BIOLOGIA E TRATTAMENTO RADIANTE CURATIVO DELLA **MALATTIA OLIGOMETASTATICA**

VIRTUAL
26 MARZO 2021

Trattamento della malattia oligometastatica ed oligoprogressiva: stato dell' arte e prospettici in termini di studi clinici – Tumori del colon-retto e tratto gastroenterico

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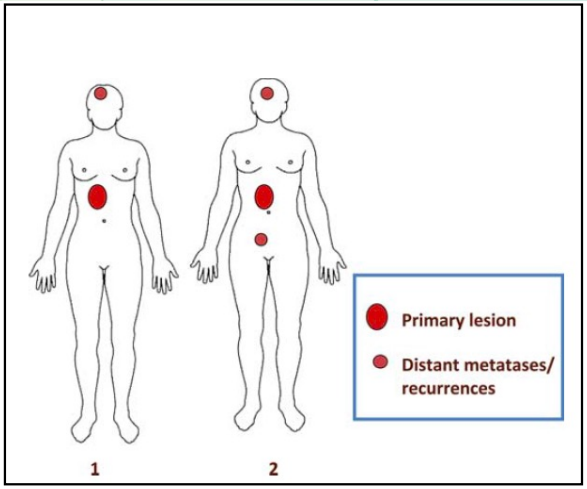
UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

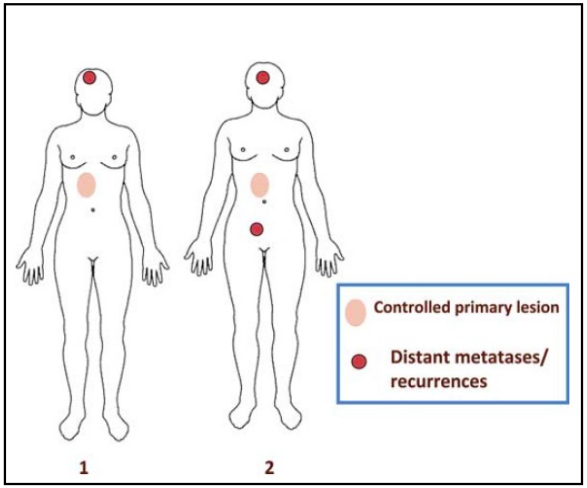
Colorectal cancer

- ✓ Up to 20% of pts have metastatic CRC at presentation
  - ✓ Metastatic rate: 60-70% liver; 25-40% lung; 5-10% bone; 3-5% ovary; 1% adrenal gland; 1% CNS
  - ✓ 50% have disease limited to the liver at the time of death
  - ✓ 20% liver-only disease

- ✓ An additional 25-50% will develop metastasis after initial early or locally advanced stage disease

- ✓ Median overall survival: up to 36 months (from 16 months in 10 years) but **within clinical trials**
- ✓ Long-term survivors: around 14% at 5 years (population-based data from NCI)





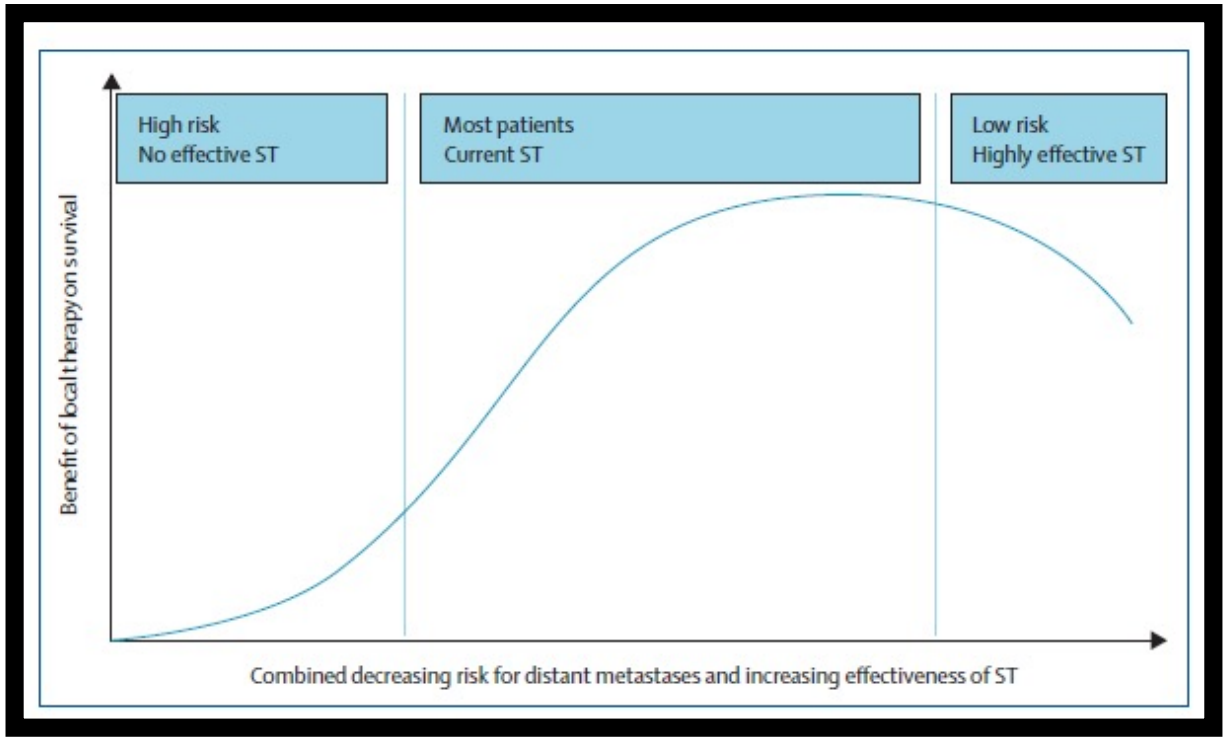
DE NOVO metastatic CRC- Around 20%

Recurrence after previously treated localized disease - around 40%
Metastatic rate

- Stage I (T1/T2N0) – around 10%
- Stage II (T3/T4N0) – 10-20%
- Stage III (Any T/N+) – 25-50%

R0 surgical resection + adjuvant CT reduces risk of relapse to 20-30%

Intrinsic biology and systemic therapy effectiveness drives local control effect on survival



Poortmans et al; Lancet 2014

Molecular tumor profiling in CRC

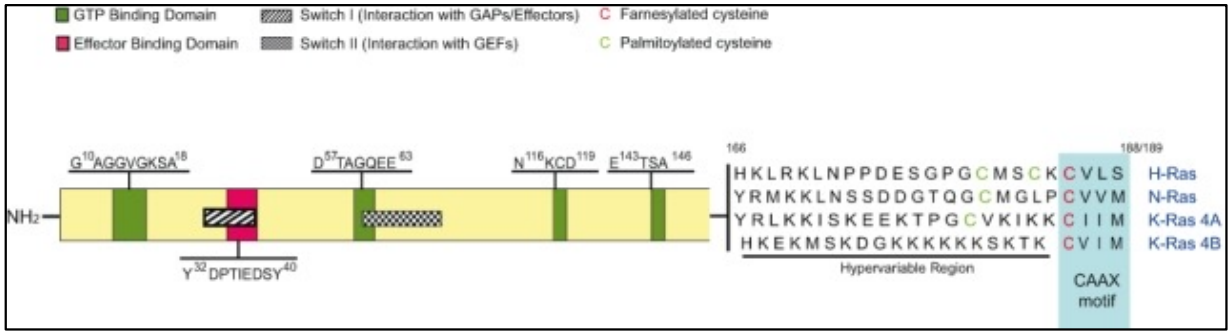
- ✓ Pathologic testing of tumor tissue to assess:
  - ✓ Sequential variants in NRAS, KRAS, BRAF
  - ✓ MSI-H and MMR-D
  - ✓ c-erb-B2 amplification

- ✓ Valuable for all pts with metastastic CRC willing to receive systemic treatment
- ✓ Molecular profiling can be performed on primary tumor specimen
- ✓ If tissue unavailable: re-biopsy

Survival depends on the molecular subtype which informs prognosis:

- ✓ Identifying tumor's natural history
- ✓ Selecting the most suitable therapeutic approach

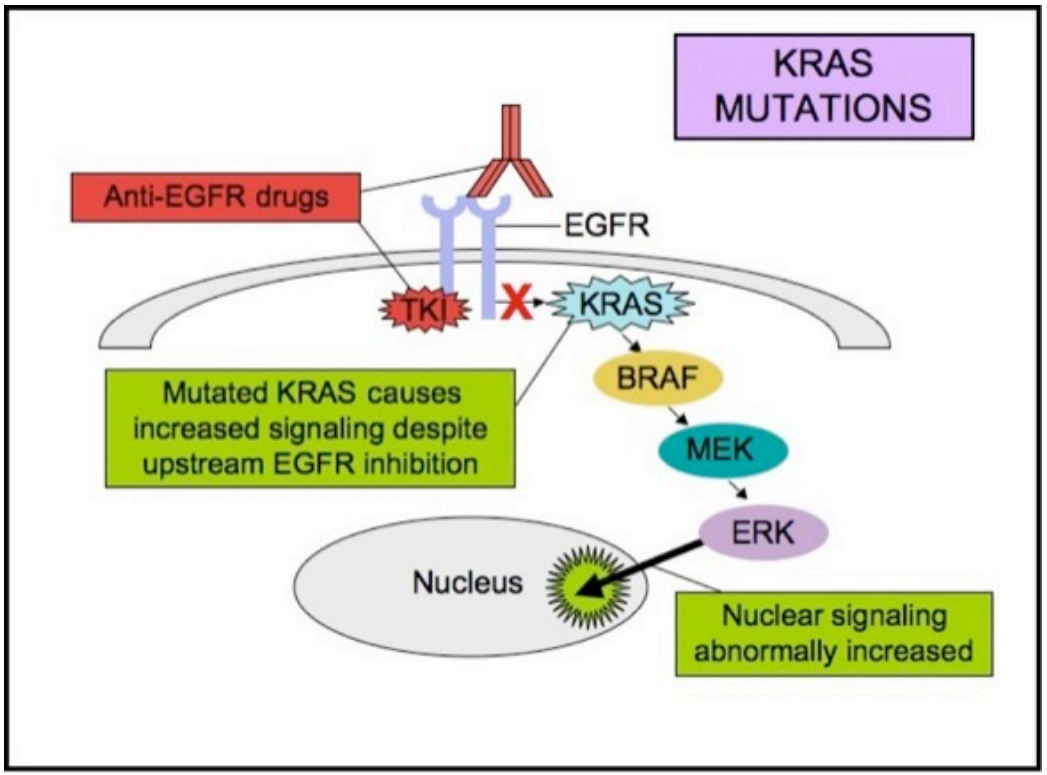
RAS protein



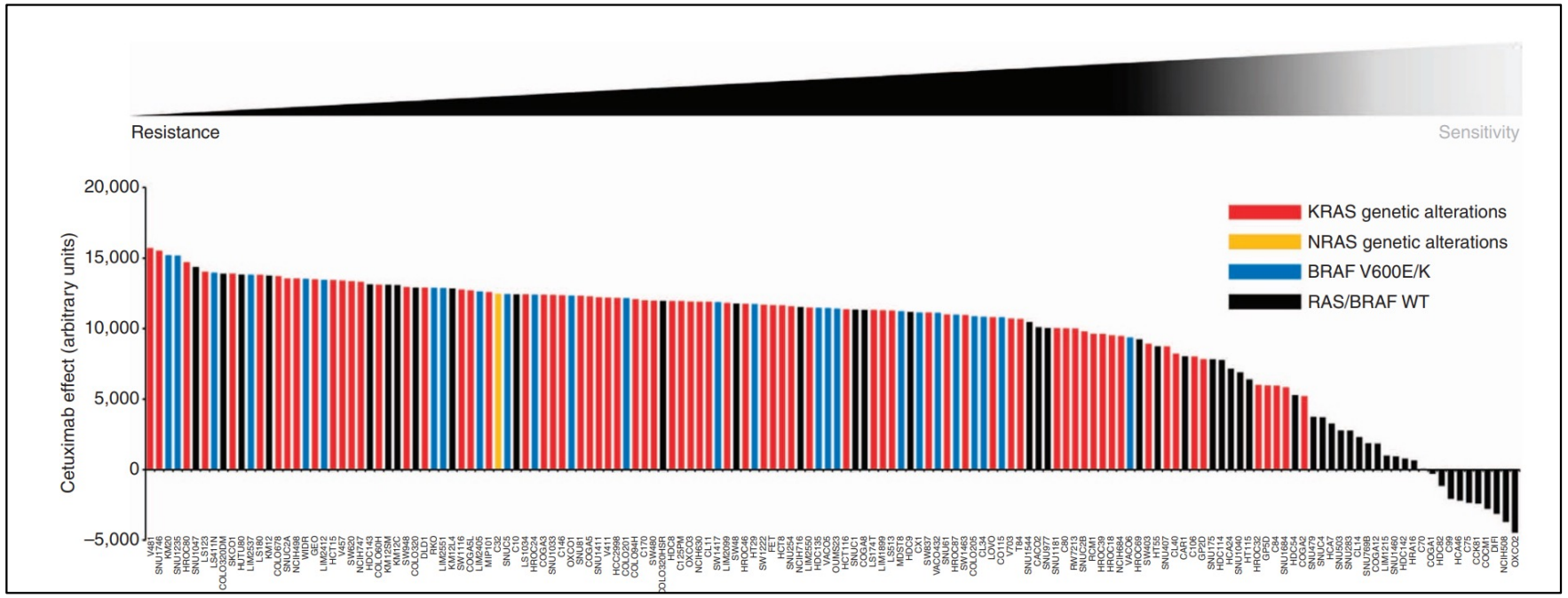
- ✓ KRAS/NRAS/BRAF wt (50%): median survival 30 months (with therapy); OS: 80% (1-yr); 40% (3-yr); 20% (5-yr) from start I line CT
- ✓ Median survival: 19 months R-sided (⇧ KRAS and BRAF sequence variations, ⇧ MSI-H) vs 34 months L-sided CRC
- ✓ Pooled analysis 5 RCT: median OS CRC with KRAS sequence variations: 21 months and 11.7 months for those with BRAF sequence variations

Nitsche U et al, Dig Surg 2016; Modest DP et al, Ann Oncol 2016; Biller LH et al, JAMA 2021

