

SBRT nei tumori secondari del fegato: un nuovo standard?

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HUMANITAS
CANCER CENTER

Background

- The liver is a common site of metastases for **gastrointestinal, lung and breast cancers**
- **Colorectal cancer liver metastases** are present at the time of diagnosis in roughly 20% of patients and it developed during the course of disease in an additional 40% of cases.
- **Curative-intent local treatments** are currently considered the only realistic treatment options that can provide long-term disease control and cure in a select group of patients
- Advances in **systemic regimens** greatly contributed by **downstaging** patients for liver surgery and/or tumor ablation
- Furthermore, it opens a window **to identify biologically aggressive** fast disseminating cancers that cannot be controlled by local invasive treatments

HIGHLIGHTS in RADIOTERAPIA

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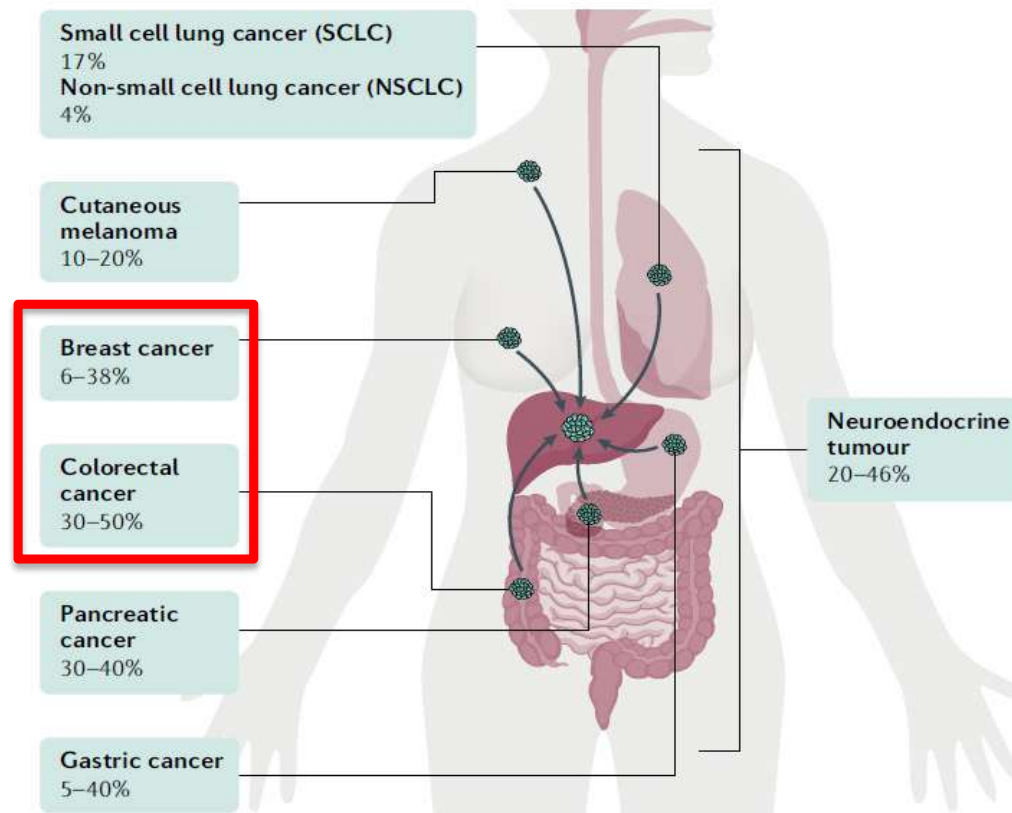


Fig. 2 | **Common primary cancers metastasizing to the liver.** The percentage of common primary tumours that metastasize to the liver are shown^{1,9,10}.

Table 2. Contraindications to hepatic resection in patients with colorectal cancer liver metastases

Category	Contraindication
Technical (A)	
1. Absolute	Impossibility of R0 resection with $\geq 25\%$ – 30% liver remnant Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolization, two-stage hepatectomy, hepatectomy combined with ablation ^a) R1 resection
Oncological (B)	
1.	Concomitant extrahepatic disease (resectable)
2.	Number of lesions ≥ 5
3.	Tumor progression

Any patient should be categorized as A1 or A2/B1, B2, or B3. This classification may help to clearly define the type of unresectable patients included in all clinical trials.

^aIncludes all methods, including radiofrequency ablation.

Although the eligibility for hepatic resection continues to expand, **in approximately 60-80% upfront surgical excision of all CRLM is not possible.**

