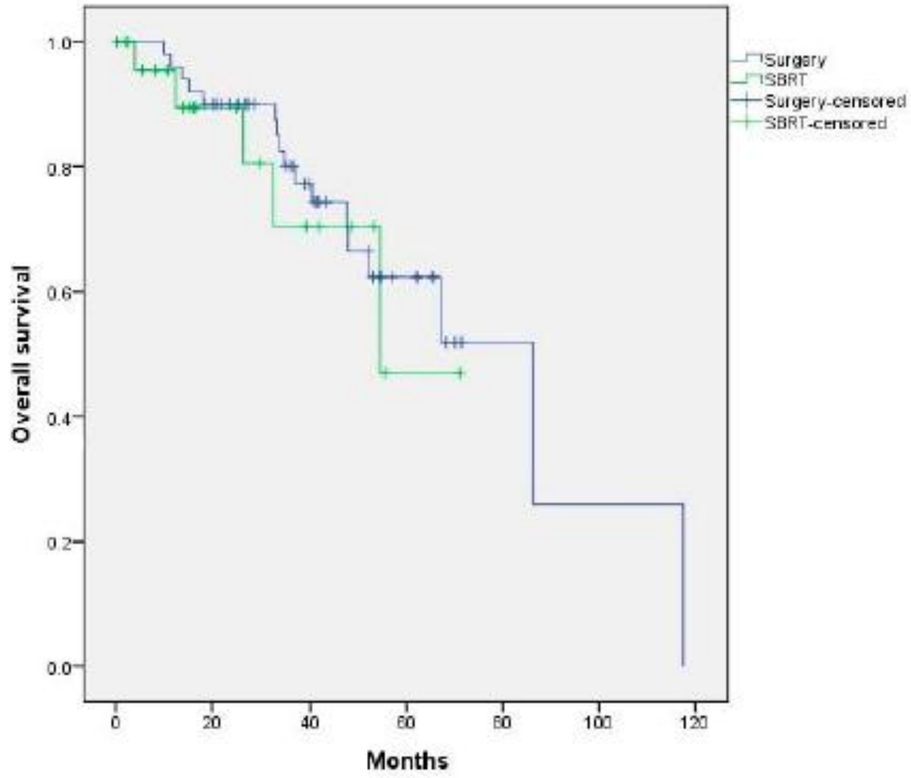
**SBRT group:**
- 1-year L-PFS: 87%
- 2-years L-PFS: 71%

Median BED10: 122.25 Gy



# Lung Oligomets from CRC




Median OS 86 months → **No significant differences in OS between the two groups**

# Liver Oligometastasis from different tumors

**Stereotactic Body Radiation therapy for Liver Metastases: Systematic Review and Meta-Analysis With International Stereotactic Radiosurgery Society (ISRS) Practice Guidelines**

Ciro Franzese,[a,b,*] Alexander V. Louie,[c] Rupesh Kotecha,[d,e] Zhenwei Zhang,[f] Matthias Guckenberger,[g] Mi-Sook Kim,[h] Alison C. Tree,[i] Ben J. Slotman,[j] Arjun Sahgal,[c] and Marta Scorsetti[a,b]

2024

practical radiation oncology
pro
www.practicalradonc.org

Literature review
33 studies with a total of 3101 patients and 4437 liver mets

Pooled LC rates at 1, 2, and 3 years: 85%, 75%, and 68%
Pooled OS rates at 1, 2, and 3 years: 79%, 54%, and 37%

≥G3 toxicities in only 3% of patients

| PRACTICAL RECOMMENDATIONS | |
|---|---|
| **Patient Selection** | |
| Primary Tumor Histology | Consider SBRT as a treatment option for patients with liver metastases arising from various primary tumors, including colorectal cancer. |
| Disease Characteristic | Give priority to patients with oligometastatic disease, particularly those with 3 or fewer liver metastases, and selected patients with 4 or 5 lesions. Consider SBRT for patients with metastases smaller than 3 cm. Recommend SBRT for larger lesions measuring 3 cm or more, as they can be effectively treated with long-term control. Metastases in other organs can be present if amenable to local treatment or in control. |
| Disease Location | Consider SBRT also for anatomically difficult liver locations (eg, close proximity to major vessels, biliary tracts, diaphragm) not easily reachable with other local approaches. |
| Patient Condition | Evaluate patients' overall health and performance status to assess their suitability for SBRT. Consider SBRT as a preferential option for patients with comorbidities, patients with failure after previous liver-directed treatment, or patients with unresectable lesions. |
| **Treatment** | |
| Technological equipment | Modern radiation technologies are recommended, and they include IGRT with gantry-based linac, robotic-arm linac, and MRI-based linac. |
| Motion Management | Implement motion management strategies to account for respiratory motion during SBRT, including 4D simulation CT or other specific techniques such as active breathing control. |
| Dose and Fractionation | Tailor dose fractionation to each patient's specific condition. Consider delivering radiation in 1 to 6 fractions and a BED of >100 Gy when feasible. Higher dose of radiation might be associated with improved local control for radioresistant tumors, including colorectal cancer. |
| Toxicity Prevention | Implement strategies to minimize grade 3-4 toxicities, which include motion management, accurate patient immobilization, precise identification of the targets, and respect of dose constraints. |

*Abbreviations:* BED = biologically effective dose; CT = computed tomography; IGRT = image guided radiation therapy; linac = linear accelerator; MRI = magnetic resonance imaging; SBRT = stereotactic body radiation therapy.

Not yet recruiting

**Systemic Therapy in Combination With Stereotactic Radiotherapy in Patients With Metastatic Colorectal Cancer up to 10 Metastatic Sites (SIRIUS)**

**ClinicalTrials.gov ID** NCT05375708

**Sponsor** UMC Utrecht

**Information provided by** Guus Bol, UMC Utrecht (Responsible Party)

**Last Update Posted** 2023-05-11

Recruiting

**RESOLUTE Trial Aims to Investigate the Value of Adding Local Ablative Treatment to Standard Systemic Treatment for Unresectable Oligometastatic Colorectal Cancer (RESOLUTE)**

**ClinicalTrials.gov ID** NCT05862051

**Sponsor** Australasian Gastro-Intestinal Trials Group

**Information provided by** Australasian Gastro-Intestinal Trials Group (Responsible Party)

**Last Update Posted** 2023-10-17

Recruiting

**Low and Intermediate Risk OliGometastatic ColoREctal CancEr PatieNts Treated with Stereotactic ABlative Radiotherapy (GREENLaIT-SABR)**

**ClinicalTrials.gov ID** NCT06310564

**Sponsor** IRCCS Sacro Cuore Don Calabria di Negrar

**Information provided by** IRCCS Sacro Cuore Don Calabria di Negrar (Responsible Party)

**Last Update Posted** 2024-12-02

# Agenda

- Oligometastatic disease: definitions and rationale
- Oligometastatic disease in lower GI cancer
- **Oligometastatic disease in upper GI cancer**
- Oligometastatic disease in renal cancer
- Conclusions

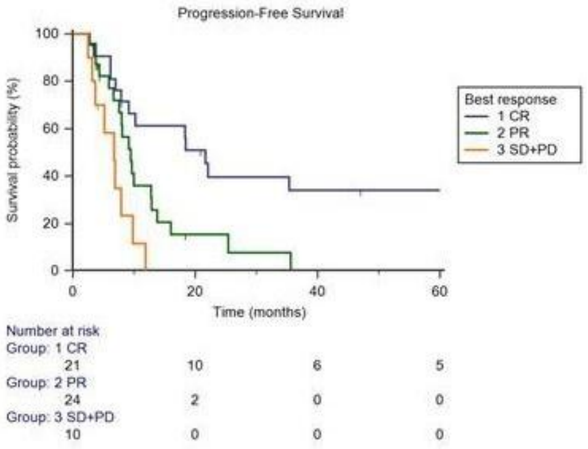
# ESOPHAGEAL CANCER

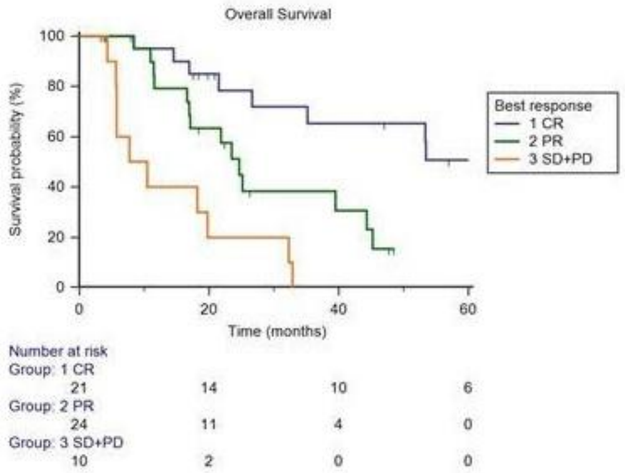
# Oligometastatic disease: Esophageal Cancer