Resistance to anti-EGFR drugs

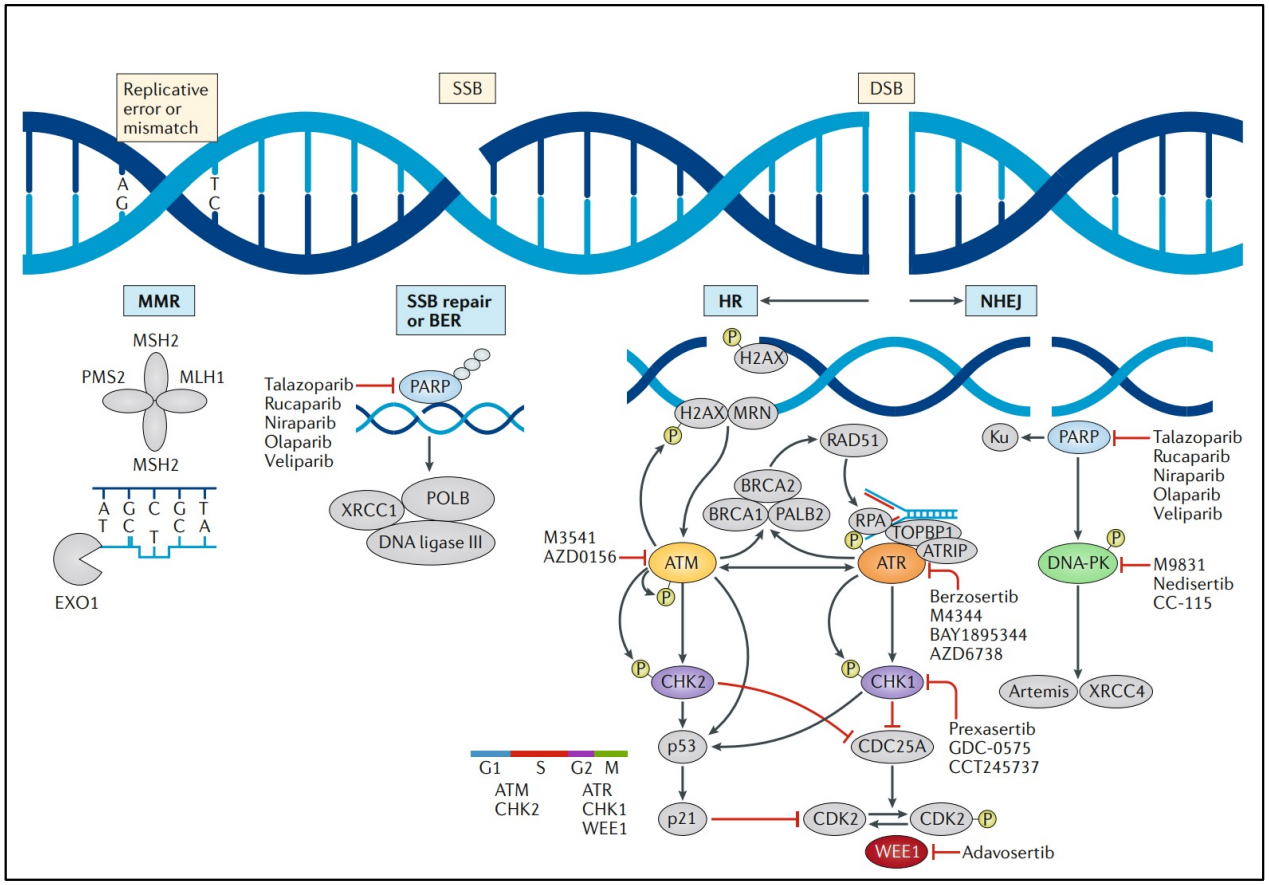


Cetuximab screening on CRC cell lines



The indicated cell lines were treated with increasing concentrations of cetuximab for 4 days and the cell viability was assessed by measuring ATP content. Bars represent an arbitrary index of cetuximab effect on each cell line as detailed in the methods. Cell lines sensitive to cetuximab are shown with a negative index. Red bars represent KRAS altered lines; yellow bars indicate NRAS-mutated cells; blue bars indicate genetic alterations affecting codon V600 of BRAF; black bars indicate RAS/BRAF wild-type cells. NCIH630 cells are KRAS amplified46

Medico E et al, Nat Commun 2015



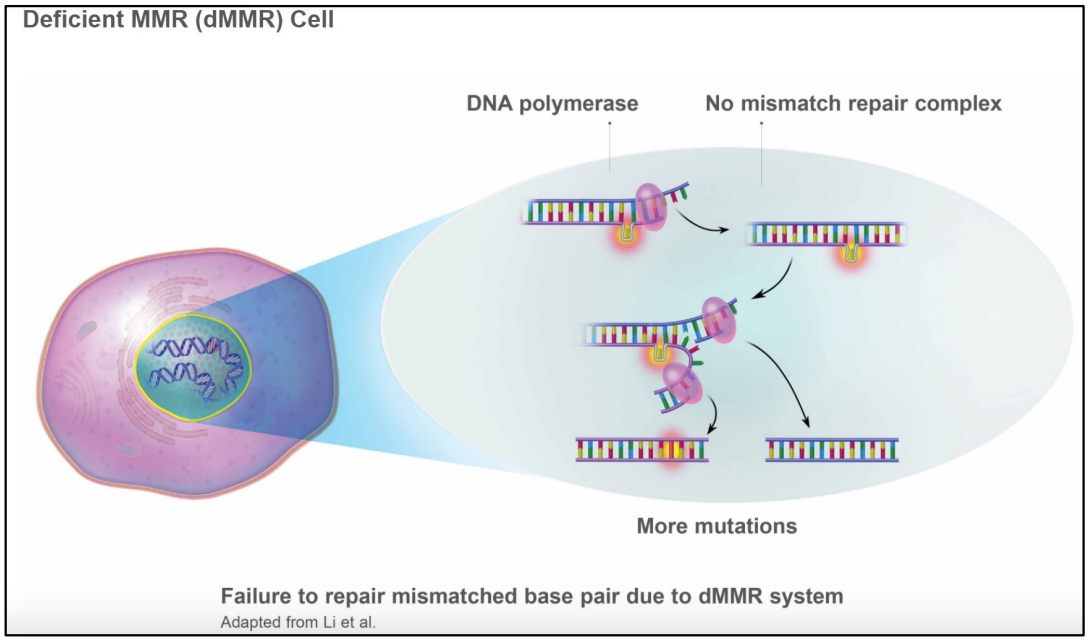
DNA damage response pathway

Errors in base-pair matching during DNA replication are repaired by the MMR system

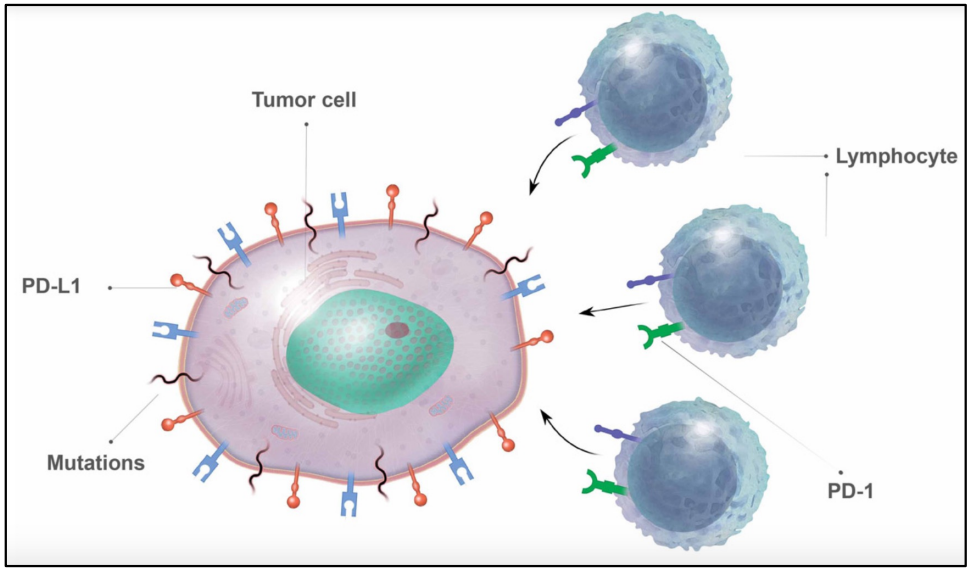
Yap et al; Nat Rev Cancer 2018

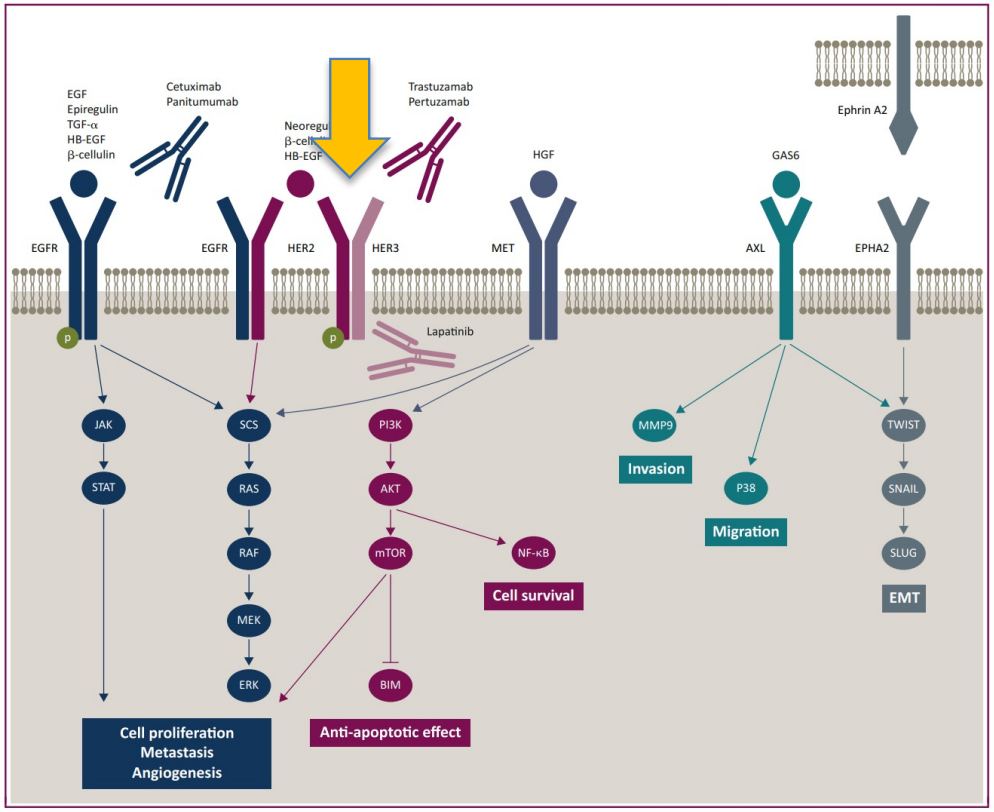
- ✓ MMR-D: mismatch repair deficiency (via IHC)
- ✓ MSI-H: microsatellite instability-high (via PCR)

- Faulty mismatch repair process: accumulation of insertions/deletions at sites of repetitive DNA units called MICROSATELLITES. This situation is called Microsatellite instability
- Tumors having MSI due to MMR-D can exhibit MSI-high (MSI-H) phenotype



- ✓ Tumors with MMR-D/MSI-H harbors thousands mutations which are a trigger for the immune system
- ✓ MSI-H tumors contain high levels of lymphocyte infiltrates and strong expression of immune checkpoints, including PD-1 and PD-L1
- ✓ In colorectal MSI-H cancers, the dominant source of PD-L1 may be macrophages or other tumor-infiltrating lymphocytes and myeloid cells, rather than tumor cells





c-erbB2/HER2

- Human epidermal growth factor receptor 2 (*HER2*) is an oncogenic driver
- A subset (approximately 5%) of metastatic colorectal cancer (CRC) tumors is driven by amplification or mutation of *HER2*.

- HER2 is a clinically actionable target in CRC, with relevance as a therapeutic target
- Substantial clinical benefit in patients treated with biomarker-driven HER2-targeted therapies, with an impact on response rates and duration of response
- HER2-targeted therapeutic strategies have the potential to change the treatment paradigm for a clinically relevant subgroup of metastatic CRC patients.