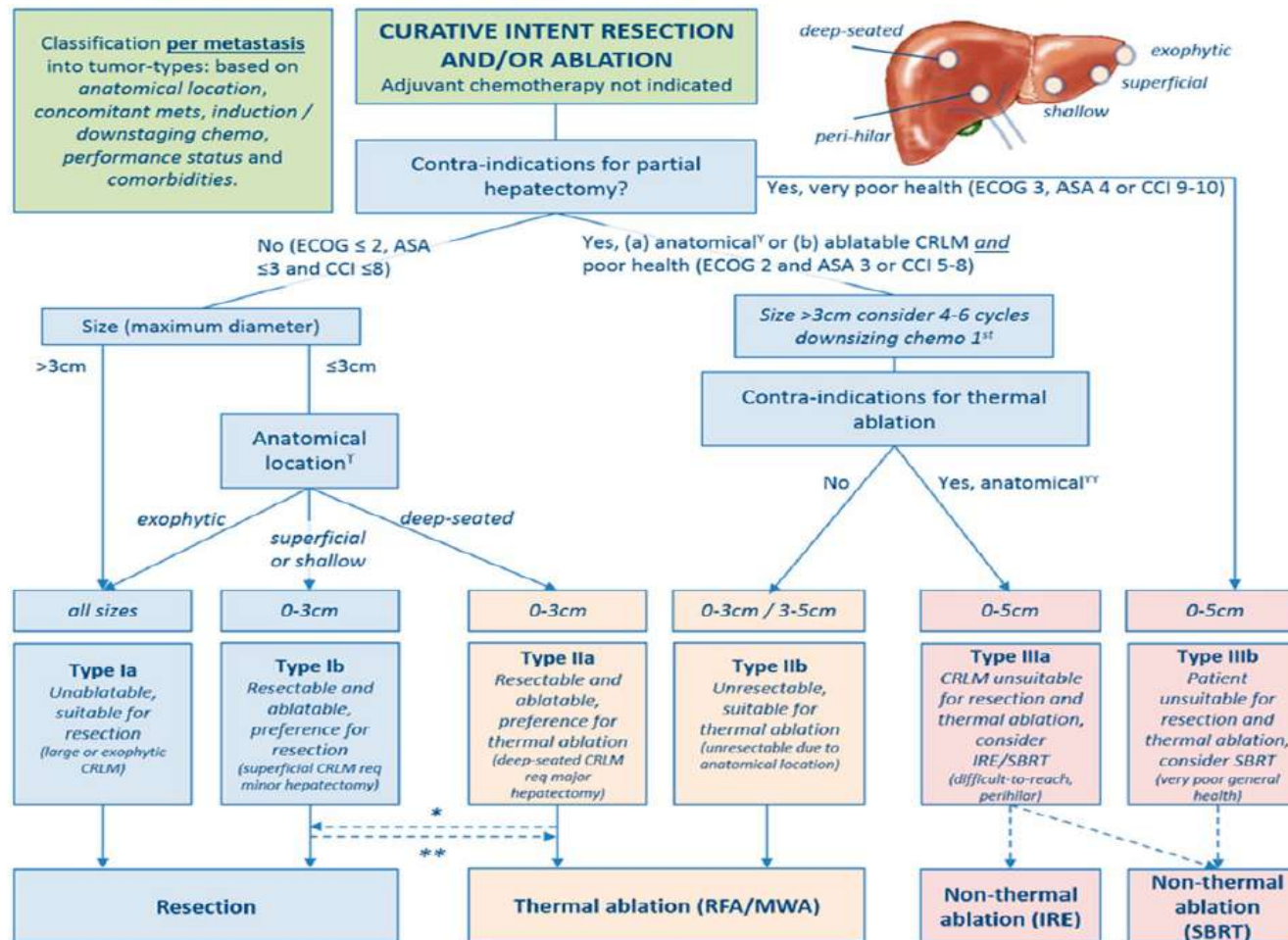
Adam, de Gramont. *The Oncologist*, 2012.
Fong Y. et al. *CA Cancer J.Clin*, 1995.
Simmonds P.C. et al. *Br.J.Cancer*, 2006
Lam VW et al. *J Gastrointest Surg*, 2013.

- **Radiofrequency ablation (RFA) and microwave ablation (MWA) are heat-based thermal ablation modalities, currently adopted as standard of care to treat unresectable small (0-3 cm) CRLM**
- **Two recently published systematic reviews and meta-analyses comparing thermal ablation to chemotherapy alone and to partial hepatectomy, both labelled thermal ablation superior to chemotherapy alone but inferior to surgery with regards to overall survival.**

Meijerink et al. Cardiovasc Intervent Radiol. 2018
Van Amerongen, M.J et al. HPB (Oxford) 2017
- **Although most superficial, shallow- and deep-seated, small-size CRLM seem to be suitable for thermal ablation, peritumoral vicinity of the common, left or right hepatic bile duct are considered absolute contra-indications as this is associated with an unacceptable risk of inducing biliary tract injuries**
- **With stereotactic body radiotherapy (SBRT), high radiation doses are delivered to a target volume within the liver, while minimizing collateral damage to healthy surrounding tissue**

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Factors	Studies	Results
Tumor size	<ul style="list-style-type: none"> • Rusthoven, JCO 2009 • Lee, JCO 2009 • Scorsetti, IJROPB 2017 and Radiat Oncol. 2018 	<p>< 3 cm < 75.2 mL No correlation between size and LC</p>
Histology	<ul style="list-style-type: none"> • Hamed, IJROPB 2016 • Klement, Radioth Onc 2017 	<p>Primary histology played a significant role in determining radiosensitivity</p>
Radiation dose	<ul style="list-style-type: none"> • Rusthoven, JCO 2009 • Lee, JCO 2009 • Chang, Cancer 2017 • Scorsetti, IJROPB 2017 and Radiat Oncol. 2018 • Comito, BMC 2014 • Joo, IJROPB 2017 • McPartlin, , IJROPB 2017 • Klement, Radioth Onc 2017 	<p>48-75 Gy/3-6 fr – BED10> 100 Gy</p>
Prior therapies	<ul style="list-style-type: none"> • Klement, Radioth Onc 2017 	<p>Dose, histology and pre-SBRT chemotherapy strongly influenced local tumor control.</p>

The Dutch–Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases

Between 2013, and 2019 a total of **515 patients** were entered in the web-based registry. In total, **668 liver metastases** were registered, and 447 were included for local control analysis.

The most common primary tumor origin was **colorectal cancer** (80.3%), followed by **lung cancer** (8.9%) and **breast cancer** (4%).

The most-used fractionation scheme was 3x18-20 Gy (36.0%), followed by 8x7.5 Gy (31.8%), 5x11-12 Gy (25.5%), and 12x5 Gy (6.7%).

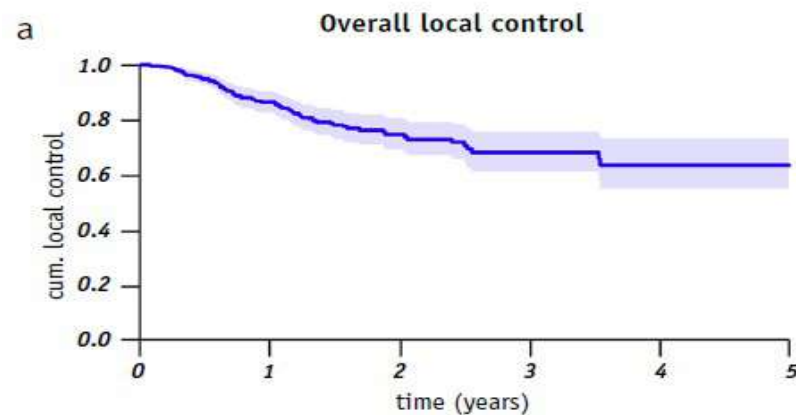
The median follow-up time was 1.1 years for local control and 2.3 years for survival.