**Stereotactic radiation therapy for oligometastatic esophagogastric adenocarcinoma: outcome and prognostic factors**

[1]DAVIDE FRANCESCHINI, MD, [1]MARIA AUSILIA TERIACA, MD, [1,2]LUCIANA DI CRISTINA, MD, [1,2]VERONICA VERNIER, MD, [1,2]LORENZO LO FARO, MD, [1,2]CIRO FRANZESE, MD, [1]TIZIANA COMITO, MD, [1]ELENA CLERICI, MD, [1]LUISA BELLU, MD, [1]LUCA DOMINICI, MD, [1]RUGGERO SPOTO, MD, [1]MARIA MASSARO, MD, [1]PIERA NAVARRIA, MD, and [1,2]MARTA SCORSETTI, FP


Retrospective study
55 patients, 80 lesions (1-3 lesions per patient)
Patients treated with SBRT between 2013 – 2021
Median follow-up 20 months




**Median LC not reached**
1 year LC: 92%
3 years LC: 78%

**Median PFS 9.6 mo**
1 year PFS: 40
3 years PFS: 15%

**Median OS 26.6 mo**
1 year OS: 78%
3 years OS: 40%.

**Median time to systemic therapy (TTS) 9 mo**

**Median time to polymetastatic progression (TTPD) 8 mo**
1 year TTPD: 44%
3 years TTPD: 52%

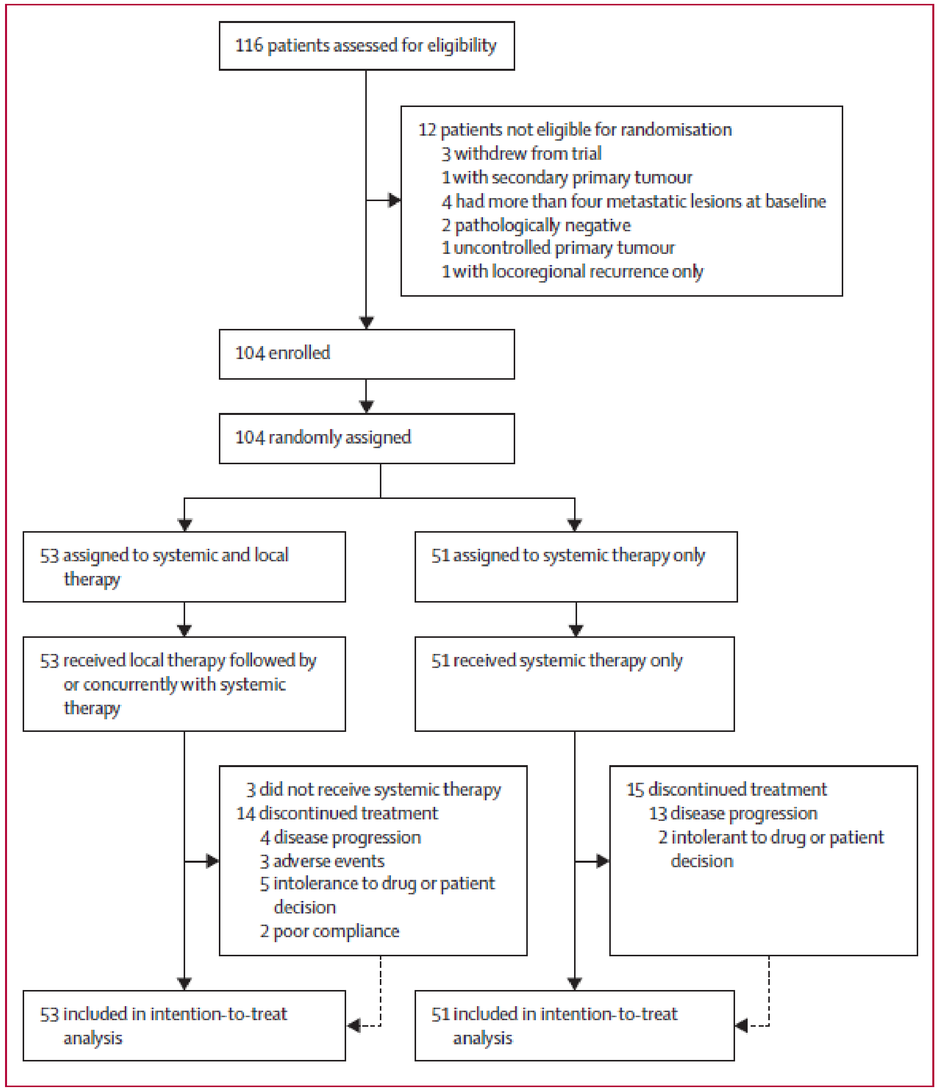
# Oligometastatic disease: Esophageal Cancer

Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial

Qi Liu, MD [a,b,c] · Prof Junqiang Chen, MD [d] · Yu Lin, MD [d] · Jinjun Ye, MD [e] · Prof Wenbin Shen, PhD [f] · Honglei Luo, MD [g] · Prof Baosheng Li, MD [h] · Wei Huang, MD [h] · Shihong Wei, MD [i] · Prof Jibin Song, PhD [j] · Yaohui Wang, PhD [b,k] · Huanjun Yang, MD [a,b,c] · Songtao Lai, PhD [a,b,c] · Hongcheng Zhu, MD [a,b,c] · Dashan Ai, MD [a,b,c] · Yun Chen, MD [a,b,c] · Jiaying Deng, MD [a,b,c] · Shengnan Hao, PhD [a,b,c] · Prof Kuaile Zhao, MD [a,b,c] Show less

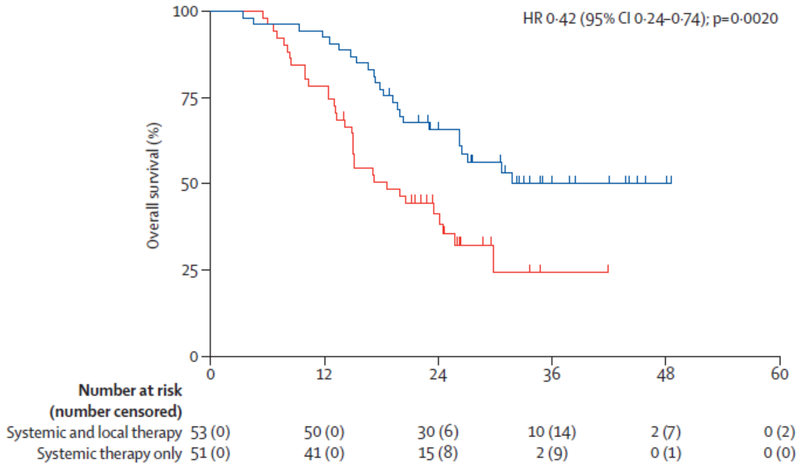

Phase II randomized trial
104 Patients with synchronous oligometastasis (18%) or oligorecurrence (82%)
Randomized in a 1:1 ratio to either CT +/- local approach to all disease sites