Martinelli et al; Ann Oncol 2020
Siena et al; Ann Oncol 2018

FDA-approved drugs for the treatment of metastatic CRC

Drug name	FDA-approval	Mechanism of action	Typical use	Common AE (% Grades 1-4)	SeverAE (% Grades 3-4)
Leucovorin	1952	Folic acid analog; interrupts DNA synthesis	Combined with 5-FU	Not reported	Not reported
5-FU	1962	Pyrimidine analog; interrupts DNA synthesis	Combined with Leucovorin	Anemia (79), diarrhea (61), mucositis (62), nausea (51), neutropenia (46)	Coronary vasospasm (<8), diarrhea (10), mucositis (14), neutropenia (8)
CPT-11	1996	Topoisomerase I inhibitor; intrrupts the breaking and rejoining of DNA strands during replication	As single agent or in combination	Anemia (97), alopecia (60), diarrhea (83), nausea (82), neutropenia (96)	Anemia (7), diarrhea (31), nausea (16), neutropenia (31)
Capecitabine	1998	Pyrimidine analog; interupts DN synthesis	As single agent or in combination	Anemia (80), diarrhea (55), H/F syndrome (54), nausea (43), neutropenia (13)	Coronary vasospasm (<8), diarrhea (10), mucositis (14), neutropenia (8), H/F syndrome (17)
Oxaliplatin	2002	Alkylating agent; causes DNA breaks	Only in combination	Anemia (64), diarrhea (46), nausea (64), peripheral neuropathy (76), thrombocytopenia (30)	Hypersensitivity reaction (<1), neuropathy (7), neutropenia (<10)
Cetuximab	2004	Recombinant chimeric monoclonal antibody to EGFR; stops cell growth	Used only for KRAS/NRAS wild-type tumors	Acneiform rash (90), constipation (54), diarrhea (42), headache (38), hypomagnesemia (55), nausea (64)	Hypersensitivity reaction (2), hypomagnesemia (6-17), rash (16)
Bevacizumab	2004	Humanized monoclonal antibody VEGF; interrupts growth of blood vessels	Combined with 5-FU/Leucovorin, oxaliplatin, CPT-11	Delayed wound healing (4), diarrhea (21), hypertension (34)	GI perforation (2), hemorrhage (4), hypertension (5), proteinuria (1), thromboses (5)

Biller LH et al, JAMA 2021

FDA-approved drugs for the treatment of metastatic CRC

Drug name	FDA-approval	Mechanism of action	Typical use	Common AE (% Grades 1-4)	SeverAE (% Grades 3-4)
Panitumumab	2006	Humanized monoclonal Ab to EGFR; interrupts cell growth	Use only for KRAS/NRAS wild-type tumors	Diarrhea (21), hypomgnesemia (38), nausea (23), skin toxicity (90), acneiform (57)	Hypersensitivity reaction (1), hypomagnesemia (2), skin toxicity (16)
Regorafenib	2012	Multikinase inhibitors; interrupts cell and blood vessels growth	Used as single agent	Diarrhea (43), H/F syndrome (53), hemorrage (18), hypophosphathemia (57), hypertension (30), pain (59)	Cardiac ischemia (1), H/F syndrome (17), hemorrage (3), hepatotoxicity (0.3)
Ziv-aflibercet	2012	Recombinant fusion protein that function as a decoy receptor to bind VEGF-A and B and placental growth factor; interrupts blood vessels growth	In combination with FOLFIRI	Diarrhea (69), hypertension (41), proteinuria (62)	Diarrhea (19), gastrointestinal perforation (0.8), hemorrage (3), proteinuria (8)
Ramucirumab	2015	Recombinant humanized monolonal antibody to VEGF-R2; interrupts growth of blood vessels	In combination with FOLFIRI	Diarrhea (14), hypertension (16), proteinuria (15)	Arterial thromboses (2), gastrointestinal perforation (0.7), hemorrage (4), hypertentsion (8)
Pembrolizumab	2017, 2020	Humanized monoclonal Ab against PD-1 receptor; activates T-cell-mediated immune response	Used only for MSI-H/MMR-D tumors; approved in the first or subsequent line of therapy	Arthralgia (16), nausea (16), diarrhea (13), pruritus (13), hypothyroidism (10)	Colitis (2), hepatitis (2), pancreatitis (3), pneumonitis (2)
Nivolumab	2017	Humanized monoclonal Ab against PD-1 receptor; activates T-cell-mediated immune response	Used only for MSI-H/MMR-D tumors	Diarrhea (21), hypothyroidism (10), pruritus (14), rash (13)	Colitis (1), hepatitis (1), pancreatitis (8)
Ipilimumab	2018	Humanized monoclonal Ab against CTLA-4 receptor; activates T-cell-mediated immune response	Used only for MSI-H/MMR-D tumors in combination with nivolumab	Diarrhea (32), pruritus (31), rash (29)	Pneumonitis (<1), colitis (7), hepatitis (4)
Encorafenib	2020	BRAF inhibitor; interrupts cell growth	Used only for BRAF V600E-variant tumors in combination with cetuximab	Anemia (34), arthralgia (26), nausea (34), rash (26)	Anemia (4), cutaneous malignancies (1), hemorrage (2)

Biller LH et al, JAMA 2021

Oxaliplatin-containing regimens	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
FOLFOX	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	Yes	Pancytopenia, neuropathy, hypersensitivity	Most common adjuvant regimen
CAPOX	Every 3 weeks with infusion in clinic and oral capecitabine for 2 weeks, 1 week off	Yes	Pancytopenia, diarrhea, H/F syndrome, neuropathy, hypersensitivity	Common adjuvant regimen; subsitutes oral capecitabine for intravenous 5-FU
FOLFOXIRI	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, neuropathy, hypersensitivity	Intensive regimes used for fit pts, potentially operable on or with limited metastatic disease or both
FOLFOX + cetuximab or panitumumab	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, H/F syndrome, hypomagnesemia, hypersensitivity reactions, neuropathy, skin toxicity	For tumors with KRAS/NRAS/BRAF wilde type; ineffective for tumors with sequence variations in these genes

Irinotecan-containing regimens	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Irinotecan	Frequency depending on dosing schema	No	Diarrhea	Severe diarrhea and neutropenia may occur in pts with UGT1A (NCBI 7361) polymoprphism
FOLFIRI	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea	Not used in adjuvant regimens; dosing schedule as FOLFOX
CAPIRI	Every 3 weeks with infusion in clinic and oral capecitabine for 2 weeks, 1 week off	Yes	Pancytopenia, diarrhea, H/F syndrome	Substitutes oral capecitabine for iv 5-FU
Irinotecan + cetuximab or panitumumab	Either weekly of every 2 weeks by infusion	No	Diarrhea, hypomagnesemia, infusion reactions, skin toxicity	KRAS/NRAS/BRAF wild type
FOLFIRI + cetuximab or panitumumab	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, hypomagnesemia, infusion reaction, skin toxicity	KRAS/NRAS/BRAF wild type

Biller LH et al, JAMA 2021

Fluorouracil-containing regimens	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Fluorouracil and leucovorin	Bolus and continous infusion regimens	Yes	Pancytopenia, mucositis	Single-agent regimen; often optimal for frail pts with major comorbidities
Capecitabine	Oral regimen given for 3 of every 4 weeks	Yes	Pancytopenia, H/F syndrome	May be preferred if no plans to intensify treatment

VEGF-containing regimens	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Bevacizumab + FOLFOX, CAPOX, FOLFIRI, CAPIRI, FOLFOXIRI, 5-FU and leucovorin, or capecitabine	Infusion time depends on specific CT given	Yes	Hypertension, bowel perforation, poor wound healing, proteinuria, thrombosis	All molecular subtypes
FOLFIRI + Ramicirumab	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	No	Pancytopenia, diarrhea, hypertension, poor wound healing, proteinuria	All molecular subtypes
FOLFIRI + zif-aflibercept	Every 2 weeks; half day infusion in the clinic; 5-FU as continuous infusion via pump for 2 days as outpatient	No	Pancytopenia, diarrhea	All molecular subtypes

EGFR Ab monotherapy	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Cetuximab	Either weekly or every 2 weeks by infusion	No	Infusion reaction, hypomagnesemia, skin toxicity	KRAS/NRAS wild type
Panitumumab	Every 2 weeks by infusion	No	Infusion reaction, hypomagnesemia, skin toxicity	KRAS/NRAS wild type

Biller LH et al, JAMA 2021

Immunotherapy regimens for metastastic CRC with MSI-H/MMR-D	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Pembrolizumab	Every 3 or 6 weeks by infusion	Yes	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only
Nivolumab	Every 2 by infusion	No	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only
Nivolumab + ipilumumab	Every 2 by infusion	No	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only

Combination regimens for metastastic CRC expressing BRAF V600E sequence variation + RAS wt	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Encorafenib + Cetuximab	Either weekly or every 2 weeks infusion with continuous oral regimen	No	Diarrhea, pancytopenia, skin toxicity	BRAF V600E variant

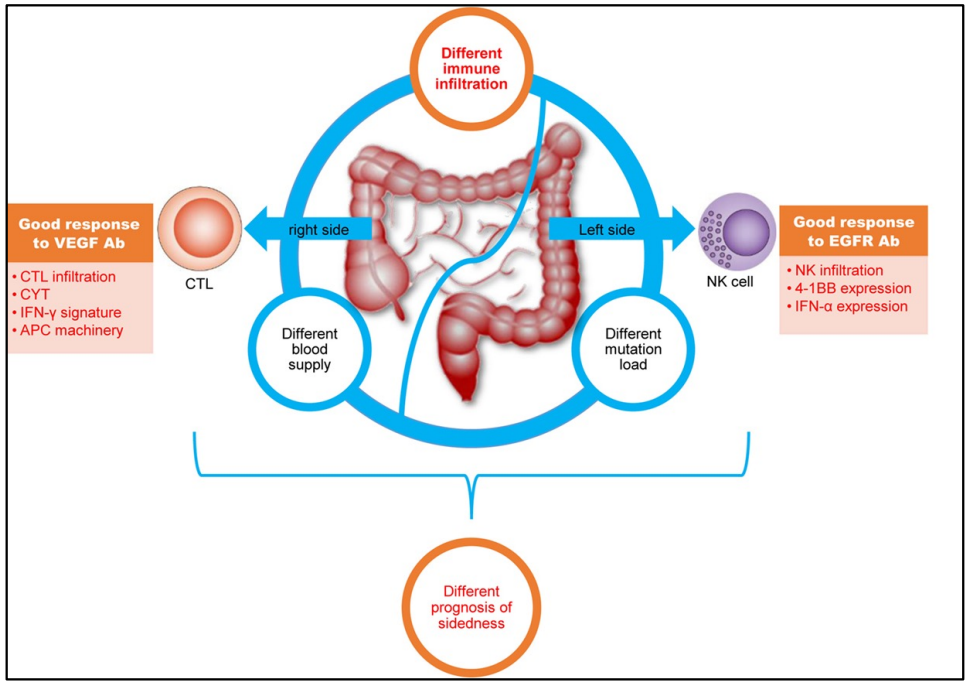
Other regimens for refractory metastastic CRC	Dosing schedule	First-line use	Dose limiting toxicity/AE	Comments
Regorafenib	Oral regimen given for 3 ot 4 weeks	No	H/F syndrome, hypophosphatemia, hepatotoxicity	All molecular subtype
Trastuzumab + pertuzumab or palatinib or tucatinib	Every 3 weeks or weekly infusion with continuous oral regimen	No	Diarrhea, hypokalemia, cardiotoxicity	ERBB2 amplified

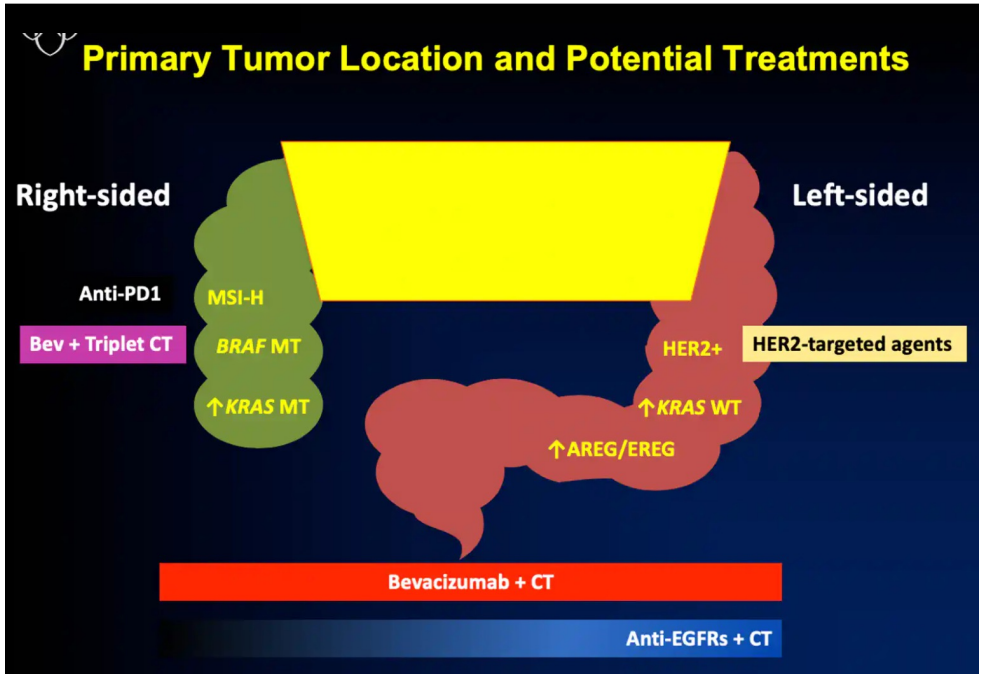
Biller LH et al, JAMA 2021

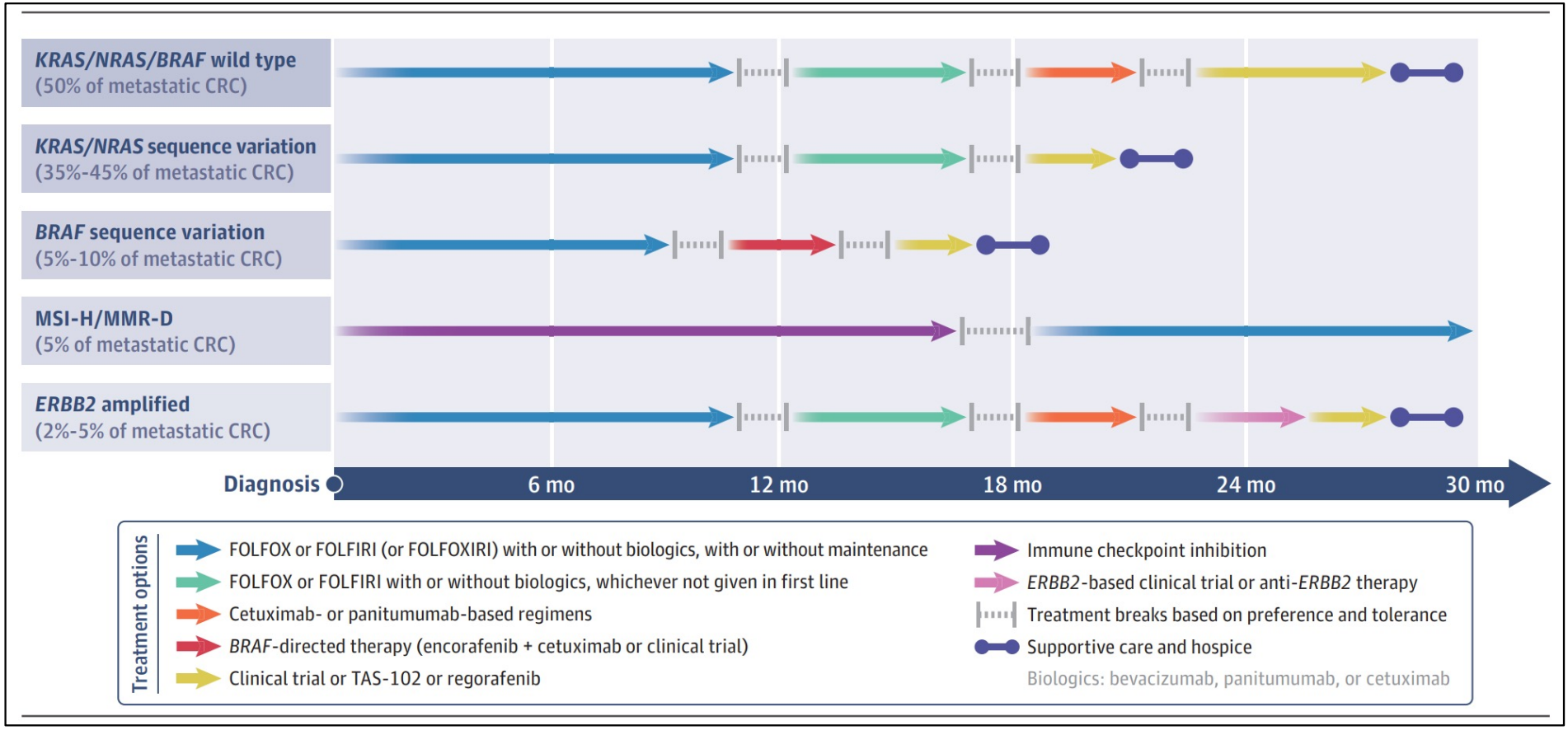
Biomarker	Incidence	Gene	Predictive	Prognostic	Treatment
KRAS	40%	Exon 2,3,4	Resistance to anti-EGFR	Decreased OS	Chemotherapy + Bevacizumab
NRAS	3%-5%	Exon 2,3,4	Resistance to anti-EGFR	Reduced OS	Chemotherapy + Bevacizumab
BRAF	8%-12%	Exon 15	Resistance to anti-EGFR (unclear)	Reduced OS	FOLFOXIRI + Bevacizumab
HER2	5%	Chromosome 17 amplification	Sensitivity to anti-HER2	None	Trastuzumab +/- Pertuzumab OR +/-Lapatinib
MSI/MMR	12%-15%	Not applicable	Sensitivity to checkpoint inhibitors	None	Pembrolizumab Nivolumb+/- Ipilimumab