	Number	%
Primary histology*		
Colorectal	359	80.4
Lung	40	9.0
Breast	18	4.0
Stomach	2	0.4
Ovary	2	0.4
Melanoma	2	0.4
Other	24	5.4
Couinaud segment*		
8	134	30.0
7	72	16.1
6	51	11.4
5	37	8.3
4a,b	60, 24	13.4, 5.4
3	14	3.1
2	22	4.9
1	33	7.4
Fractionation scheme*		
3 × 18-20 Gy	161	36.0
5 × 11-12 Gy	114	25.5
8 × 7.5 Gy	142	31.8
12 × 5 Gy	30	6.7

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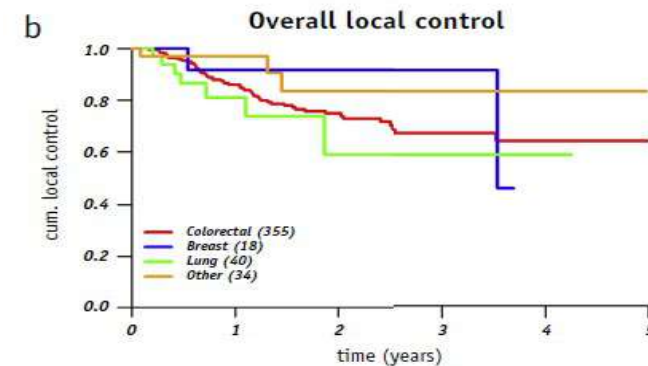
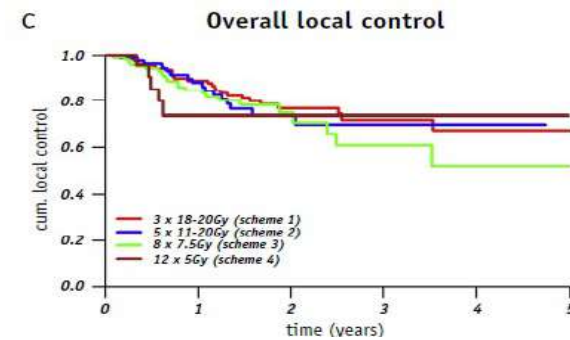
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Actuarial 1-year local control was 87%

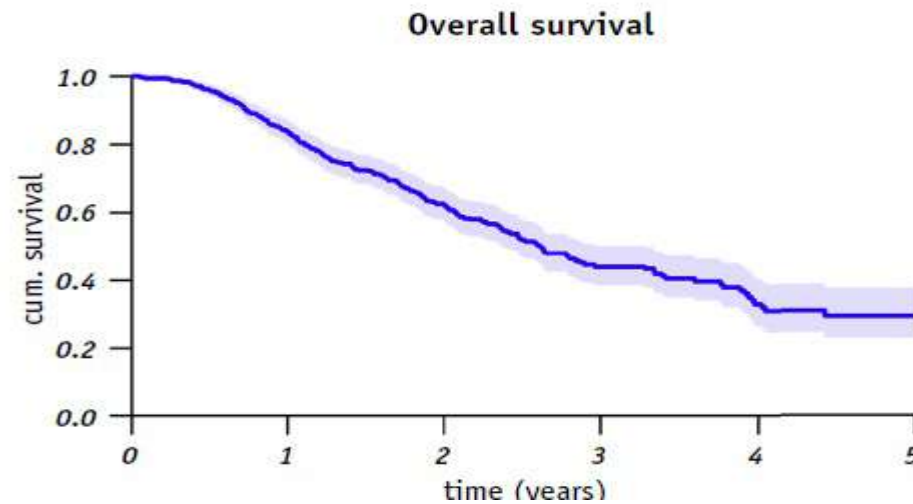


Toxicity of G3 or greater was found in 3.9% of the patients

This multi-institutional study of liver metastases treated with SBRT in a large patient cohort confirms earlier findings of **high rates of local control** and **limited toxicity**.



Overall survival rates were 84% at 1 year, 63% at 2 years, and 44% at 3 years



Stereotactic body radiation therapy should be considered a valuable part of the multidisciplinary approach to treating liver metastases

2021

JGO JOURNAL OF GASTROINTESTINAL ONCOLOGY
AN OPEN ACCESS JOURNAL FOR PRACTICAL INFORMATION IN GASTROINTESTINAL ONCOLOGY

Proton stereotactic body radiation therapy for liver metastases — results of 5-year experience for 81 hepatic lesions

Alex R. Coffman¹, Daniel C. Sufficool², Joseph I. Kang¹, Chung-Tsen Hsueh³, Sasha Swenson⁴, Patrick Q. McGee⁴, Gayathri Nagaraj³, Baldev Patyal¹, Mark E. Reeves⁵, Jerry D. Slater¹, Gary Y. Yang¹

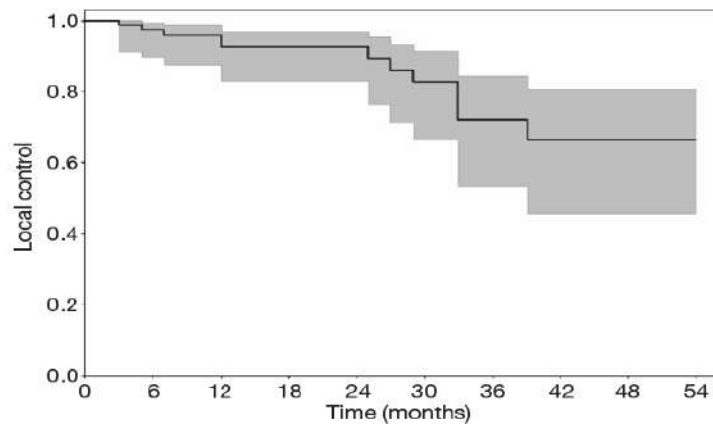
46 patients with 81 lesions were treated with **Proton SBRT**

- Two or more lesions were treated in 56.5% of patients, with one patient receiving treatment to a total of five lesions.
- There were 37 lesions treated with a BED ≤ 60 , 9 lesions with a BED of 61–80, 22 lesions with a BED of 81–100 and 13 lesions with a BED > 100 .