**SBRT in 83% of patients**

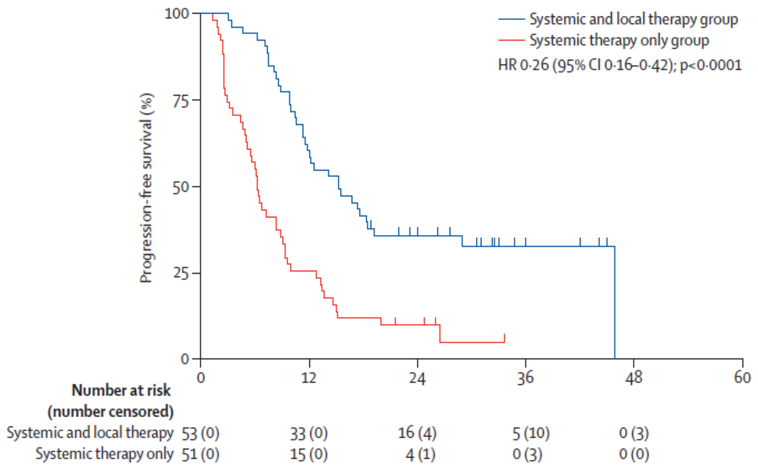


# Oligometastatic disease: Esophageal Cancer

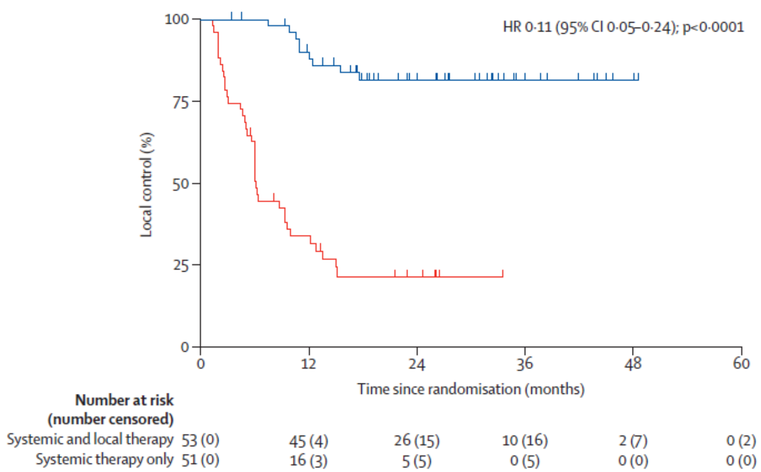
## OS




## PFS




## LC




**Results:**

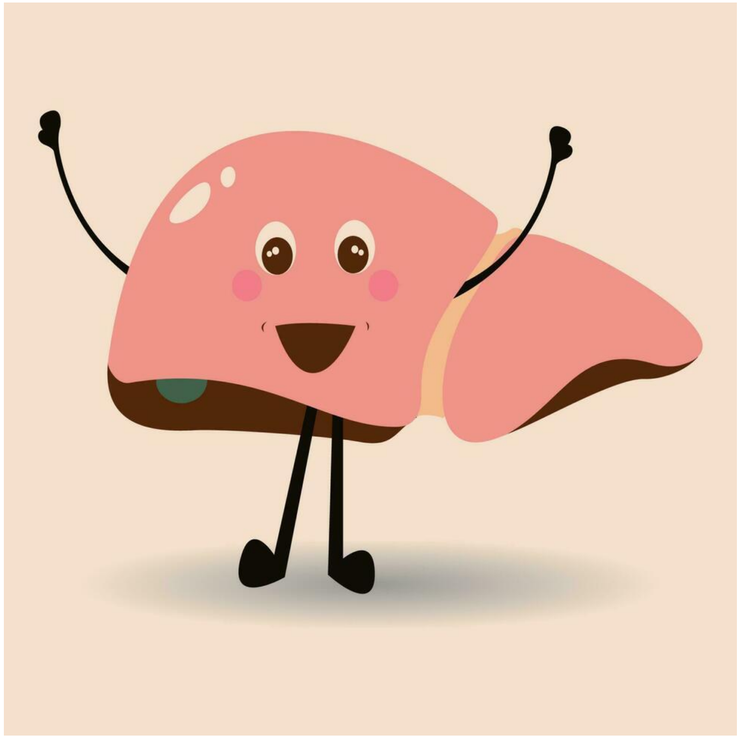
- Median OS **not reached** in the LCT group *vs.* **18.6 months** in the systemic therapy arm, HR 0.42 (95% CI: 0.24–0.74; P=0.0020).
- Median PFS **15.3 months** in the LCT arm *vs* **6.4 months** in the systemic therapy only group (stratified HR 0.26; P<0.0001).
- 2-year PFS was **60.4%** in the LCT arm *vs.* **9%** in the systemic arm

## Is metastasis-directed local therapy the new standard of care for patients with oligometastasic esophageal squamous cell carcinoma?—a perspective on the ESO-Shanghai 13 Trial

Neil B. Newman[1], Krishan R. Jethwa[2]

- The wide therapeutic ratio with significant clinical benefit and limited morbidity does **support LCT as a new option** for clinicians to treat patients with limited oligometastatic ESCC.
- Questions remain regarding generalizability and future work is needed to better identify **optimal candidates** for LCT.
- Future larger confirmatory trial trials with more nuanced secondary correlates (**biomarkers**, circulating tumor DNA, immune correlates) will certainly expand upon this important study by informing **patient selection**, guiding prognosis.
- Understanding of the unique **biology of metastases** and the likelihood of further metastatic spread could elucidate which patients may derive best benefit

# LIVER TUMORS



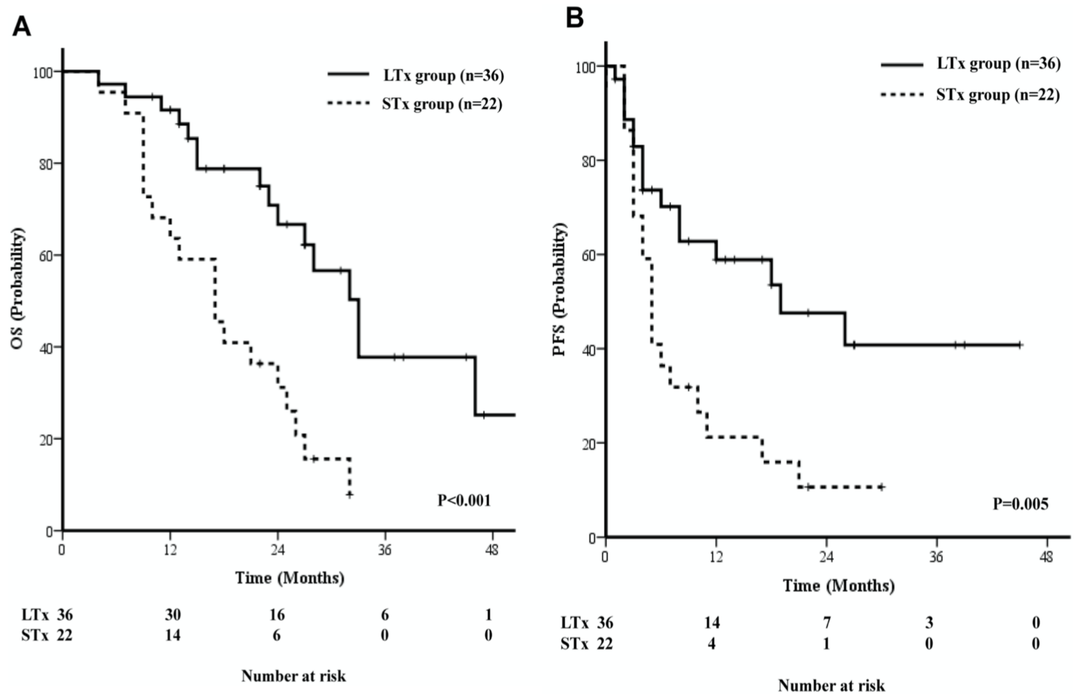
# Oligometastatic disease: HCC

## Efficacy of Local Therapy for Oligometastatic Hepatocellular Carcinoma: A Propensity Score Matched Analysis

Kangpyo Kim[1] | Tae Hyung Kim[1] | Tae Hyun Kim[2] | Jinsil Seong[1]

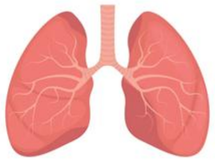

58 patients affected by HCC with 1-4 oligometastasis to the **lungs**
- 22 pts: systemic therapy alone (STx group)
- 36 pts: RT +/- systemic therapy (LTx group)

Propensity score matching analysis




2-year **OS rate**:
- LTx group: **66.6%** vs STx group: 31.2%, p<0.001

2-year PFS rate:
- LTx group: **47.0%** vs STx group: 10.6%, p=0.005



**AFP levels less than 400 ng/mL** and the **use of local therapy** were found to be significant **favorable prognostic factors**.