Summary features of biomarkers in stage IV colorectal cancerEGFR = epithelial growth factor receptor; FOLFOXIRI = regimen of chemotherapy consisting of 5-fluorouracil, folinic acid, oxaliplatin and irinotecan; MMR = mismatch repair; MSI = microsatellite instability; OS = overall survival; WT = wild type

Afrasanie et al; Radiol Oncol 2019


Different immune infiltration
Good response to VEGF Ab
• CTL infiltration
• CYT
• IFN-γ signature
• APC machinery
CTL
right side
Left side
NK cell
Good response to EGFR Ab
• NK infiltration
• 4-1BB expression
• IFN-α expression
Different blood supply
Different mutation load
Different prognosis of sidedness


Primary Tumor Location and Potential Treatments
Right-sided
Left-sided
Anti-PD1
MSI-H
Bev + Triplet CT
BRAF MT
↑KRAS MT
HER2+
HER2-targeted agents
↑KRAS WT
↑AREG/EREG
Bevacizumab + CT
Anti-EGFRs + CT



Biller LH et al, JAMA 2021

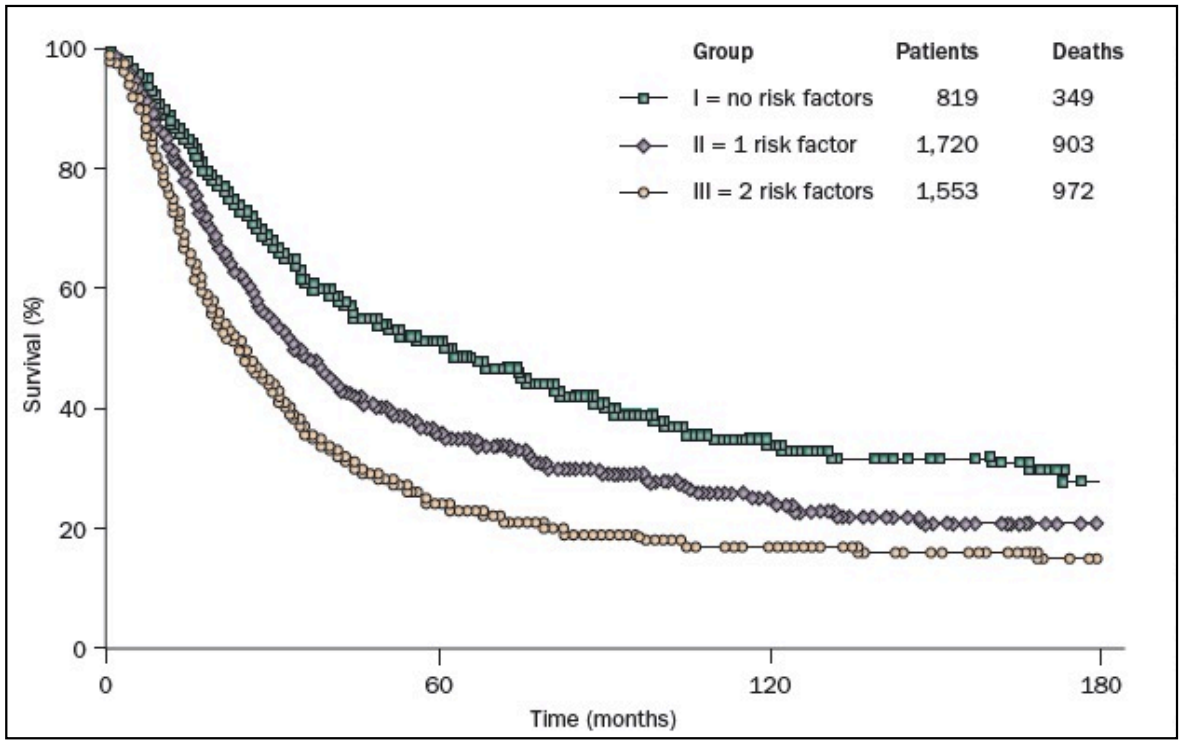
What about metastasis-directed therapy in CRC oligometastatic patients?

Anselmo Bucci, Fuoco! 1918, collezione Mazzei Buizza

The Oligometastatic State

- Patients with few (1-5) metastases may be at a continuum between truly local disease and widely disseminated cancer
- In such a state of limited disease burden, the eradication of all sites of metastatic disease could result in long-term survival or even cure in a subgroup of pts
- This hypothesis is based on long-term survival following surgical resection of limited lung and liver metastases in some tumors (especially CRC)

Long term results of lung metastasectomy: prognostic analyses based on 5206 cases



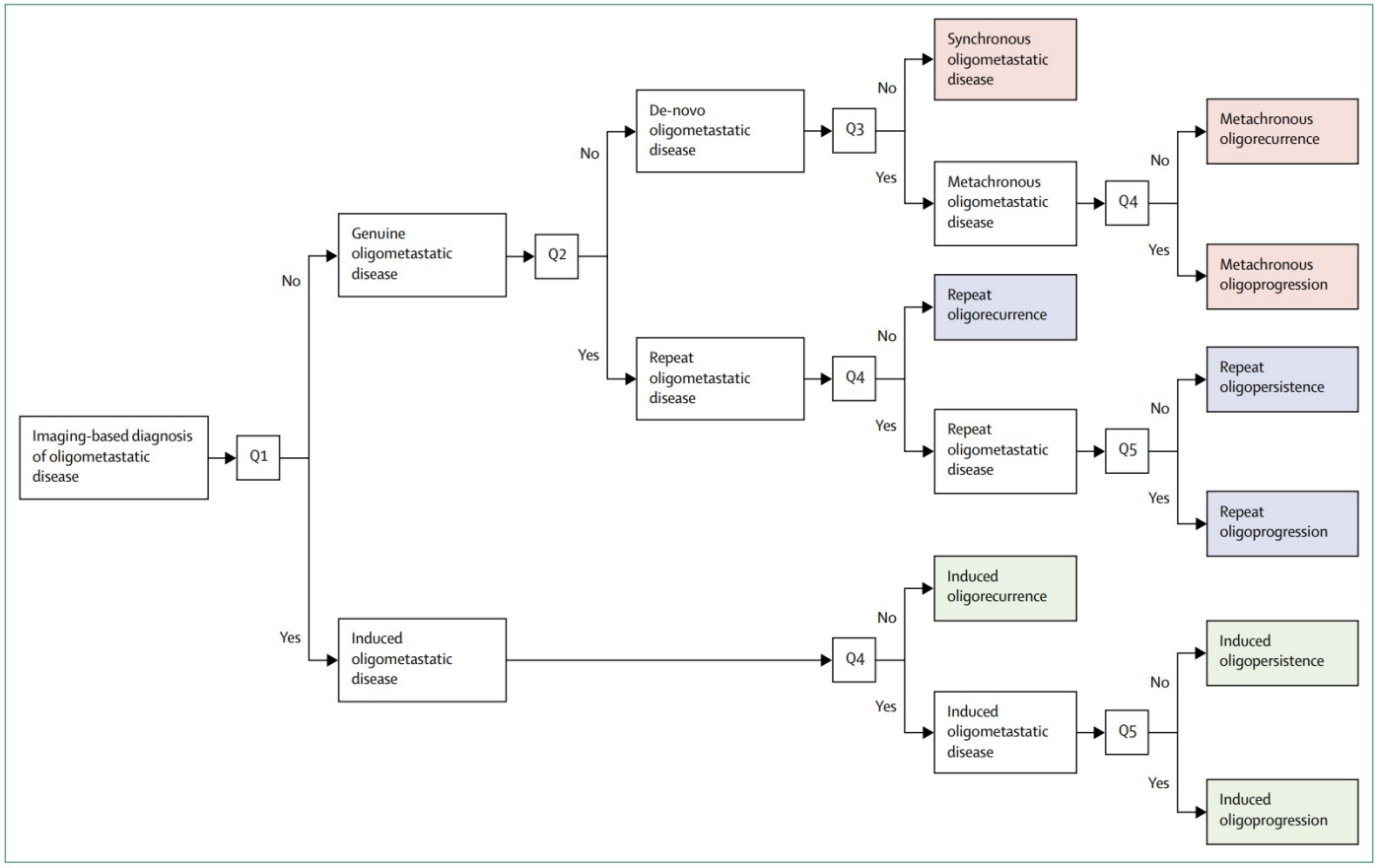
MEDIAN SURVIVAL TIME:

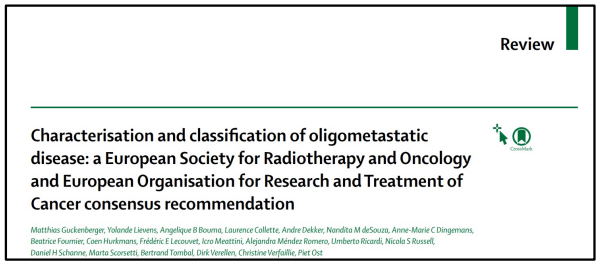
- Group I: 61 mo
- Group II: 34 mo
- Group III: 24 mo

RISK FACTORS:
- Disease-Free Interval from primary tumor to mts < 36 months
- Multiple metastases

Pastorino U et al; J Thorac Cardiovascul Surg 1997

ESTRO-EORTC consensus recommendation for the characterisation and classification of oligometastastic disease




Review

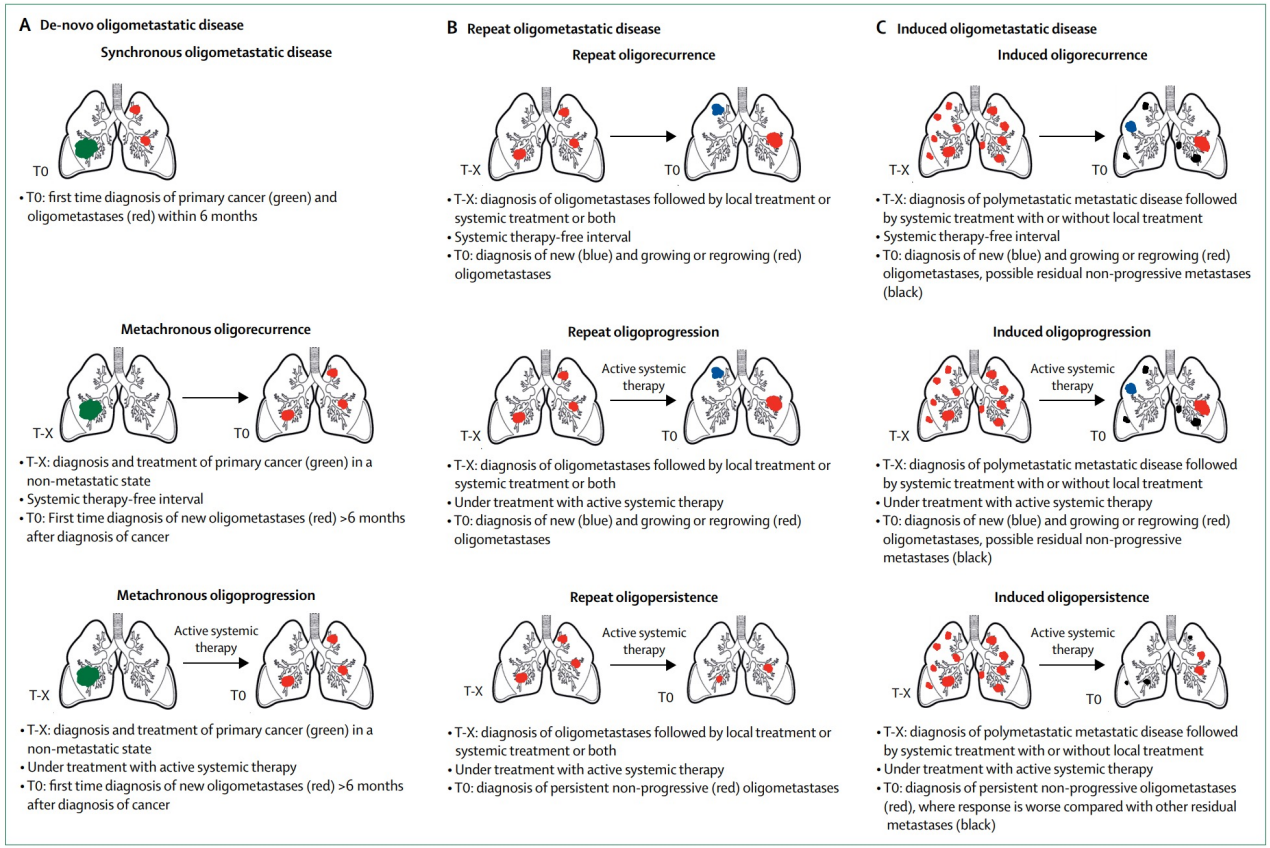
Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

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 M Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost

- ✓ Q1: Does the pt have a history of polymetastatic disease before current diagnosis of oligometastatic disease?
- ✓ Q2: Does the pt have a history of oligometastatic disease before current diagnosis of oligometastatic disease?
- ✓ Q3: Has oligometastastic disease been first diagnosed more than 6 months after the primary cancer diagnosis?
- ✓ Q4: Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis?
- ✓ Are any oligometastatic lesions progressive on current imaging?