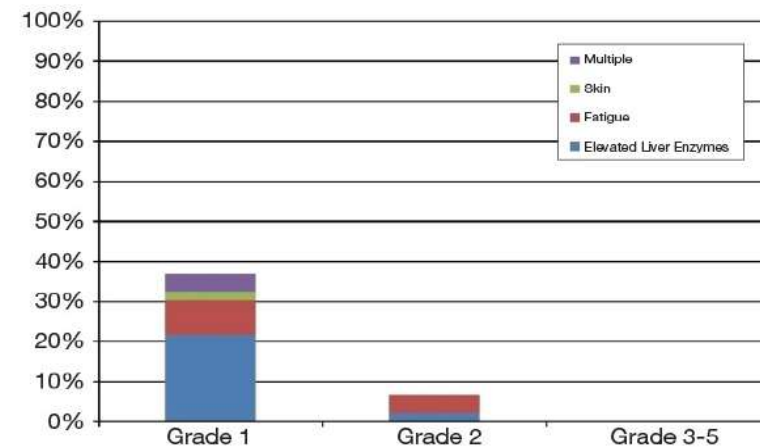
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2-year LC for all lesions was 92.5%



The G1 and G2 toxicity rates were 37% and 6.5%, respectively. There were no grade 3 or higher toxicities and no cases of radiation-induced liver disease (RILD).



CONCLUSIONS: Proton SBRT for the treatment of liver metastases has **promising LC rates** with the ability to **safely treat multiple liver metastases**. Accrual continues for our phase II trial treating liver metastases with Proton SBRT to 60 GyE (Gray equivalent) in 3 fractions.



2021 ASCO ANNUAL MEETING

During the 2021 ASCO Annual Meeting Education Session “**Locoregional Therapies for Colorectal Cancer Liver Metastases: Options Beyond Resection**,” a panel of experts discussed locoregional therapy options for CRC liver metastases beyond resection

Laura Dawson (Princess Margaret Cancer Centre and University of Toronto, Canada) discussed **the evolving role of stereotactic body radiation therapy (SBRT) in the treatment of CRC liver metastases**.

She noted that noninvasive therapies, such as SBRT, may have an increasing role in patients with **chemorefractory disease**, those with **multiple organ/lymph node involvement**, or those with **multiple prior liver resections**, as long as they do not impede the patients' quality of life.

Dr. Dawson highlighted the results of several studies reporting on the long-term outcomes of patients with liver metastases treated with SBRT.

JAMA Network | Evaluation of Definitive Stereotactic Body Radiotherapy and Outcomes in Adults With Extracranial Oligometastasis

2020

Ian Poon, MD; Darby Eler, MRT(T), MHSc; Roi Dagan, MD; Kristin J. Redmond, MD; Matthew Foote, MD; Serena Badellino, MD; Tithi Biswas, MD; Alexander V. Louie, MD, PhD; Young Lee, PhD; Eshetu G. Atenafu, MSc; Umberto Ricardi, MD; Arjun Sahgal, MD

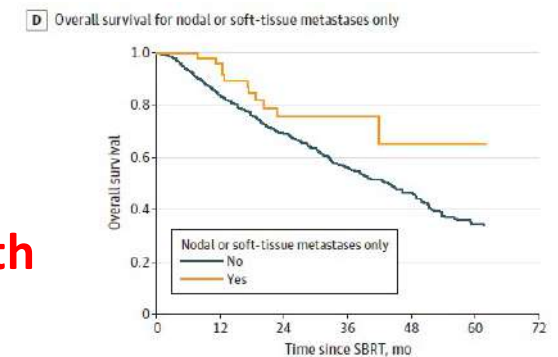
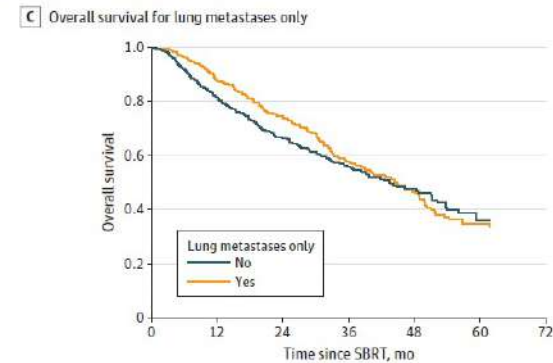
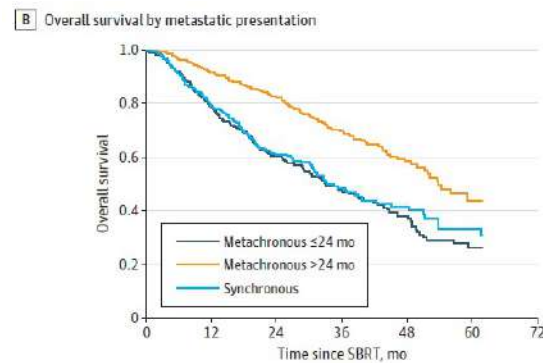
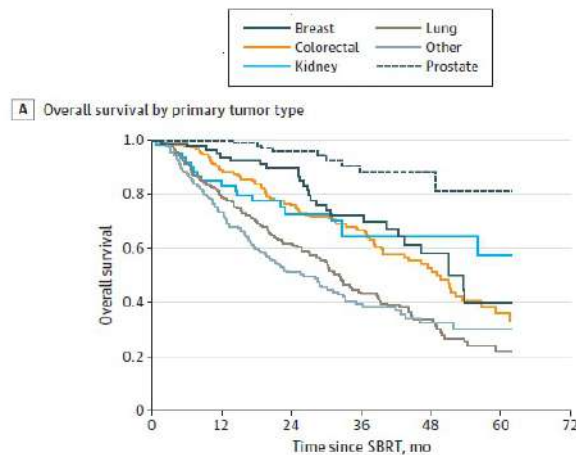
In a large cohort study of **1,033 patients with oligometastases**, the median overall survival was 44 months; at 5 years, 46% of patients were free of widespread metastases and the rate of progression-free survival was 15%.⁴

Table 3. Summary of Phase 2 RCTs Using SBRT in the Setting of Oligometastasis, With Reference to the Present Series