# Oligometastatic disease: HCC

## Stereotactic Ablative Radiotherapy for Oligometastatic Hepatocellular Carcinoma: A Multi-Institutional Retrospective Study (KROG 20-04)

cancers

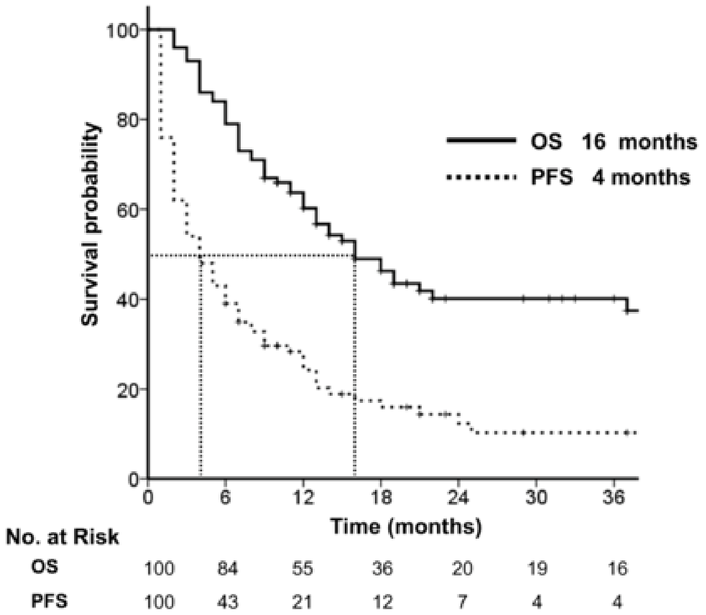
2022

Tae Hyung Kim [1,2], Taek-Keun Nam [3], Sang Min Yoon [4], Tae Hyun Kim [5], Young Min Choi [6] and Jinsil Seong [1,*]

100 patients with 121 metastasis, treated with SBRT with a fraction dose ≥6 Gy (30-60 Gy in 3-6 fractions)

71% of pts received systemic therapy

- Median OS: 16 months; 2-year OS rate: 40%
- Median PFS: 4 months
- No patients experienced acute treatment-related toxicities, only nine patients experienced G1 radiation pneumonitis

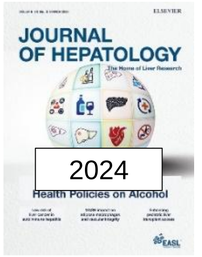



**Performance status** (p =0.040) and **Child-Pugh class** (*p*=0.018) were significant factors for OS

# Oligometastatic disease: HCC

## Efficacy of stereotactic ablative radiotherapy in patients with oligometastatic hepatocellular carcinoma: A phase II study

Seo Hee Choi[1], Byung min Lee[1,†], Jina Kim[1], Do Young Kim[2], Jinsil Seong[1,*]

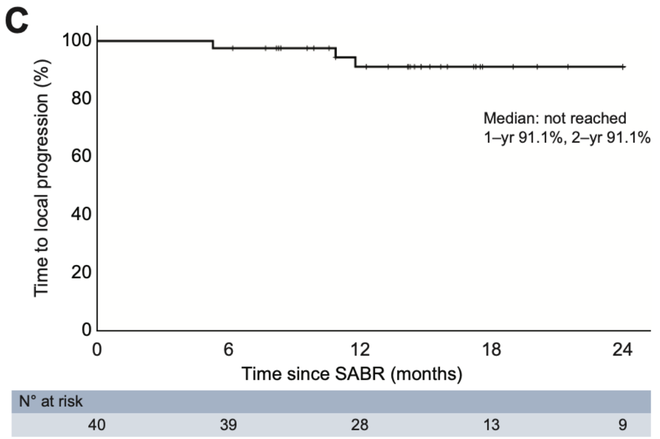



40 patients with 62 metastasis treated with SBRT.
Systemic therapy could be administered concomitant or sequentially.

| Location | Description | Dose |
|---|---|---|
| Lungs | Peripheral tumour<br>Central tumour | 48-60Gy/4<br>60Gy/8 |
| Bones | Vertebral body<br>Other bones | 24Gy/3<br>40-50Gy/5 |
| Lymph nodes | | 40Gy/5, 48Gy/8 |
| Adrenal glands | | 48-64Gy/8 |

- 2-year OS rate: 80%
- Median PFS: 5.3 months; 1- and 2-year PFS rates: 21.2% and 0%
- **2-year time to local progression: 91.1%, median not reached**
- 2-year objective response rate: 75.8%
- **2-years disease control rate: 98.4%**

- Acute toxicity in 10% of pts, 7.5% late toxicity, no G3+ toxicity.
- **All QOL scores remained stable**



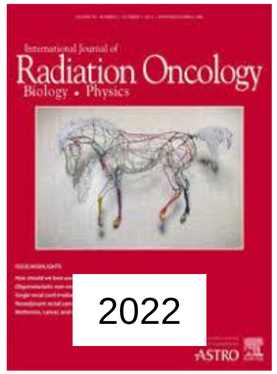

**Factors correlated to PFS**: shorter time to OMD from the controlled primary (p=0.039), age (p=0.002), Child-Pugh class (p = 0.004), and alpha-fetoprotein (p=0.019)

# PANCREATIC CANCER

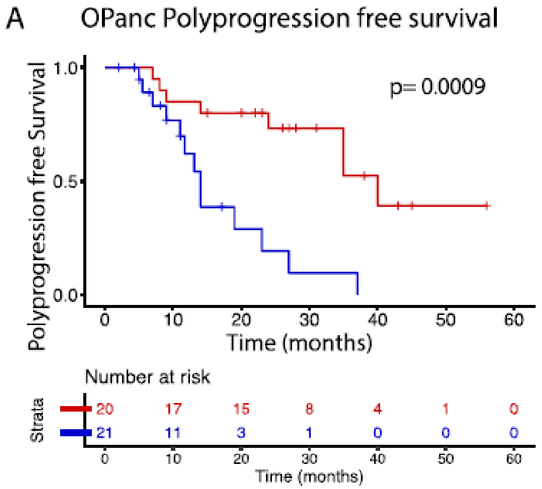
# Oligometastatic Pancreatic cancer: CT +/- SBRT

## Ablative Radiation Therapy in Oligometastatic Pancreatic Cancer to Delay Polyprogression, Limit Chemotherapy, and Improve Outcomes

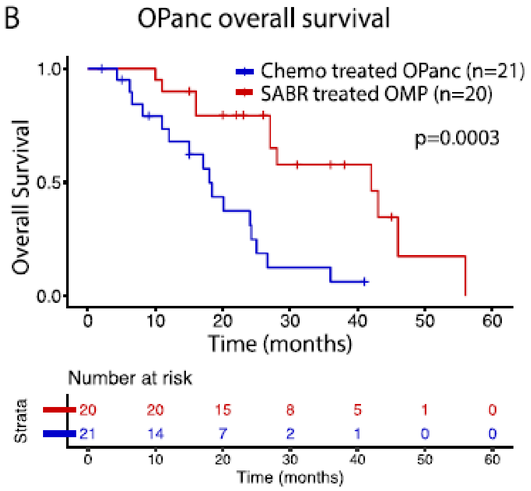
Ahmed M. Elamir, MD,* John D. Karalis, MD,† Nina Niu Sanford, MD,* Patricio M. Polanco, MD,† Michael R. Folkert, MD, PhD,‡ Matthew R. Porembka, MD,† Syed Ali Kazmi, MD,§ Ravikanth Maddipati, MD,§ Herbert J. Zeh, MD,† Robert D. Timmerman, MD,* Song Zhang, PhD,‖ Matteo Ligorio, MD, PhD,† Muhammad Shaalan Beg, MD,§ and Todd A. Aguilera, MD, PhD*




2022




Retrospective review
20 pts, 38 lesions (liver = 19, lung = 16 and bone = 3) vs 21 pts no SBRT
Synchronous or metachronous pancreatic oligomets (1 to 5)
SBRT to all active metastatic sites was performed
Results compared with a similar pool of patients who did not receive SBRT




Median polyprogression-free survival **40 mo** vs **14 mo** (HR = 0.2; 95% CI 0.07-0.54; P = .0009)
Overall survival **42 mo** vs **18 mo** (HR = 0.21; 95% CI 0.08-0.53; P = .0003)