Guckenberger M et al; Lancet Oncol 2020

ESTRO-EORTC consensus recommendation for the characterisation and classification of oligometastastic disease

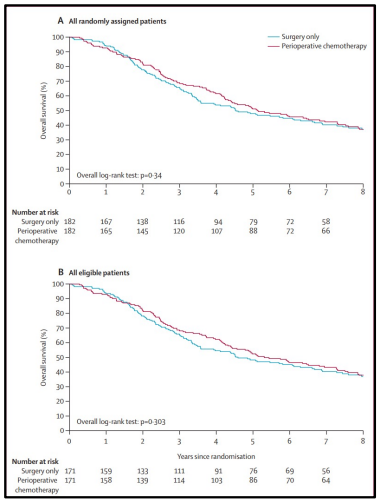


Guckenberger M et al; Lancet Oncol 2020

EORTC 40983

Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial

Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Euan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Murielle Mauer, Erik Tanis, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger, for the EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, Arbeitsgruppe Lebermetastasen und -tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), Australasian Gastro-Intestinal Trials Group (AGITG), and Fédération Francophone de Cancérologie Digestive (FFCD)



5-year OS: 51% for pts with metastatic CRC with 1 to 4 liver mets receiving peri-operative CT and surgery to mets

Nordingler B et al; Lancet Oncol 2013

EORTC 4004

OXFORD

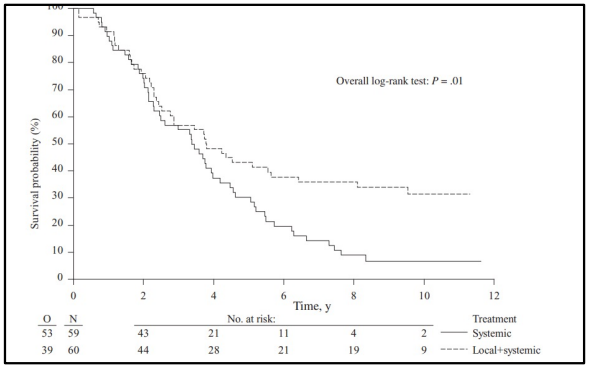
JNCI J Natl Cancer Inst (2017) 109(9): djx015

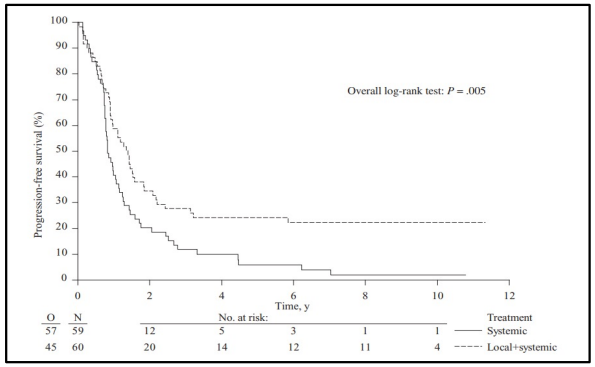
doi: 10.1093/jnci/djx015
First published online March 17, 2017
Article

ARTICLE

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

Theo Ruers, Frits Van Coevorden, Cornelis J. A. Punt, Jean-Pierre E. N. Pierie, Inne Borel-Rinkes, Jonathan A. Ledermann, Graeme Poston, Wolf Bechstein, Marie-Ange Lentz, Murielle Mauer, Gunnar Folprecht, Eric Van Cutsem, Michel Ducreux, Bernard Nordlinger; for the European Organisation for Research and Treatment of Cancer (EORTC) Gastro-Intestinal Tract Cancer Group, Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), and the National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG)



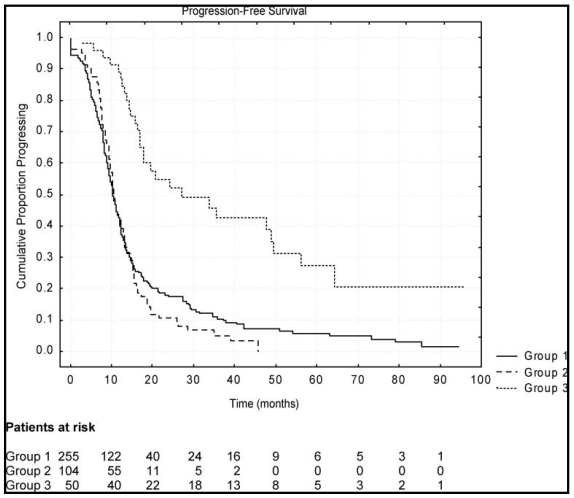


Improved OS for pts with up to 9 mets receiving RFA + systemic therapy vs systemic therapy alone (Combined modality treatment arm: 5-year OS: 43.1%; 8-year OS: 35-9%). Median OS: 45.6 months

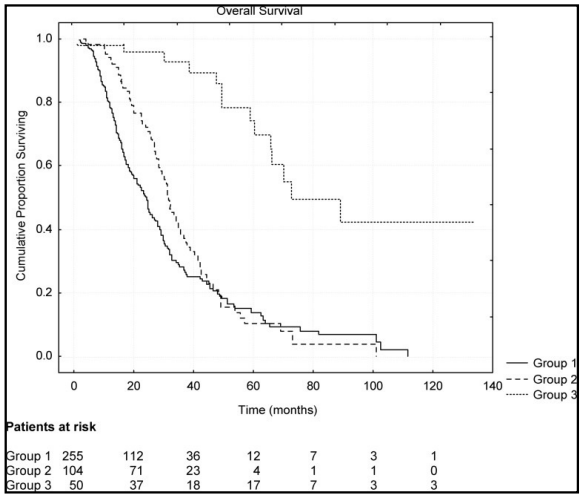
Ruers T et al; JNCI 2017

The Role of Lung Metastasis Resection in Improving Outcome of Colorectal Cancer

Progression-free survival



Overall survival



Group 1
Lung and
Extrapulmonary metastases
255 pts

Group 2
Only lung metastases
Not submitted to surgery
104 pts

Group 3
Only lung metastases
submitted to surgery
50 pts (19 after CT)

Tampellini M et al; Oncologist. 2012

Randomised studies of MDT in oligometastatic cancer

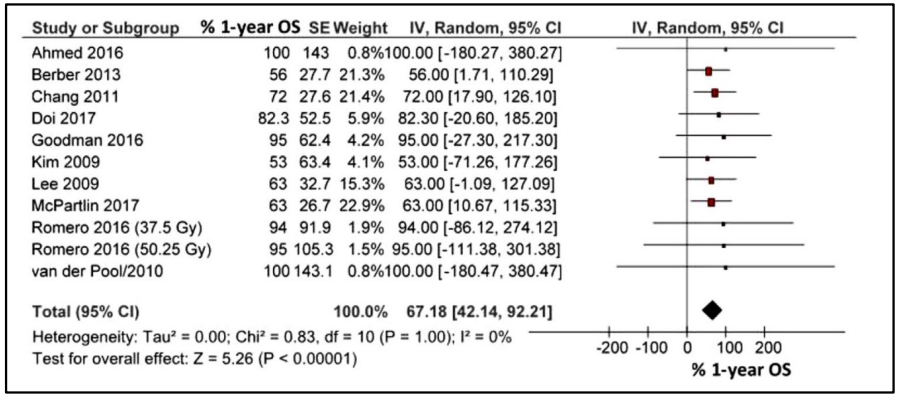
Author	Population	Intervention	Clinical benefit
Ruers et al	≤ 10 unresectable colorectal liver metastases, no extrahepatic disease	Standard systemic therapy vs standard systemic therapy with RFA ± resection	HR for OS: 0.58 (p=0.01)
Gomez et al	n=49, ≤ 3 NSCLC metastases without progression after 3 months' systemic therapy	Maintenance CT vs maintenance CT vs MDT	Median PFS: 14.2 months vs 23.1 months (p=0.022); median OS: 17 months vs 41.2 months (p=0.017)
Lyengar et al	n=29, ≤ 5 NSCLC metastases with stable disese after ICT	Maintenance CT vs consolidative ablative RT of SABR followed by maintenance CT	Median PFS: 3.5 months vs 9.7 monthd (p=0.01)
Ost et al	n=62; ≤ 3 asymptomatic, extracranial prostate cancer metastases	Observation vs MDT (SABR in 25 pts; surgery in 6)	ADT-free survival: 13 months vs 21 months (p=0.11)
Palma et al/ SABR-COMET Trial	n=99; ≤ 5 solid tumor metastases	Standard of care vs SABR + standard of care	Median OS: 28 months vs 41 months (p=0.09); 5-year OS: 42.3% vs 17.7% (p=0.006)
Phillips et al/ORIOLE Trial	N=54; ≤ 3 castrate-sensitive prostate cancer metastases	Observation vs SABR	PSA progression at 6 months: 61% vs 19% (p=0.005); median PFS: 5.8 months vs not reached (p=0.002); new lesions at 6 months: 16% vs 63% (p=0.006)

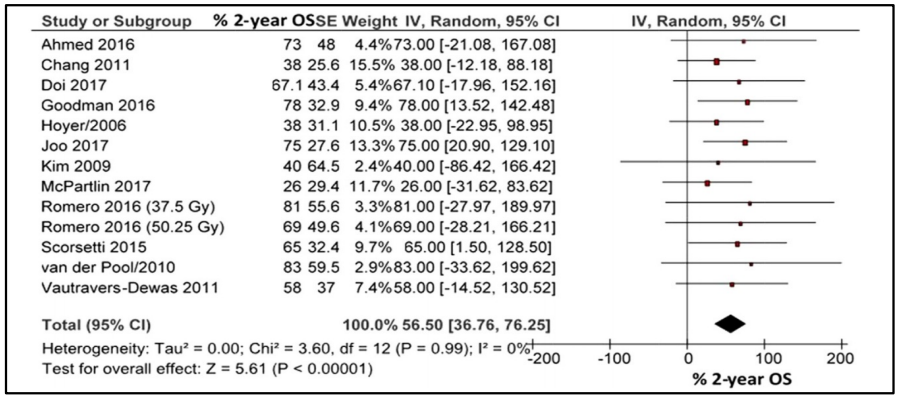
Beckham TH, BJC 2020

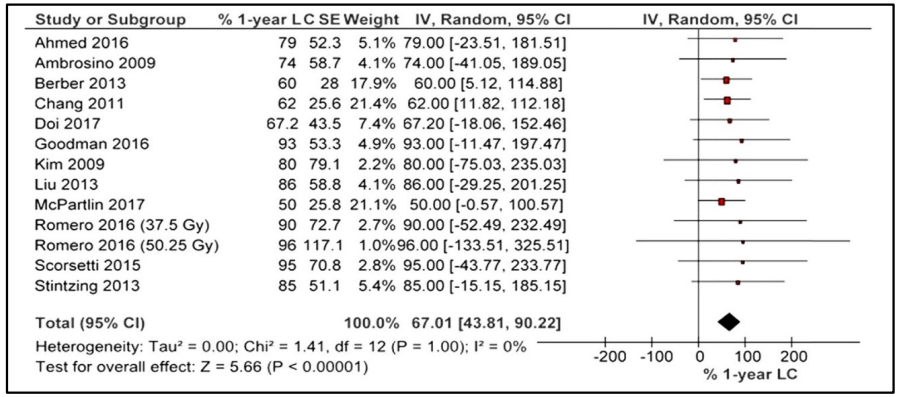
Liver metastases from CRC

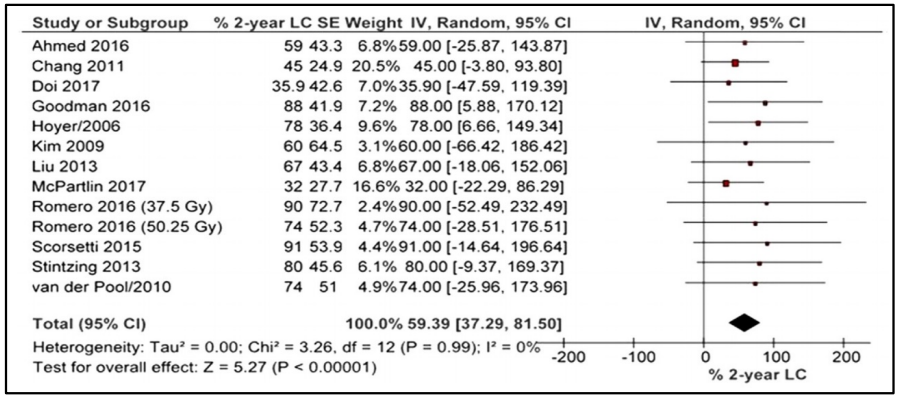
Pooled 1- and 2-year OS: 67.2% and 56.5%

Pooled 1- and 2-year LC: 67% and 59.3%









Petrelli F et al; Radiother Oncol 2018

Critical Reviews in Oncology / Hematology 129 (2018) 91–101

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review

J. Kobiela[a], P. Spychalski[a,*], G. Marvaso[b], D. Ciardo[b], V. Dell'Acqua[b], F. Kraja[c], A. Błażyńska-Spychalska[a], A.J. Łachiński[a], A. Surgo[b], R. Glynne-Jones[d], B.A. Jereczek-Fossa[b,e]