Source	Sample size	Tumor type	Study design	Results
Gomez et al ⁶	49	NSCLC	Phase 2 RCT, multi-institutional; 1:1 maintenance systemic therapy or observation vs local consolidative therapy to all disease sites	OS 41.2 vs 17.0 mo ($P = .02$); PFS 14.2 vs 4.4 mo ($P = .02$)
Iyengar et al ¹⁰	29	NSCLC, EGFR/ALK negative	Phase 2 RCT, single institution; 1:1 maintenance chemotherapy vs SABR to all disease sites, followed by maintenance chemotherapy	PFS 9.7 vs 3.5 mo ($P = .01$)
SABR-COMET ⁸	99	Any	Phase 2 RCT, multi-institutional; 1:2 standard of care vs standard of care plus SABR to all sites of disease	OS 41 vs 28 mo ($P = .09$); PFS 12 vs 6 mo ($P = .001$)
Ost et al ⁹	62	Prostate	Phase 2 RCT, multi-institutional; 1:1 ADT vs SBRT to all metastatic disease sites	ADT-free survival 21 vs 13 mo ($P = .11$)
Present series	1033	Any	Retrospective, multi-institutional; SBRT to metastatic sites, with definitive primary disease treatment	OS 44 mo; PFS 12.9 mo

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This study found **favorable long-term OS rates associated with extracranial OM ablated with SBRT.**

Factors that can inform clinical decision-making and clinical trial design include **primary tumor type**, a **metachronous presentation more than 24 months since diagnosis**, and the site of **OM presentation**.

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THE LANCET
Oncology

2021

Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study

Anastasia Chalkidou, Thomas Macmillan, Mariusz T Grzeda, Janet Peacock, Jennifer Summers, Saskia Eddy, Bola Coker, Hannah Patrick, Helen Powell, Lee Berry, Gareth Webster, Peter Ostler, Peter D Dickinson, Matthew Q Hatton, Ann Henry, Stephen Keevil, Maria A Hawkins, Nick Slevin, Nicholas van As

Primary tumour diagnosis	
Prostate cancer	406 (28.6%)
Colorectal cancer	397 (27.9%)
Renal cancer	143 (10.1%)
Breast cancer	78 (5.5%)
Lung cancer	64 (4.5%)
Melanoma	58 (4.1%)
Other†	276 (19.4%)
Site of first treated metastases (n=1404)	
Lung	411 (29.3%)
Spine	132 (9.4%)
Bone	169 (12.0%)
Adrenal	41 (2.9%)
Liver	135 (9.6%)
Lymph nodes	439 (31.3%)
Other‡	77 (5.5%)
Number of metastases (n=1421)	
1	1074 (75.6%)
2	279 (19.6%)
3	68 (4.8%)

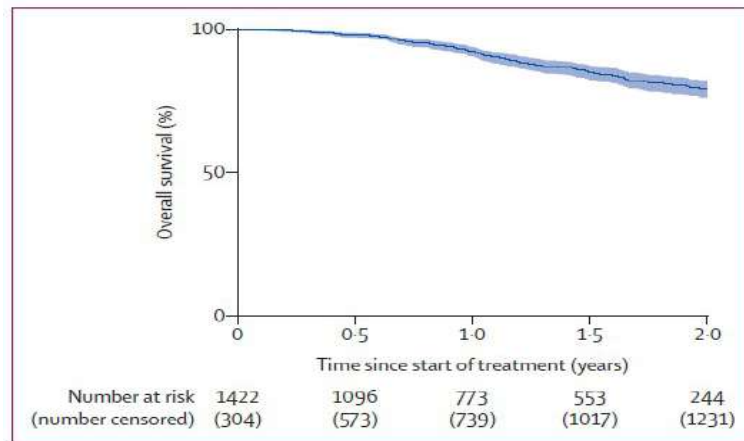
1422 patients were recruited from 17 hospitals in England.

Median follow-up was 13 months

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Overall survival was 92.3% at 1 year and 79.2% at 2 years



- The most common grade 3 adverse event was fatigue and the most common serious (G4) event was increased liver enzymes. No treatment-related deaths were reported.

	Overall survival (95% CI)
Prostate cancer (n=406)	
1 year	NA*
2 year	94.6% (90.4-97.0)
Colon cancer (n=233)	
1 year	92.0% (86.6-95.3)
2 year	80.3% (71.8-86.5)
Rectal cancer (n=164)	
1 year	93.7% (87.2-97.0)
2 year	77.8% (66.5-85.7)
Renal cancer (n=143)	
1 year	95.3% (89.0-98.0)
2 year	82.4% (70.6-89.8)
Breast cancer (n=78)	
1 year	93.7% (84.0-97.6)
2 year	83.2% (69.5-91.2)
Lung cancer (n=64)	
1 year	80.2% (67.1-88.6)
2 year	65.4% (50.6-76.7)
Melanoma (n=58)	
1 year	NA*
2 year	60.5% (38.0-77.0)

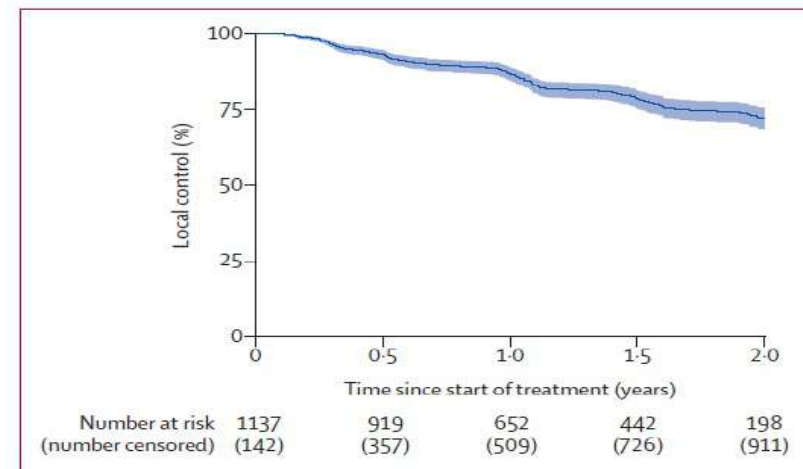
In patients with extracranial oligometastatic cancer, **use of SABR was associated with high overall survival and low toxicity.**

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Median time to local control failure was longer than 2 years

Local control was 86.9% at 1 year and 72.3% at 2 years, and variation was observed according to primary tumour site.