# Oligometastatic Pancreatic cancer: ESMO

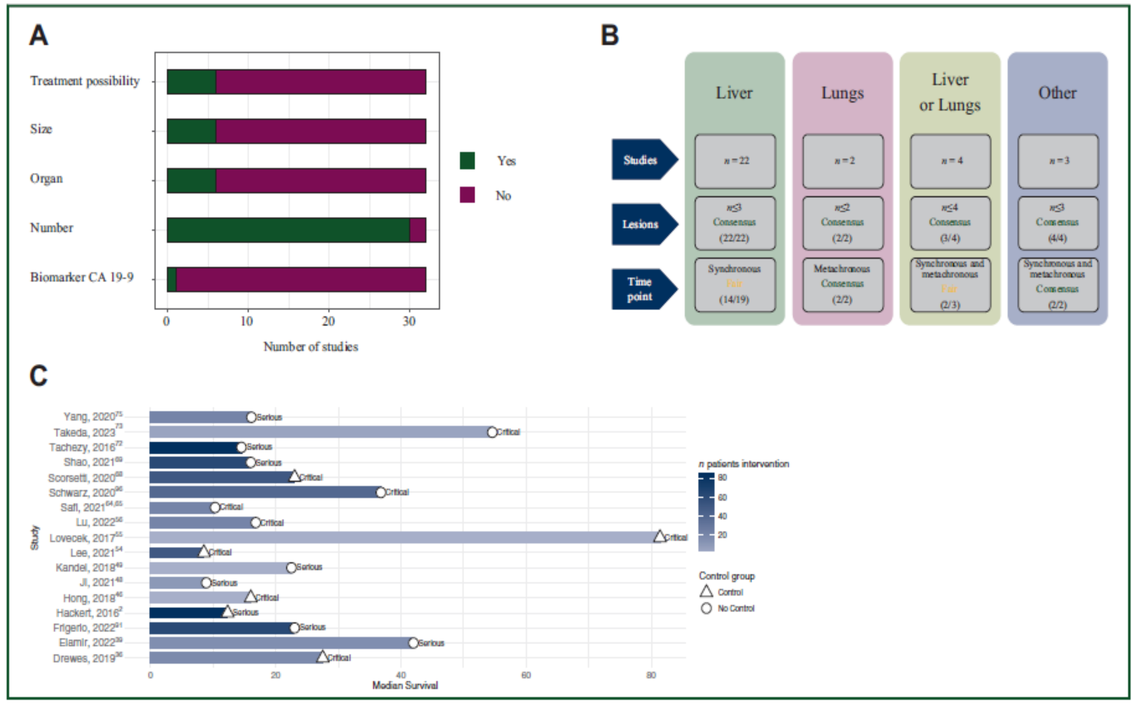
## Defining oligometastatic pancreatic cancer: a systematic review and critical synthesis of consensus

C.-S. Leonhardt[1], T. Stamm[2,3], T. Hank[1], G. Prager[4] & O. Strobel[1,*]

[1]Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna; [2]Institute of Outcomes Research, Center for Medical Data Science, Medical University of Vienna; [3]Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna; [4]Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria

2023

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE




Review of 76 studies, mostly retrospective
32 studies (42%) reported a definition of OMD, 44 (58%) did not

**Consensus reached for:**

- Involvement limited to a single organ
- Number of lesions (Liver could involve 3 or fewer lesions, lung metastases could involve 2 or fewer lesions and metachronous disease)

**Fair agreement** for synchronous disease

**Poor agreement for**:

- Metastatic site and metastatic size
- Treatment possibilities
- Biomarker response

**OligoPanc Project**
ongoing

## OligoPanc project collaboration

ESTRO

Project aim: develop interdisciplinary consensus on oligometastatic pancreatic cancer

Project lead: O. Strobel (Surgeon), G. Prager (Oncologist), M. Scorsetti (RO)

Background: systematic review in inclusion criteria for oligomet definition in oligopacreatic cancer studies revealed large variations (Leonhardt et al.)

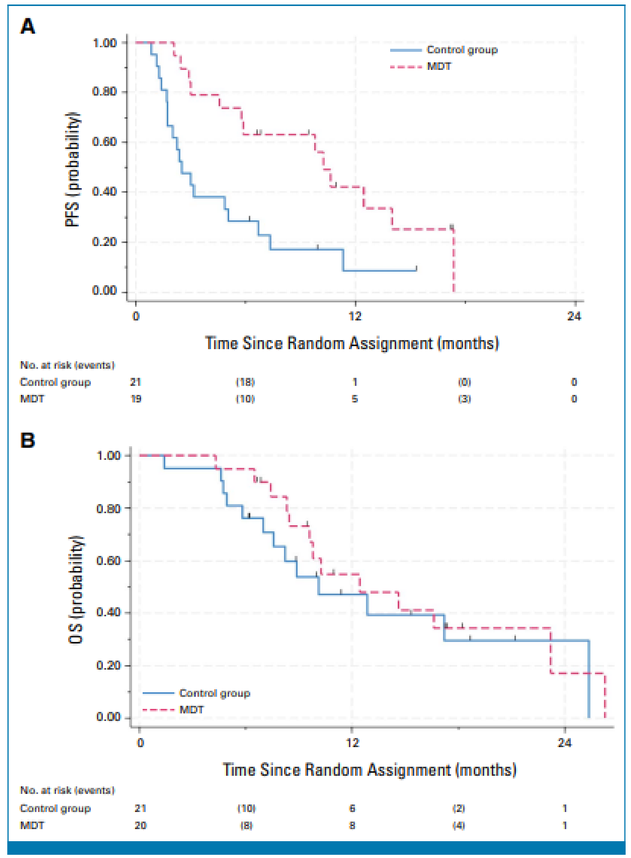
Method: Delphi consensus

ESTRO represantatives (as listed) are involved
First and second Delphi round finished, analysis of the results ongoing

# Oligometastatic Pancreatic cancer: CT +/- SBRT

## Addition of Metastasis-Directed Therapy to Systemic Therapy for Oligometastatic Pancreatic Ductal Adenocarcinoma (EXTEND): A Multicenter, Randomized Phase II Trial

Ethan B. Ludmir, MD[1,2]; Alexander D. Sherry, MD[3]; Bryan M. Fellman, MS[2]; Suyu Liu, PhD[2]; Tharakeswara Bathala, MD, MBBS[4]; Cara Haymaker, PhD[5,6]; Marina N. Medina-Rosales, PhD[5,6]; Alexandre Reuben, PhD[7]; Emma B. Holliday, MD[1]; Grace L. Smith, MD, PhD, MPH[1]; Sonal S. Noticewala, MD, MAS[1]; Sarah Nicholas, MD[8]; Tracy R. Price, MD[9]; Rachael M. Martin-Paulpeter, PhD[10]; Luis A. Perles, PhD[10]; Sunyoung S. Lee, MD, PhD[11]; Michael S. Lee, MD[11]; Brandon G. Smaglo, MD[11]; Ryan W. Huey, MD, MS[11]; Jason Willis, MD, PhD[11]; Dan Zhao, MD, PhD[11]; Lorenzo Cohen, PhD[12]; Cullen M. Taniguchi, MD, PhD[1,13,†]; Eugene J. Koay, MD, PhD[1]; Matthew H.G. Katz, MD[14]; Robert A. Wolff, MD[11]; Prajnan Das, MD, MS, MPH[1]; Shubham Pant, MD, MBBS[11]; Albert C. Koong, MD, PhD[1]; and Chad Tang, MD[5,15,16]


40 patients with ≤ 5 metastases from pancreatic cancer
Randomization in 1:1 ratio:

- 19 patients in the MDT arm (systemic therapy + SBRT)
- 21 patients in the control arm (systemic therapy alone)

Median follow-up 17 months

**Median PFS in MDT arm**: 10.3 months (95% CI, 4.6 to 14.0)
**Median PFS in control arm**: 2.5 months (95% CI, 1.7 to 5.1)
Median time to next line systemic therapy : 19 months MDT vs 8 months control arm

No G3 or greater MDT-related toxicities

# Addition of Metastasis-Directed Therapy to Systemic Therapy for Oligometastatic Pancreatic Ductal Adenocarcinoma (EXTEND): A Multicenter, Randomized Phase II Trial