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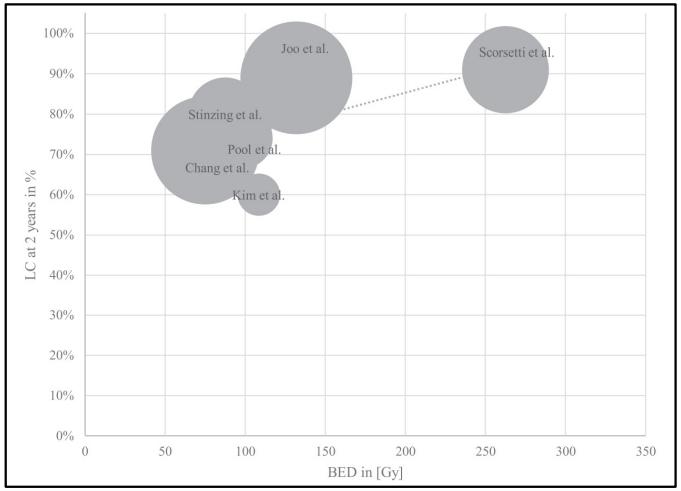
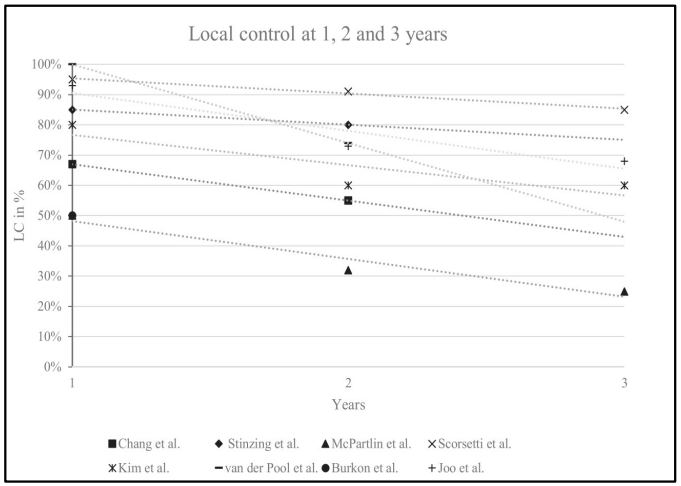
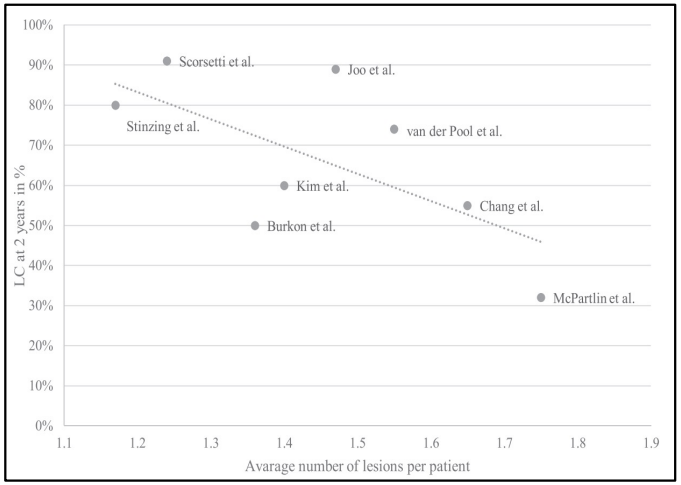
[b] Department of Radiotherapy, European Institute of Oncology, Milan, Italy
[c] Department of Oncology, University Hospital Centre "Mother Theresa", Tirana, Albania
[d] Mount Vernon Centre for Cancer Treatment, Northwood, Middlesex, HA6 2RN, UK
[e] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Local control in the liver at 2 years over BED



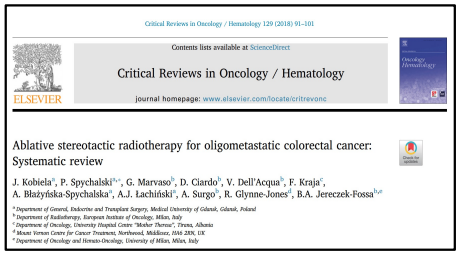


Liver metastases from CRC



Local control in the liver at 2 years over average number of liver mets

Kobiela J et al; CROH 2018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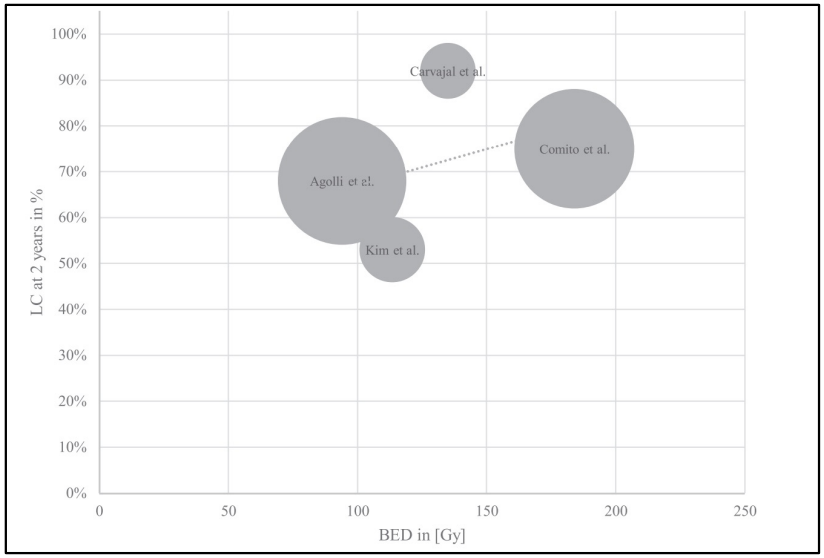
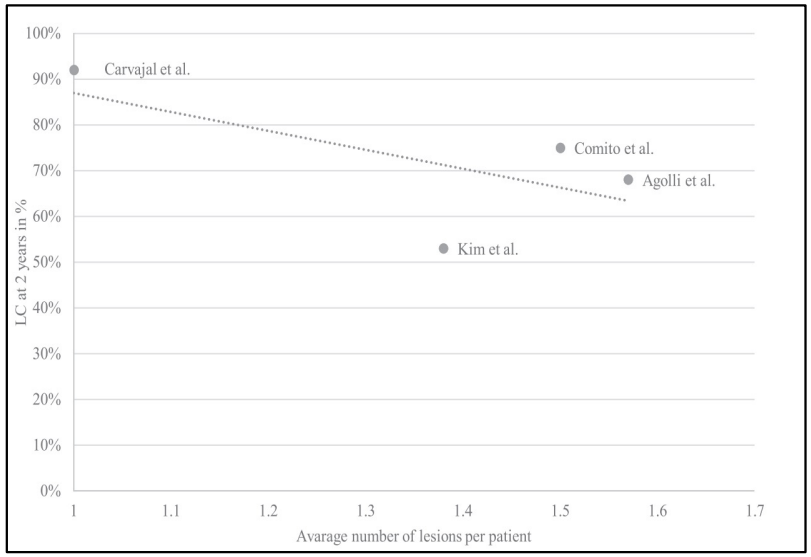
Lung metastases from CRC

Local control in the lung at 2 years over BED



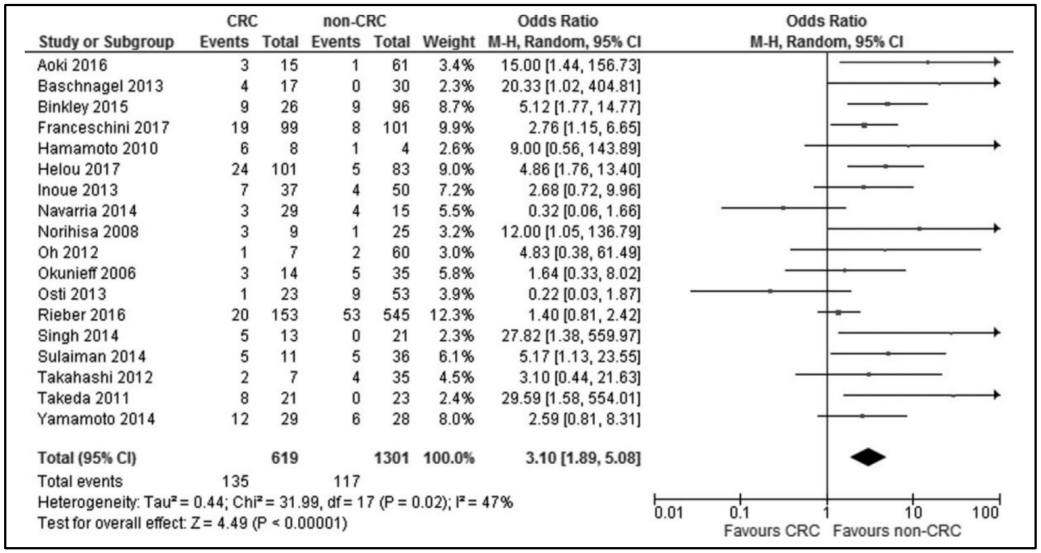
Local control in the lung at 2 years over average number of lung mets



Kobiela J et al; CROH 2018

Lung oligometastases from CRC

Author		No. of Patients	No. of Failures	Median Follow-up Period	Dose/Fraction	Median BED10	Local Control Rate
Aoki[7]	CRC*	15	3	31.7 months	50 Gy/5 fractions	100 GyBED	3 years: 47.6%
	non-CRC	61	1				3 years: 97.5%
Baschnagel[8]	CRC	17	4	27.6 months	60 Gy/4 fractions	132 GyBED	2 years: 80%
	non-CRC	30	0				2 years: 100%
Binkley[9]	CRC	26	9	22 months	25 Gy/1 faraction or 50 Gy/4 fractions	85 GyBED	2 years: 57.6%
	non-CRC	96	9				2 years: 90.1%
Franceschini[10]	CRC	99	19	24.2 months	48 Gy/4 fractions	105.6 GyBED	3 years: 75.7%
	non-CRC	101	8				3 years: 88.2%
Hamamoto[12]	CRC	8	6	19 months	48 Gy/4 fractions	105.6 GyBED	25%
	non-CRC	4	1				75%
Helou[4]	CRC	101	24	22 months	52 Gy/4 fractions	119.6 GyBED	2 years: 76.4%
	non-CRC	83	5				2 years: 91.7%
Inoue[13]	CRC	37	7	NA	48 Gy/4 fractions	105.6 GyBED	81%
	non-CRC	50	4				92%
Navarria[14]	CRC	29	3	18 months	48 Gy/4 fractions	105.6 GyBED	89.7%
	non-CRC	15	4				73.3%
Norihisa[21]	CRC	9	3	27 months	48 Gy/4 fractions	105.6 GyBED	66.7%
	non-CRC	25	1				96%
Oh[15]	CRC	7	1	21 months	60 Gy/5 fractions	132 GyBED	85.7%
	non-CRC	60	2				96.7%
Okunieff[16]	CRC	14	3	14.9 months	50 Gy/ 10 fractions	75 GyBED	78.6%
	non-CRC	35	5				85.7%
Osti[5]	CRC	23	1	15 months	30 Gy/1 fraction	120 GyBED	95.7%
	non-CRC	53	9				83.0%
Rieber[11]	CRC	153	20	14.3 months	NA	84.4 GyBED	86.9%
	non-CRC	545	53				90.3%
Singh[17]	CRC	13	5	16.7 months	50 Gy/5 fractions	100 GyBED	61.50%
	non-CRC	21	0				100%
Sulaiman[18]	CRC	11	5	17 months	NA	110 GyBED	54.50%
	non-CRC	36	5				86.10%
Takahashi[19]	CRC	7	2	20 months	48 Gy/4 fractions	105.6 GyBED	2 years: 67%
	non-CRC	35	4				2 years: 89%
Takeda[3]	CRC	21	8	29 months	50 Gy/5 fractions	100 GyBED	2 years: 73%
	non-CRC	23	0	15 months			2 years: 94%
Yamamoto[2]	CRC	29	12	35 months	48 Gy/4 fractions	105.6 GyBED	2 years: 25.5%
	non-CRC	28	6				2 years: 70.0%

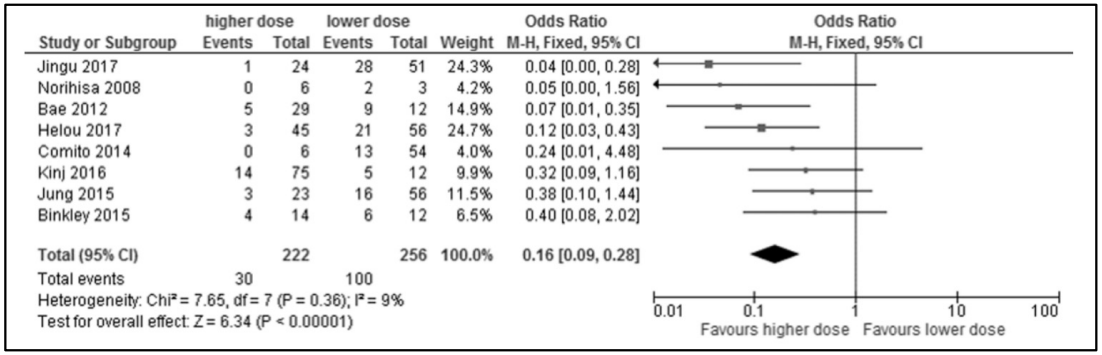


Pulmonary oligometastases from colorectal cancer are more difficult to control by SBRT than those from other cancers

Jingu K et al; TCRT 2018

Lung oligometastases from CRC

Author	Median Follow-up Period	Higher Dose Group				Lower Dose Group			
		Median BED10	No. of Patients	No. of Failures	Local Control Rate	Median BED10	No. of Patients	No. of Failures	Local Control Rate
Jingu[6]	28 months	132 GyBED	24	1	3 years: 95.5%	105.6 GyBED	51	28	3 years: 59.6%
Norihisa[20]	27 months	132 GyBED	6	0	3 years: 100%	105.6 GyBED	3	2	NA
Bae[21]	28 months	180 GyBED	29	5	3 years: 69%	124.8 GyBED	12	9	3 years: 49%
Helou[4]	22 months	150 GyBED	45	3	2 years: 90%	119.6 GyBED	56	21	2 years: 70%
Kinj[22]	33 months	180 GyBED	75	14	2 years: 82.1%	87.5 GyBED	12	5	2 years: 57.1%
Comito[23]	24 months	180 GyBED	6	0	3 years: 100%	105.6 GyBED	54	13	3 years: 70%
Jung[24]	42.8 months	150 GyBED	23	3	3 years: 84%	105.6 GyBED	56	16	3 years: 64.6%
Binkley[9]	22 months	112.5 GyBED	14	4	2 years: 62.5%	87.5 GyBED	12	6	2 years: 16.7%