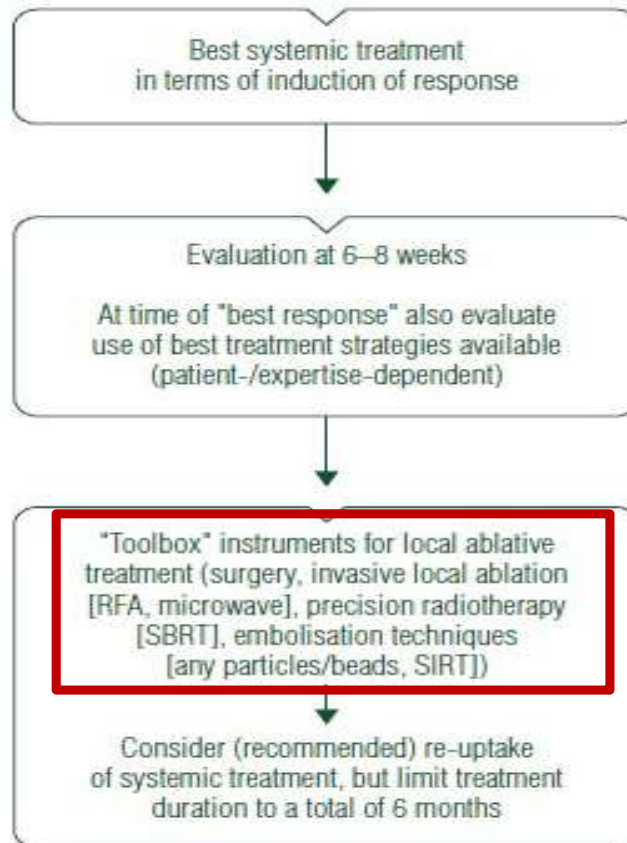
Based on the selection criteria in this study, **SABR was commissioned by NHS England in March, 2020, as a treatment option for patients with oligometastatic disease.**

The treatment will continue to be offered by centres involved in the SABR CtE scheme with progressive expansion and **full implementation across all providers expected by March, 2022**



2016

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer



"the best local treatment should be selected from a 'toolbox' of procedures according to disease localization, treatment goal, treatment-related morbidity and patient-related factors such as comorbidities and age".

11.3 Terapie locoregionali

11.3.1. Terapie locoregionali epatiche in pazienti che presentino metastasi epatiche isolate non candidabili a chirurgia (metastasi non resecabili e/o paziente non operabile)

Questi pazienti costituiscono una percentuale non trascurabile, variabile dal 40 al 90 % (1). L'indicazione chirurgica può essere negata per vari motivi legati a presentazione non favorevole delle lesioni (numero, dimensioni, localizzazione anatomica) e comorbidità del paziente.

In questa situazione una possibile opzione può essere rappresentata dalle metodiche ablativistiche quali la termoablazione con radiofrequenze o micro-onde (RFA), la crioablazione e la radioterapia stereotassica corporea (SBRT) (2).

TUMORI DEL COLON

LINEE GUIDA
2021



Qualità globale delle prove	Raccomandazione clinica	Forza della raccomandazione
Moderata	In pazienti con malattia epatica limitata non suscettibili di chirurgia e che <u>presentino le condizioni atte a garantire un completo trattamento delle lesioni</u> , può essere presa in considerazione una combinazione di terapia sistemica con radiofrequenza o la radioterapia stereotassica (3-6).	Condizionata a favore



2021 ASCO ANNUAL MEETING

“SBRT is an effective option for metastases near porta but **is not as effective for those tumors adjacent to luminal gastrointestinal tissues.**”

We need higher level of evidence in **biomarkers** and colorectal-based trials”.

Toward Personalized Radiation Therapy of Liver Metastasis: Importance of Serial Blood Biomarkers

2021

Ali Ajdari, PhD¹; Yunhe Xie, PhD¹; Christian Richter, PhD²; Maximilian Niyazi, MD³; Dan G. Duda, DMD, PhD¹;
Theodore S. Hong, MD¹; and Thomas Bortfeld, PhD¹

89 patients were retrospectively included. Pre- and mid- treatment blood samples were analyzed for **potential biomarkers of the treatment response**

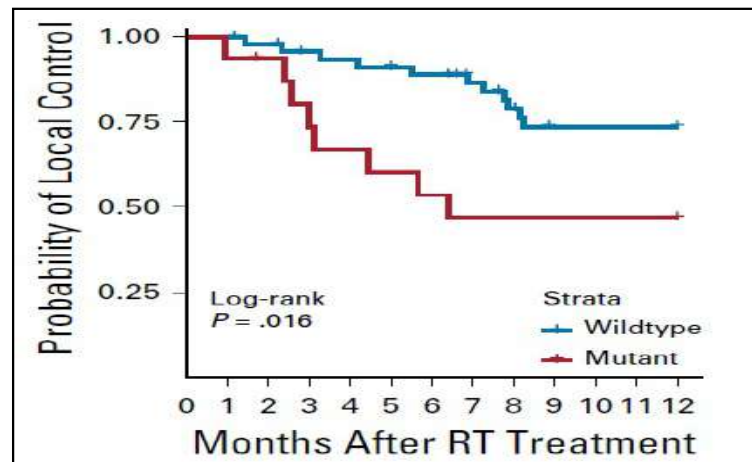
Three biomarker classes were studied:

1. **gene mutation status**
2. **complete blood count**
3. **inflammatory cytokine concentration in plasma**

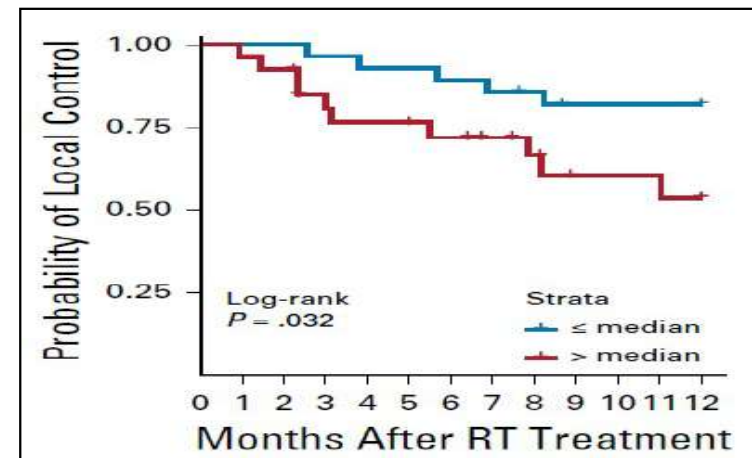
End points: 1-year local failure (LF) and 2-year overall survival (OS)