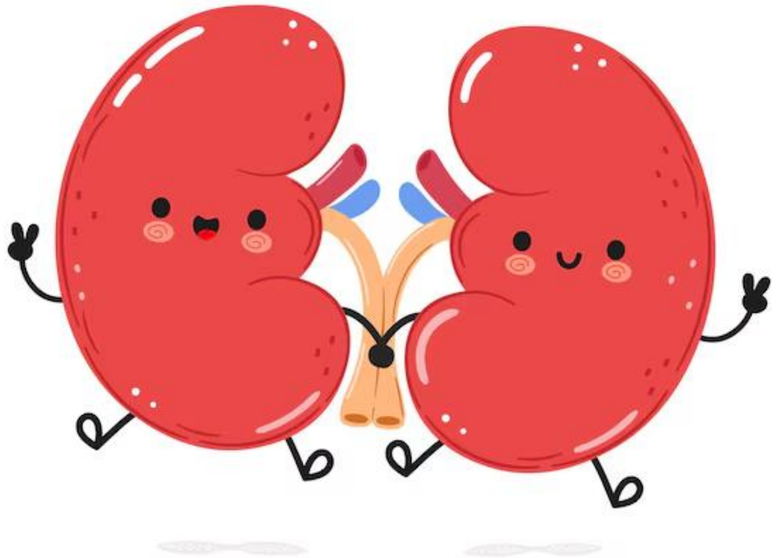
Ethan B. Ludmir, MD[1,2]; Alexander D. Sherry, MD[3]; Bryan M. Fellman, MS[2]; Suyu Liu, PhD[2]; Tharakeswara Bathala, MD, MBBS[4]; Cara Haymaker, PhD[5,6]; Marina N. Medina-Rosales, PhD[5,6]; Alexandre Reuben, PhD[7]; Emma B. Holliday, MD[1]; Grace L. Smith, MD, PhD, MPH[1]; Sonal S. Noticewala, MD, MAS[1]; Sarah Nicholas, MD[8]; Tracy R. Price, MD[9]; Rachael M. Martin-Paulpeter, PhD[10]; Luis A. Perles, PhD[10]; Sunyoung S. Lee, MD, PhD[11]; Michael S. Lee, MD[11]; Brandon G. Smaglo, MD[11]; Ryan W. Huey, MD, MS[11]; Jason Willis, MD, PhD[11]; Dan Zhao, MD, PhD[11]; Lorenzo Cohen, PhD[12]; Cullen M. Taniguchi, MD, PhD[1,13,†]; Eugene J. Koay, MD, PhD[1]; Matthew H.G. Katz, MD[14]; Robert A. Wolff, MD[11]; Prajnan Das, MD, MS, MPH[1]; Shubham Pant, MD, MBBS[11]; Albert C. Koong, MD, PhD[1]; and Chad Tang, MD[5,15,16]


- **Improved PFS** from the combination of MDT plus systemic therapy compared with systemic therapy
- This is the only **randomized trial** of patients with oligometastatic PDAC to date, and PDAC represents the most aggressive histology evaluated in an oligometastatic disease trial conducted. Our results support the **efficacy and safety** of adding MDT to standard-of-care chemotherapy for oligometastatic PDAC.
- **Translational** correlatives suggest a novel mechanism of action that may be exploited therapeutically
- Additional studies needed to validate these results and investigate **potentially favorable immunostimulatory effects of MDT** (Systemic CD8+ T-cell activation and proliferation observed after MDT but not after systemic therapy alone, activated (PD1+) or highly activated (CD25+) CD8+ T cells increased over time in the MDT arm, but not in the control arm).

# Agenda

- Oligometastatic disease: definitions and rationale
- Oligometastatic disease in lower GI cancer
- Oligometastatic disease in upper GI cancer
- **Oligometastatic disease in renal cancer**
- Conclusions

# RENAL CANCER



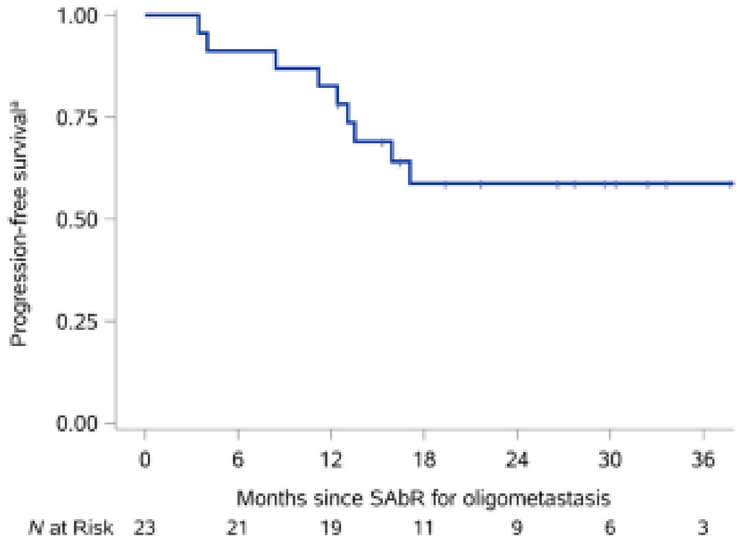
# Oligorecurrent Renal Cancer

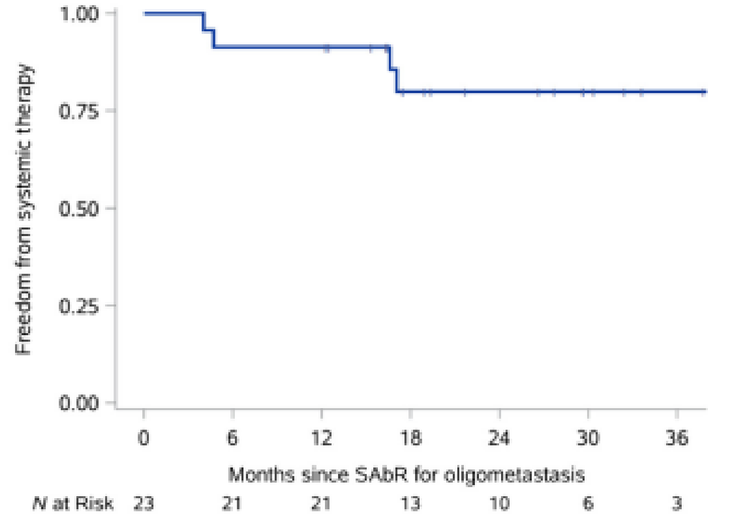
## Stereotactic Ablative Radiation for Systemic Therapy–naïve Oligometastatic Kidney Cancer

*Raquibul Hannan [a,b,*], Michael Christensen [a], Alana Christie [b], Aurelie Garant [a,b], Ivan Pedrosa [b,d], Liliana Robles [a], Samantha Mannala [a], Chiachien Wang [a], Hans Hammers [b,c], Waddah Arafat [b,c], Kevin Courtney [b,c], Isaac A. Bowman [b,c], David Sher [a], Chul Ahn [b], Suzanne Cole [b,c], Hak Choy [a], Robert Timmerman [a,b,*], James Brugarolas [b,c,*]*

European Association of Urology
2022

- **Prospective phase II single-arm trial**
- **23 patients** underwent SBRT to 33 initial and **57 total oligorecurrent lesions**
- **Primary endpoint: freedom from systemic therapy > 60% at 1 year**
- Secondary endpoints: PFS, LC, Cancer Specific Survival, OS, toxicity, QOL



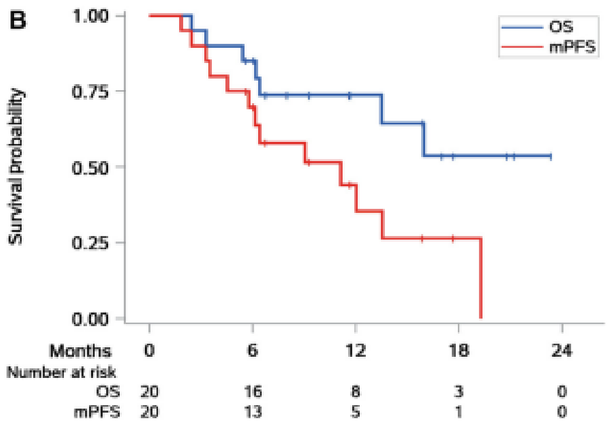




Freedom from systemic therapy at 1 yr was **91.3%**
One-year **PFS 82.6%**
**LC 100%**
No G3-G4 toxicities and QOL largely unaffected