Dose escalation could achieve better local control in patients who received SBRT for pulmonary oligometastases from colorectal cancer

Jingu K et al; TCRT 2018

Radiotherapy and Oncology 145 (2020) 178–185

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Stereotactic ablative radiation therapy for pulmonary metastases: Improving overall survival and identifying subgroups at high risk of local failure

Dario Pasalic [a], Yi Lu [b], Sonia L. Betancourt-Cuellar [c], Nicolette Taku [a], Shane M. Mesko [a], Alexander F. Bagley [a], William W. Chance [a,1], Pamela K. Allen [a], Chad Tang [a], Mara B. Antonoff [d], Peter A. Balter [e], Reza J. Mehran [d], James W. Welsh [a], Zhongxing Liao [a], Daniel Gomez [a], Jeremy J. Erasmus [c], Quynh-Nhu Nguyen [a,*]

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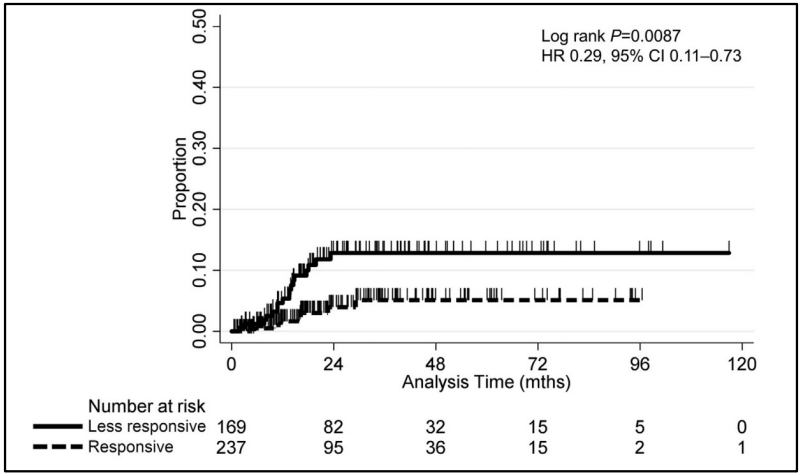
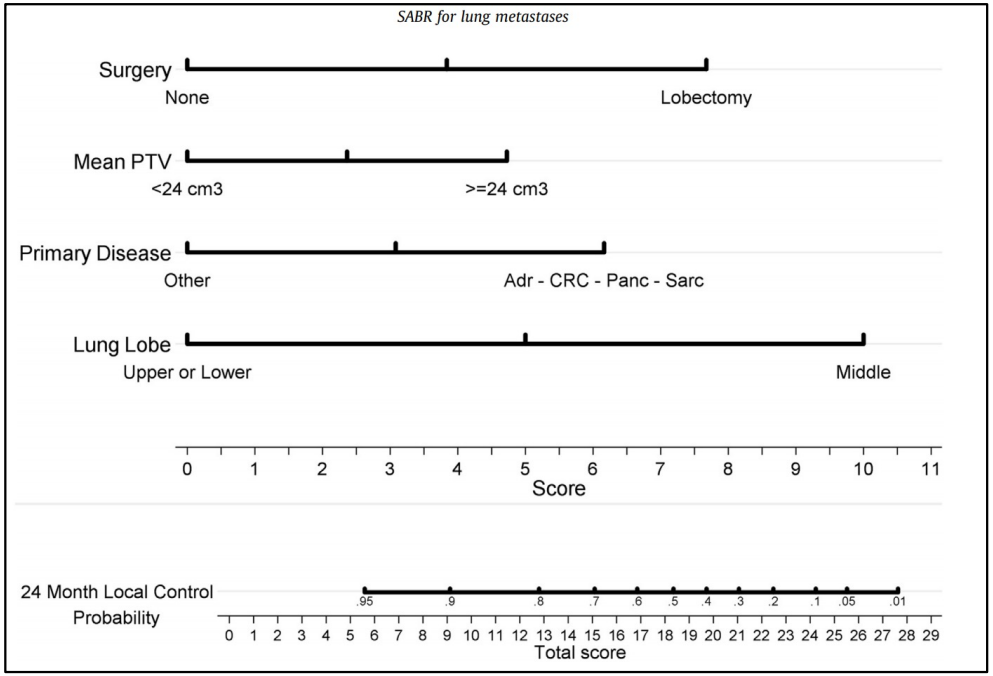
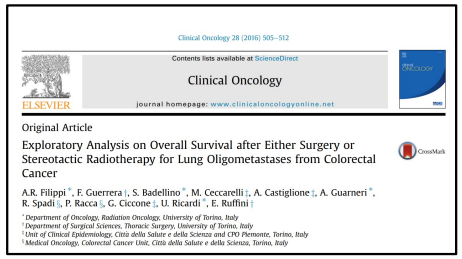




Pasalic D et al; Radiother Oncol 2020

Treatment effect on overall survival for lung oligometastases in CRC pts


Clinical Oncology 28 (2016) 505–512
Contents lists available at ScienceDirect
Clinical Oncology
journal homepage: www.clinicaloncologyonline.net

Original Article

Exploratory Analysis on Overall Survival after Either Surgery or Stereotactic Radiotherapy for Lung Oligometastases from Colorectal Cancer

A.R. Filippi *, F. Guerrera †, S. Badellino *, M. Ceccarelli ‡, A. Castiglione ‡, A. Guarneri *, R. Spadi §, P. Racca §, G. Ciccone ‖, U. Ricardi *, E. Ruffini †
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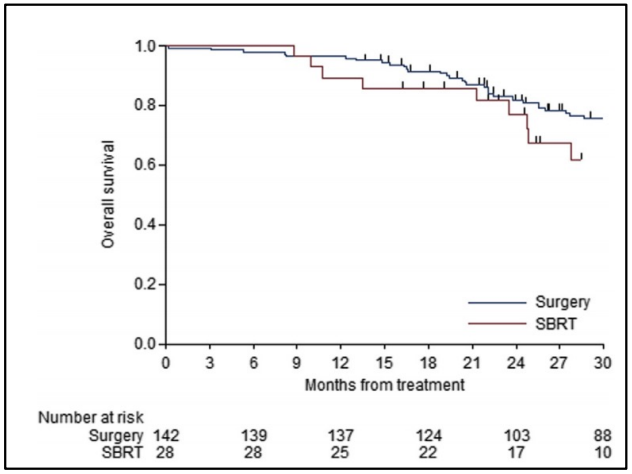
OS according to treatment received



Crude and adjusted effects on OS of SBRT vs surgery as estimated via Cox's models

	Crude effect (univariate)			Adjusted effect (multivariable)			Adjusted effect (IPTW, multivariable)		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Treatment									
Surgery	1			1			1		
SBRT	1.70	(0.84; 3.43)	0.139	1.71	(0.82; 3.54)	0.149	1.28	(0.58; 2.82)	0.547
Gender									
Male	1			1			1		
Female	1.00	(0.56; 1.79)	0.993	0.91	(0.50; 1.65)	0.753	0.83	(0.38; 1.79)	0.630
Age at treatment (every 10 years)	1.03	(0.77; 1.38)	0.850	0.91	(0.68; 1.24)	0.558	1.11	(0.75; 1.62)	0.606
Charlson score									
0	1			1			1		
≥1	1.53	(0.85; 2.73)	0.156	1.44	(0.77; 2.67)	0.250	1.15	(0.49; 2.69)	0.755
CEA (ng/ml)									
≤5	1			1			1		
>5.0	0.88	(0.41; 1.90)	0.740	0.84	(0.38; 1.83)	0.654	0.71	(0.26; 1.91)	0.495
Unknown	1.16	(0.61; 2.23)	0.648	1.04	(0.52; 2.04)	0.921	1.14	(0.45; 2.9)	0.784
Maximum size of metastases (every 10 mm)	1.17	(0.92; 1.49)	0.208	1.17	(0.91; 1.51)	0.219	1.28	(0.89; 1.83)	0.177
Disease-free interval (every year)	0.93	(0.80; 1.08)	0.355	0.94	(0.80; 1.09)	0.411	0.89	(0.71; 1.13)	0.336

HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting; CEA, carcinoembryonic antigen.

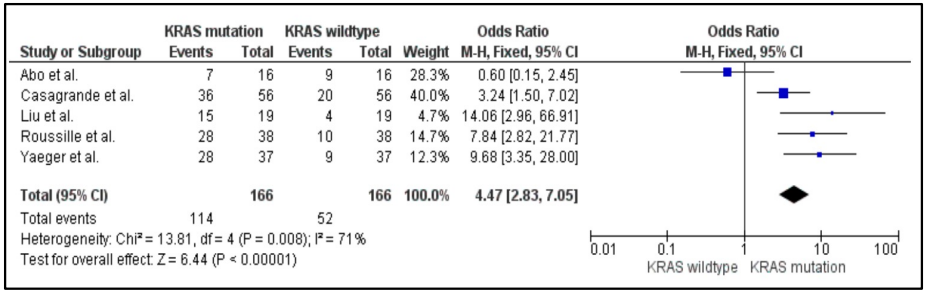
Filippi AR et al; Clin Oncol 2016

Brain metastases from CRC

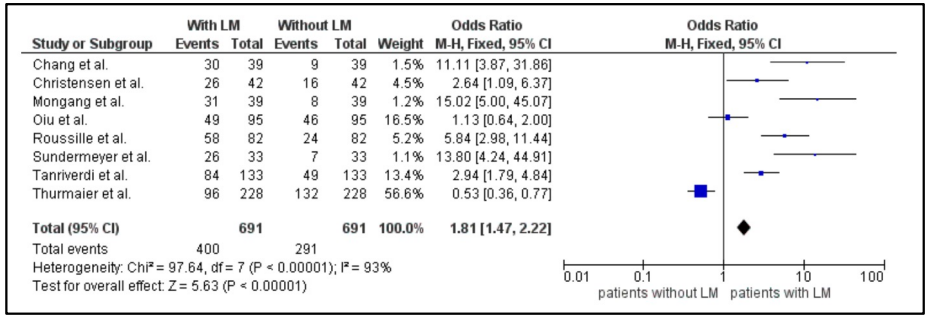
Risk factors for developing brain metastasis

	CEA Level	Staging (TNM or UICC)	Multiple Extra-Cerebral Metastases	Location of CRC	Bone Metastases	Lung Metastases	*KRAS*	Others
Mo et al. (2020)	x	High N or High T						
Lei et al. (2020)		UICC > III	x					
Thurmaier et al. (2020)		UICC IV	x		x	x		
McGovern et al. (2019) *								Asian ethnicity
Prasanna et al. (2018)				Rectal cancer	x			
Roussille et al. (2018)						x	x	
Liu et al. (2018)							x	*BRAF*
Lee et al. (2017) *							x	*ALK*
Yang X.-H. et al. (2017) *	x			Rectal cancer		x		
Christensen et al. (2016)				Rectal cancer		x		
Qiu et al. (2015)						x		
Casagrande et al. (2015)							x	
Yaeger et al. (2015)							x	
Chang et al. (2015) *						x		
Tanriverdi et al. (2014) *						x		
Zoratto et al. (2013) *						x	x	
Dhingani et al. (2012) *		UICC IV	x			x		
Mongan et al. (2009)				Left-sided CRC		x		*CXCR4*
Sundermeyer et al. (2005)						x		

Presence of KRAS sequence variations



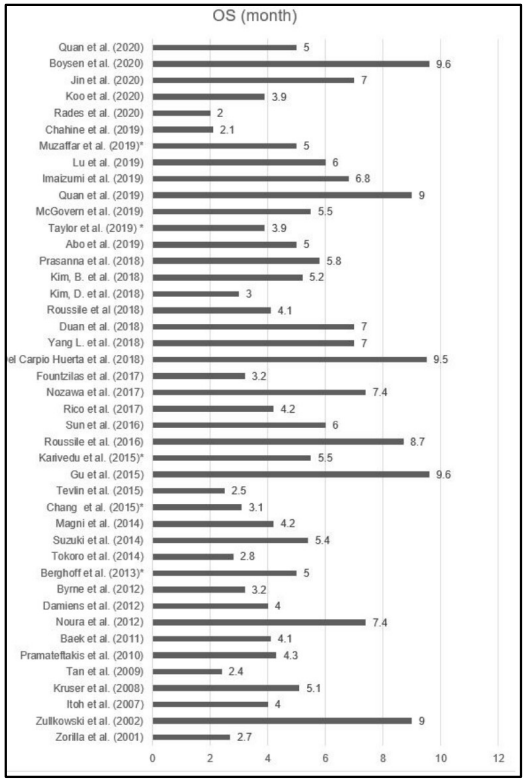
Presence of lung metastases



Muller S et al; Cancers 2021

Brain metastases from CRC

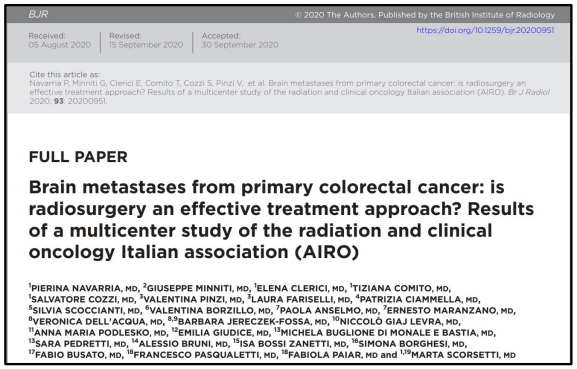
OS for pts wth brain mets from CRC



Predictors of poor OS

	Positive CEA level	Low KPS	Extracranial Metastases	Multiple BM	Age	Location of CRC	Others	Score
Thurmaier et al. (2020)			Liver					
Quan et al. (2020)	x		x		x			x
Mo et al. (2020)	x		x	x	x			x
Boysen et al. (2020)							N2	
Jin et al. (2020) *				x	x			
Rades et al. (2020)								x
Muzaffar et al. (2019) *						x		
Lu et al. (2019)		x		x				
Imaizumi et al. (2019)		x		x			History of chemotherapy	
Quan et al. (2019)		x	x					
Taylor et al. (2019) *			Liver					
Kim B. et al. (2018) *								x
Roussile et al. (2018)			Lung	x			PDL1+	
Duan et al. (2018)			Bone	x	x			
Yang L. et al. (2018)			x			x	Pathology	
Del Carpio Huerta et al. (2018)			x			x		
Berghoff et al. (2017) *						x		
Sun et al. (2016) *		x		x				
Nieder et al. (2016)								x
Roussile et al. (2016) *				x				
Karivedu et al. (2015) *		x		x				
Gu et al. (2015)			x	x				
Chang et al. (2015) *			x				*KRAS* mutation	
Berghoff et al. (2013) *				x		x		
Noura et al. (2012)	x		x					