RESULTS: The most important **predictors of LF** were mutation in **KRAS gene** and baseline and mid-treatment concentration of **plasma interleukin-6** ($p = 0.02$)

KRAS mutation



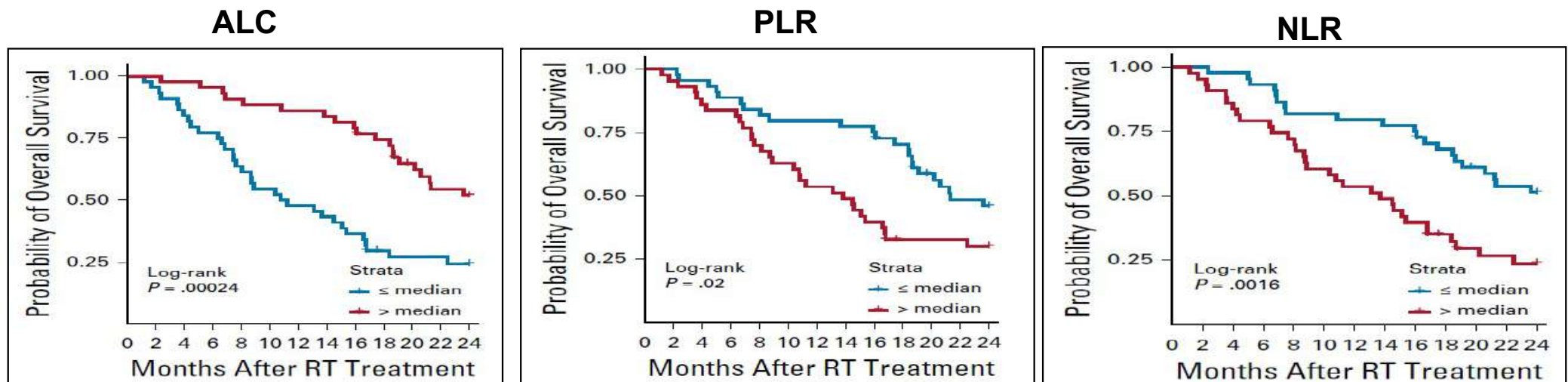
IL-6



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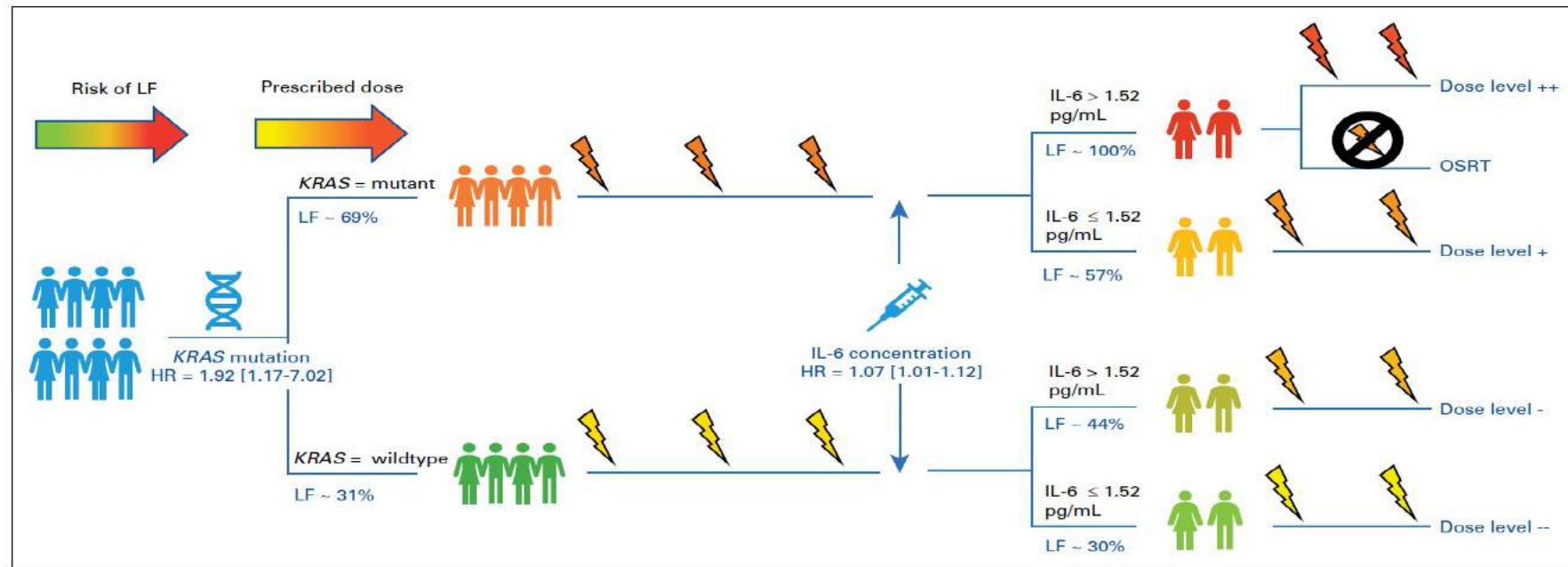
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Absolute lymphocyte count and platelet-to-lymphocyte ratio at baseline as well as neutrophil-to-lymphocyte ratio at baseline and before fraction 3 had the most significant association with OS ($p = .0003$).