# Oligoprogressive Renal Cancer

## Phase II Trial of Stereotactic Ablative Radiation for Oligoprogressive Metastatic Kidney Cancer

*Raquibul Hannan [a,b,*], Michael Christensen [a], Hans Hammers [b,c], Alana Christie [b], Brendan Paulman [a], Dandan Lin [a], Aurelie Garant [a,b], Waddah Arafat [b,c], Kevin Courtney [b,c], Isaac Bowman [b,c], Suzanne Cole [b,c], David Sher [a], Chul Ahn [c], Hak Choy [a], Robert Timmerman [a,b,*], James Brugarolas [b,c,*]*

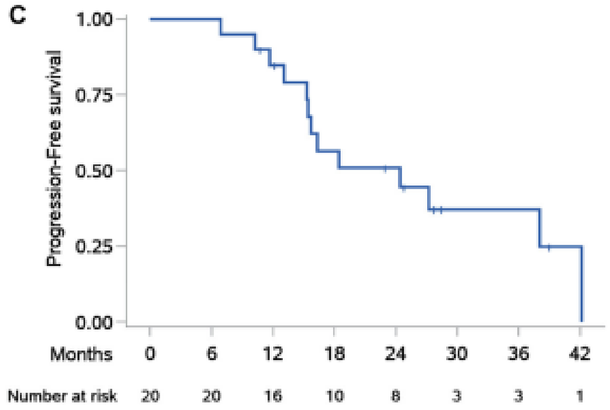




**Single-arm phase II trial**
**20 patients** with mRCC undergoing systemic therapy (first to fourth-line), **37 lesions**
SBRT on maximum 3 sites of progression (involving ≤ 30% of all sites)
**Primary endpoint:** extend ongoing systemic therapy by >6 months in >40% of patients
**Secondary endpoints:** OS, toxicity and QoL

**LC rate 100%, Median OS not reached**

At a median follow-up of 10.4 months **SBRT extended the duration of the ongoing systemic therapy by > 6 months in 14/20 patients** (70%, 95% confidence interval [CI]: 49.9–90.1).

Median time from SBRT to new systemic therapy or death was 11.1 months.




Only one G3 GI toxicity

# Oligometastatic RCC: TKI +/- SBRT

## Survival After Combining Stereotactic Body Radiation Therapy and Tyrosine Kinase Inhibitors in Patients With Metastatic Renal Cell Carcinoma

*Yang Liu[1†], Zhiling Zhang[2†], Hui Han[2], Shengjie Guo[2], Zhuowei Liu[2], Mengzhong Liu[1], Fangjian Zhou[2], Pei Dong[2*] and Liru He[1*]*

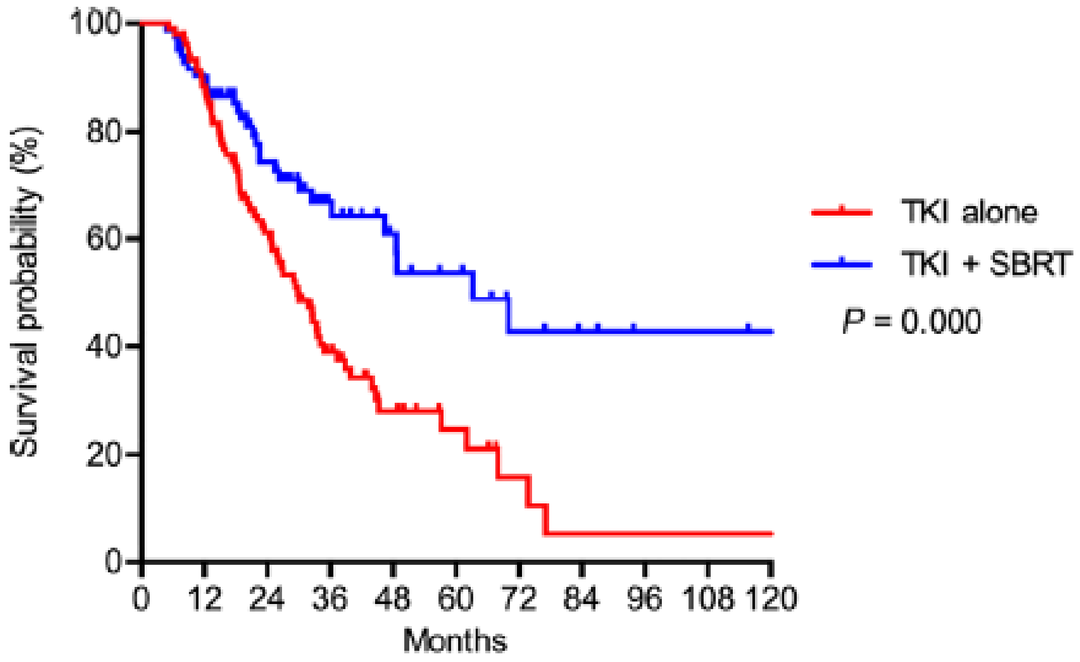
2023

frontiers in Oncology

190 patients included:
- 85 patients received TKI + SBRT
- 105 patients received TKI alone

**2-year LC rate was 92.8%**

The **median OS** in the **TKI + SBRT group** was significantly **longer** than that of the TKI alone group (63.2 vs 29.8 months; P < 0.001)



# Oligoprogressive Renal Cancer

CURRENT OPINION

## Metastasis-directed therapy in oligometastatic and oligoprogressive renal cell carcinoma

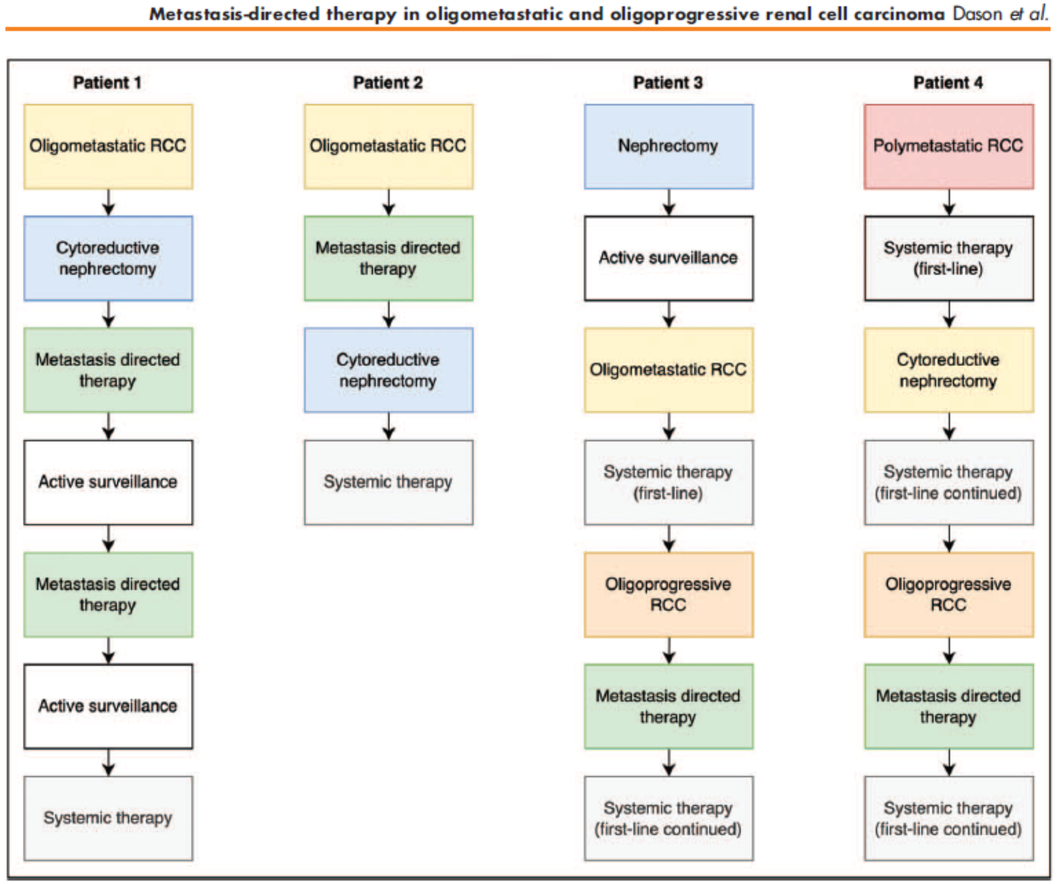
2024

*Shawn Dason*[a,b], *Shang-Jui Wang*[a,b], *Dominic Franceschelli*[a,b] *and Eric A. Singer*[a,b]

Overview on metastasis-directed approaches

Metastasis-directed therapy, including metastasectomy and SABR, **effectively controls metastatic lesions, improving quality of life and delaying systemic therapy**.