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The findings suggest that **significant benefit in predicting RT response** might be achieved by **analyzing the information contained within certain immune system and inflammatory blood biomarkers**. It might prove beneficial to continuously observe the change in the biomarker value to arrive at a more dynamic and accurate picture of the patient response, thereby **paving the way toward a fully personalized RT**

2021

JAMA Oncology | **Original Investigation**

Evaluation of Safety of Stereotactic Body Radiotherapy for the Treatment of Patients With Multiple Metastases Findings From the NRG-BROO1 Phase 1 Trial

Steve Chmura, MD, PhD; Kathryn A. Winter, MS; Clifford Robinson, MD; Thomas M. Pisansky, MD; Virginia Borges, MD; Hania Al-Hallaq, PhD; Martha Matuszak, PhD; Sean S. Park, MD; Sun Yi, MD; Yasmin Hasan, MD; Jose Bazan, MD; Philip Wong, MD; Harold A. Yoon, MD; Janet Horton, MD; Gregory Gan, MD; Michael T. Milano, MD, PhD; Elin Ruth Sigurdson, MD; Jennifer Moughan, MS; Joseph K. Salama, MD; Julia White, MD

39 Patients with oligometastatic **breast, prostate, or non-small cell lung cancer** with **3 to 4 metastases or 2 metastases in close proximity (< 5 cm)** amenable to SBRT were eligible

Primary site of disease	
Breast	13 (33.3)
Lung	13 (33.3)
Prostate	13 (33.3)

Metastases to **7 anatomic locations** were included: bone/osseous, spinal/paraspinal, peripheral lung, central lung, abdominal-pelvic, mediastinal/cervical lymph node, and **liver**

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This phase 1 trial found **that patients with multiple metastases can be treated with curative-intent SBRT** doses developed for a single metastasis or primary tumors with acceptable short-term toxic effects.

Table 2. Summary of Dose-Limiting Toxicity (DLT) Results

Metastatic location (starting dose)	No.	
	Patients enrolled for DLT assessment	DLT events
Bone/osseous (30 Gy in 3 fractions)	8	0
Spinal/paraspinal (30 Gy in 3 fractions)	7	0
Peripheral lung (45 Gy in 3 fractions)	7	0
Abdominal-pelvic (45 Gy in 3 fractions)	9	0
Central lung (50 Gy in 5 fractions)	8	0
Liver (45 Gy in 3 fractions)	9	0
Mediastinal/cervical lymph node (50 Gy in 5 fractions)	7	0

These recommended doses from NRG-BR001 are being used in ongoing trials, including **NRG- BR002**, the phase2 R/3 trial to determine the role of **this treatment for patients with metastatic breast cancer.**

SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer[☆]

Patients with **oligometastatic disease (OMD)** should be discussed in a **multidisciplinary context to individualize management.**

Multimodality treatment approaches involving LRT [**high conformal radiotherapy (RT), image-guided ablation**, elective internal radiotherapy and/or surgery] **combined with systemic treatments are recommended tailored to the disease presentation in the individual patient**

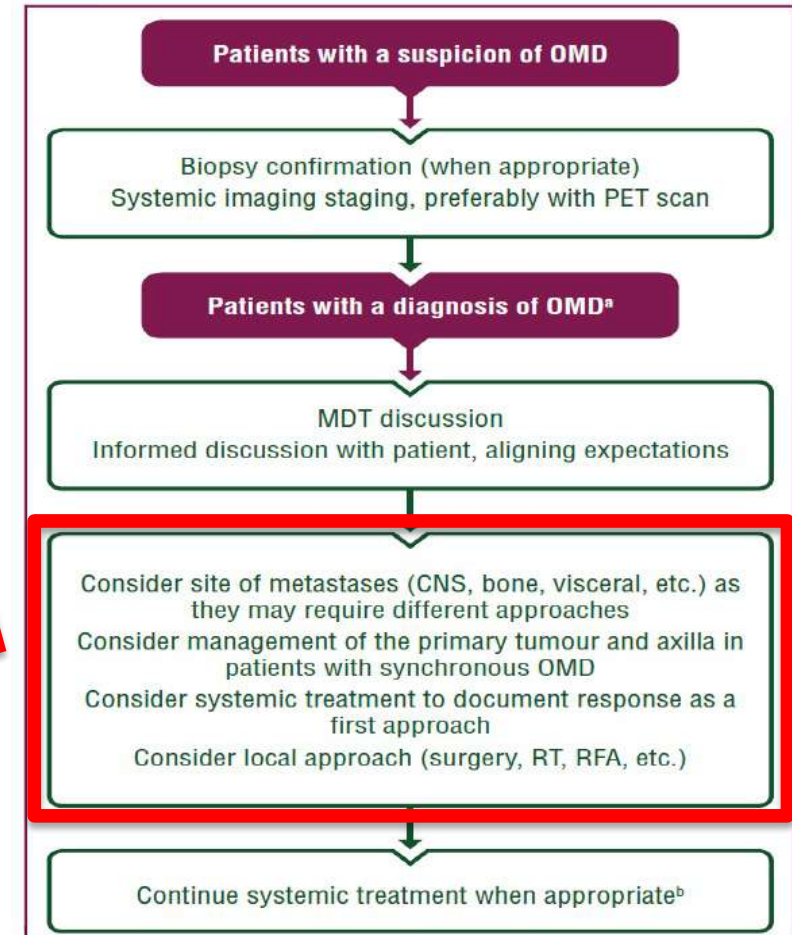


Figure 6. Treatment of OMD.

NEOPLASIE DELLA MAMMELLA

LINEE GUIDA
2021



In casi selezionati, dopo discussione multidisciplinare, la radioterapia può perseguire un intento “radicale” (radioterapia ablativa)⁹², come nel caso di pazienti con malattia oligometastatica. Sono oggi disponibili alcune evidenze da casistiche miste relative ad impatto favorevole sulla sopravvivenza libera da progressione e sopravvivenza globale derivante dall’aggiunta di una radioterapia ablativa stereotassica alla terapia standard per pazienti con tumore solido oligometastatico¹⁰¹.

TAKE HOME MESSAGES

- **Liver SBRT is an effective** local therapy as long as **ablative doses** are used.
- Liver SBRT is effective also in **heavily pre-treated patients** with a long history of illness... but not too late!
- **Multidisciplinary selection** of oligometastatic patients is mandatory
- The **integration of systemic and local therapies** is crucial.
- **Comparative RCTs with other local procedures** (SR, RF and MWA) are desirable

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Thank you!