The survival impact of MDT is still uncertain and needs to be validated in randomized trials.



# Oligometastatic disease: Renal Cancer

CURRENT OPINION

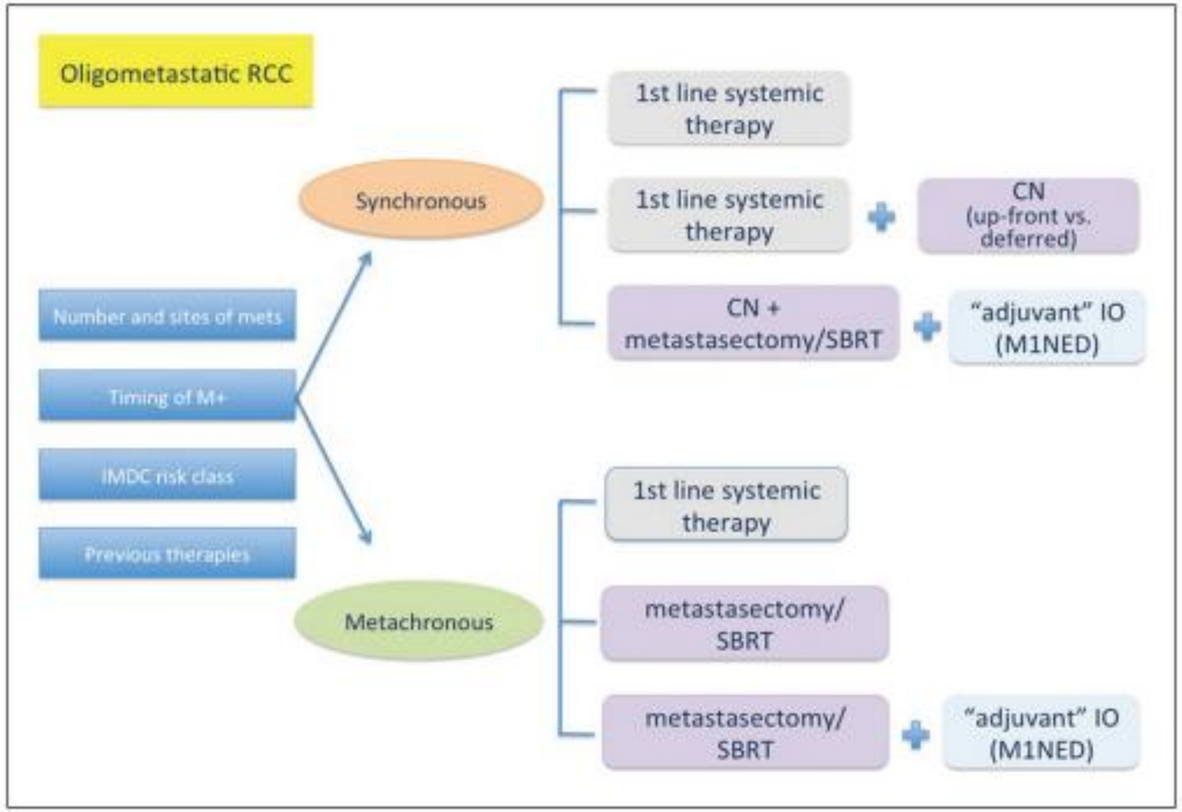
## Definitions and unmet needs in the management of oligomestatic renal cell carcinoma in the modern era

*Giulio Francolini[a,b], Riccardo Campi[b,c,d] and Chiara Ciccarese[b,e], On behalf of the European Association of Urology (EAU) Young Academic Urologists (YAU) Renal Cancer working group*

2024

**Table 1.** Main definitions of oligometastatic/oligoprogressive disease according to prospective trials testing stereotactic body radiotherapy in this scenario

| | Oligometastatic definition | Systemic treatment |
|---|---|---|
| Tang *et al.* [4] | < 5 lesions<br>< 1 previous systemic therapy stopped > 1 month before enrollment | None |
| Siva *et al.* [5] | 1–5 lesions<br>< 2 previous systemic treatments | Pembrolizumab |
| Hannan *et al.* [6] | <3 sites of progression (including new metastases)<br><4 lines of systemic treatment | Ongoing treatment at enrollment |
| Cheung *et al.* [7] | <5 progressive metastatic sites<br>previous stability or response after ≥3 mo of TKI therapy | Ongoing TKI at enrollment |




"Several unmet needs have to be further investigated, mainly regarding the **lack of prospective randomized trials** that directly compare modern therapies and different integration strategies. Furthermore, no precise criteria have been identified for an **accurate selection of patients** who might benefit most from a specific therapeutic option (loco-regional approach vs. systemic therapy alone vs. multimodal strategy)"

# Toxicities from SBRT

Acute toxicity in patients with oligometastatic cancer following metastasis-directed stereotactic body radiotherapy: An interim analysis of the E$^2$-RADIatE OligoCare cohort

Filippo Alongi [a,b], Luca Nicosia [a,*], Umberto Ricardi [c], Marta Scorsetti [d,e], Daniela Greto [f,g], Panagiotis Balermpas [h], Yolande Lievens [i], Pètra Braam [j], Barbara Alicja Jereczek-Fossa [k,l], Karin Stellamans [m], Ivica Ratosa [n,o], Inga-Malin Simek [p], Heike Peulen [q], Piet Dirix [r], Luc Verbeke [s], Sara Ramella [t,u], Hossein Hemmatazad [v], Kaouthar Khanfir [w], Xavier Geets [x], Paul Jeene [y], Thomas Zilli [z,aa], Beatrice Fournier [ab], Catherine Fortpied [ab], Felix Boakye Oppong [ab], Piet Ost [ac,ad], Matthias Guckenberger [h]


Severe adverse event within 6 months from SBRT start.

| System Organ Class + Preferred term | All patients (N=1468) | | | |
|---|---|---|---|---|
| | Grade 3 N (%) | Grade 4 N (%) | Grade 5* N (%) | Grade ≥3 N (%) |
| PATIENTS' WORST GRADE | 6 (0.4) | | 2 (0.1) | 8 (0.5) |
| INFECTIONS AND INFESTATIONS | | | | |
| Empyema | 1 (0.1) | | | 1 (0.1) |
| Pneumonia | 1 (0.1) | | | 1 (0.1) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | | |
| Radiation Pneumonitis | 1 (0.1) | | | 1 (0.1) |
| Radiation Skin Injury | 1 (0.1) | | | 1 (0.1) |
| METABOLISM AND NUTRITION DISORDERS | | | | |
| Decreased Appetite | 1 (0.1) | | | 1 (0.1) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | | |
| Bone Pain | 1 (0.1) | | | 1 (0.1) |
| NERVOUS SYSTEM DISORDERS | | | | |
| Brain Oedema | 1 (0.1) | | | 1 (0.1) |
| Cerebral Haemorrhage | 1 (0.1) | | | 1 (0.1) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | | |
| Pneumonitis | 1 (0.1) | | | 1 (0.1) |

The rate of severe adverse events was low, confirming the **safety of SBRT in the treatment of oligometastases.** The very limited complications herein reported on this large and heterogeneous population further support the integration of SBRT into multimodal treatment strategies.

# Agenda

- Oligometastatic disease: definitions and rationale
- Oligometastatic disease in lower GI cancer
- Oligometastatic disease in upper GI cancer
- Oligometastatic disease in renal cancer
- **Conclusions**

# Conclusions

- ✓ **Oligometastic patients will increase** in number in the next years
- ✓ **SBRT** represents a **non invasive**, **well tolerated** and **effective treatment** for these patients
- ✓ **Clinical evidences are increasing**, however we still need phase III RCTs
- ✓ Identification of the **true oligometastatic patient is a crucial point** (biomarkers, imaging)
- ✓ **Interaction LAT/Systemic therapies** should be regarded as an opportunity more than a challenge
- ✓ **Future research** should focus on **RT/drug interaction** and **biomarkers identification**
- ✓ All progress need to be studied, validated and established through good and trustable **clinical and translational research**

# THANKS FOR THE ATTENTION!!

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