Muller S et al; Cancers 2021



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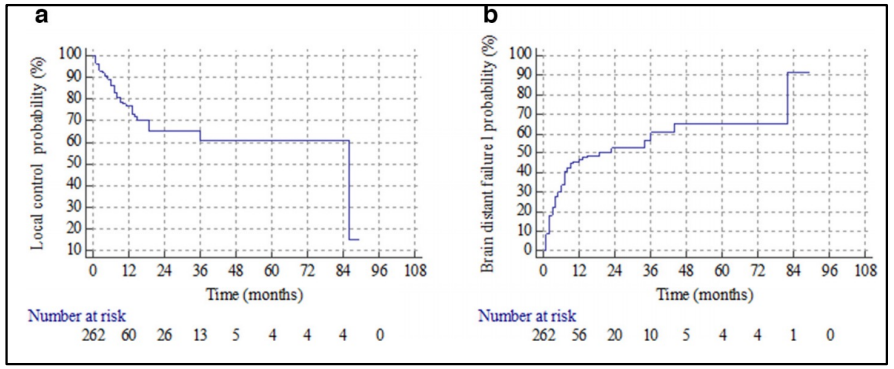
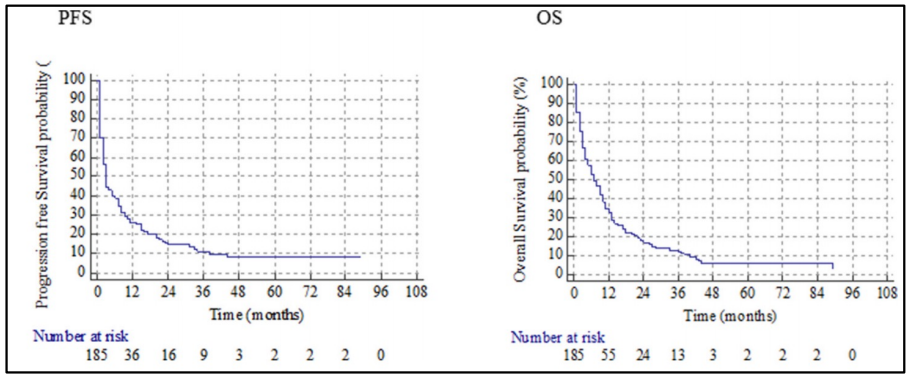
FULL PAPER

Brain metastases from primary colorectal cancer: is radiosurgery an effective treatment approach? Results of a multicenter study of the radiation and clinical oncology Italian association (AIRO)

[1]PIERINA NAVARRIA, MD, [2]GIUSEPPE MINNITI, MD, [1]ELENA CLERICI, MD, [1]TIZIANA COMITO, MD, [1]SALVATORE COZZI, MD, [3]VALENTINA PINZI, MD, [3]LAURA FARISELLI, MD, [4]PATRIZIA CIAMMELLA, MD, [5]SILVIA SCOCCIANTI, MD, [6]VALENTINA BORZILLO, MD, [7]PAOLA ANSELMO, MD, [7]ERNESTO MARANZANO, MD, [8]VERONICA DELL'ACQUA, MD, [8,9]BARBARA JERECZEK-FOSSA, MD, [10]NICCOLÒ GIAJ LEVRA, MD, [11]ANNA MARIA PODLESKO, MD, [12]EMILIA GIUDICE, MD, [13]MICHELA BUGLIONE DI MONALE E BASTIA, MD, [14]SARA PEDRETTI, MD, [14]ALESSIO BRUNI, MD, [15]ISA BOSSI ZANETTI, MD, [16]SIMONA BORGHESI, MD, [17]FABIO BUSATO, MD, [18]FRANCESCO PASQUALETTI, MD, [18]FABIOLA PAIAR, MD and [1,19]MARTA SCORSETTI, MD



- ✓ 185 pts and 262 lesions
- ✓ a) Surgery + SRS resection cavity (10.7%);b) SRS (53.8%); fSABR (35.5%)
- ✓ Mostly 24 Gy/1 fr; 28 Gy/3 fr
- ✓ Prognostic factors on distant brain failure: primary tumor site (rectum vs colon); number of BMs



Navarria P et al; BJR 2020

How to select the right (oligo)metastatic patient for MDT ?

Utley & Treasure, J Thorac Oncol 2010

Radiotherapy and Oncology 146 (2020) 29–36

Contents lists available at ScienceDirect

Radiotherapy and Oncology

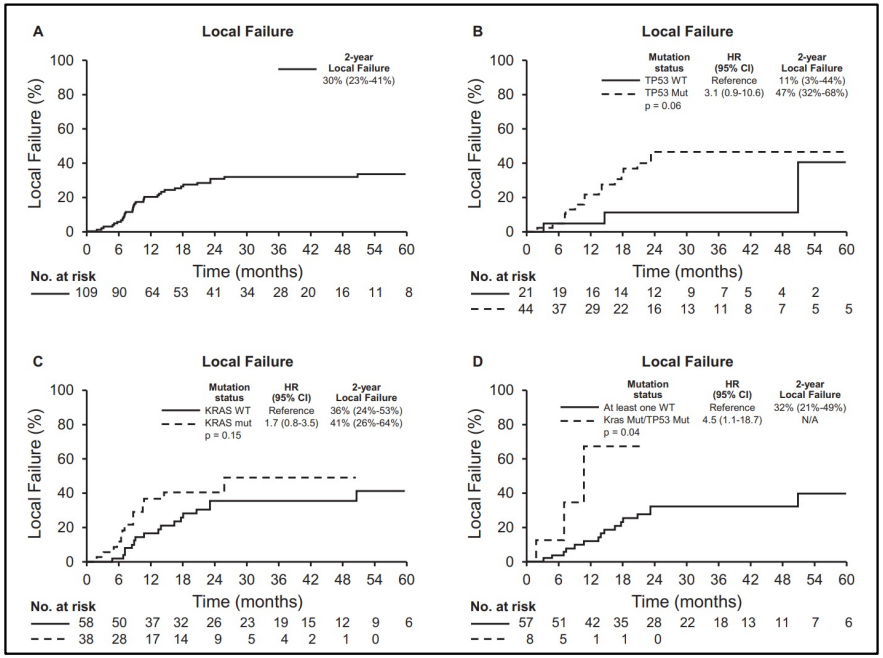
journal homepage: www.thegreenjournal.com

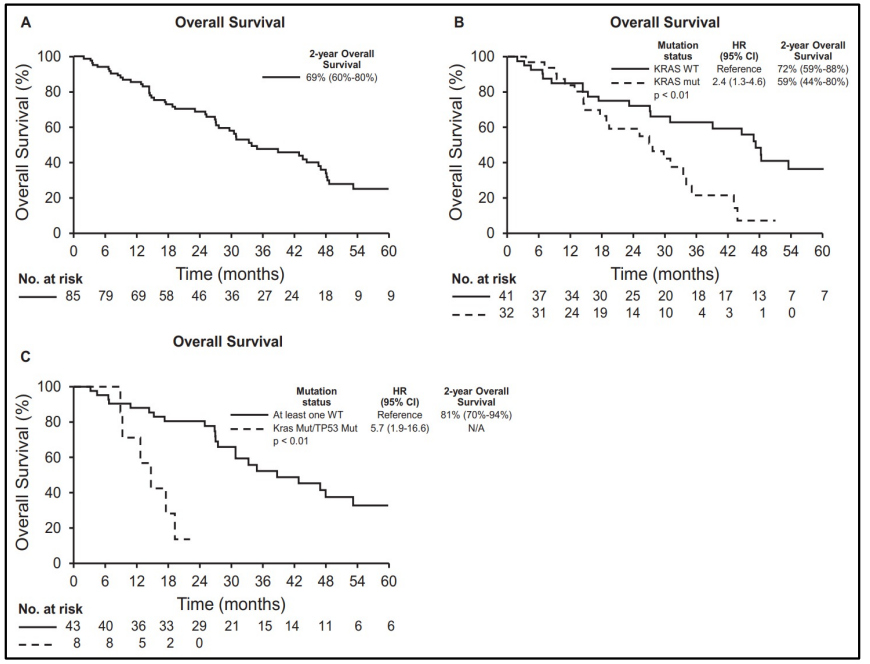
Original Article

Association of tumor genomic factors and efficacy for metastasis-directed stereotactic body radiotherapy for oligometastatic colorectal cancer

Krishan R. Jethwa [a,e], Samuel Jang [d], Trey C. Mullikin [a], William S. Harmsen [b,1], Molly M. Petersen [b,1], Kenneth R. Olivier [a], Sean S. Park [a], Michelle A. Neben-Wittich [a], Joleen M. Hubbard [c], Harigopal Sandhyavenu [a], Thomas J. Whitaker [a], Lindsey A. Waltman [d], Benjamin R. Kipp [d], Kenneth W. Merrell [a], Michael G. Haddock [a], Christopher L. Hallemeier [b,e]

[a] Department of Radiation Oncology; [b] Biomedical Statistics and Informatics; [c] Division of Medical Oncology; [d] Department of Laboratory Medicine and pathology, Mayo Clinic, Rochester; and [e] Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, United States





Jethwa KR et al; Radiother Oncol 2020

nature COMMUNICATIONS

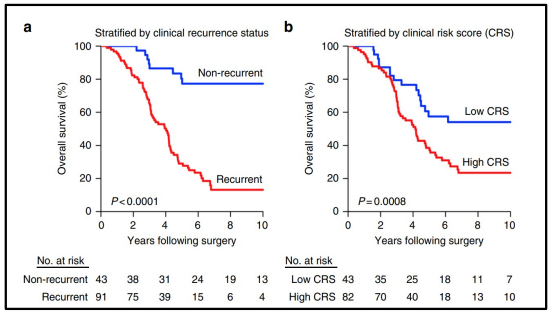
Corrected: Author correction

ARTICLE

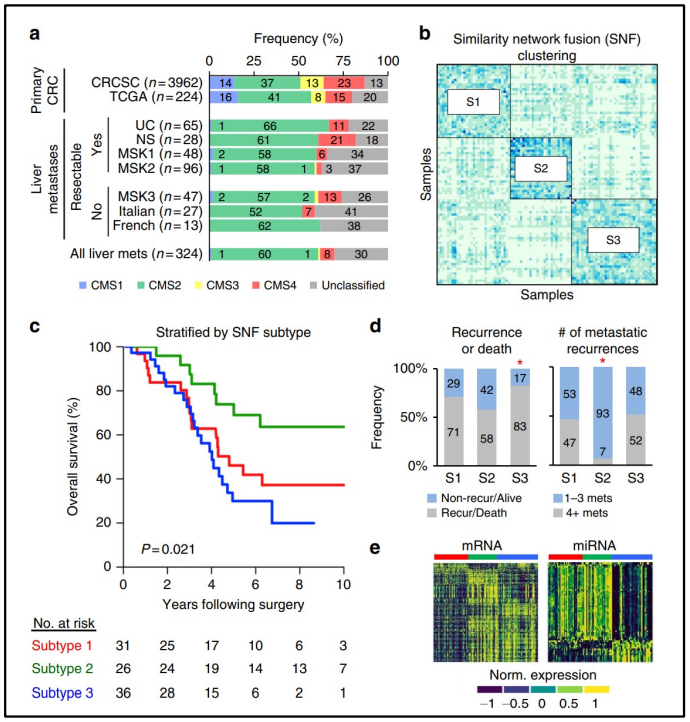
DOI: 10.1038/s41467-018-04278-6 OPEN

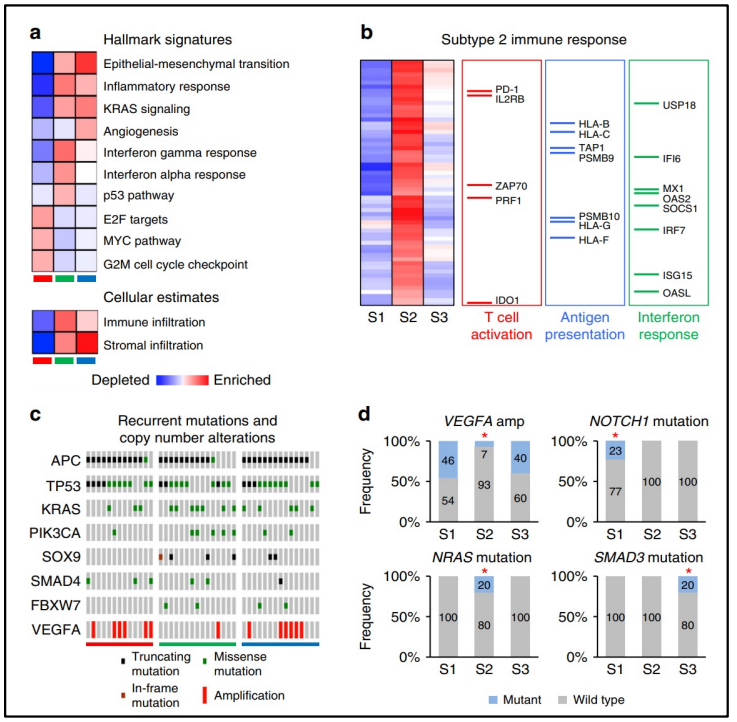
Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis

Sean P. Pitroda[1,2], Nikolai N. Khodarev[1,2], Lei Huang[3], Abhineet Uppal[4], Sean C. Wightman[4], Sabha Ganai[5], Nora Joseph[6], Jason Pitt[7], Miguel Brown[7], Martin Forde[7], Kathy Mangold[6], Lai Xue[4], Christopher Weber[8], Jeremy P. Segal[8], Sabah Kadri[8], Melinda E. Stack[4], Sajid Khan[9], Philip Paty[10], Karen Kaul[6], Jorge Andrade[3], Kevin P. White[7,11], Mark Talamonti[12], Mitchell C. Posner[4], Samuel Hellman[1,2] & Ralph R. Weichselbaum[1,2]



CRS: a) DFI < 12 mos; b) n° liver mets > 1; c) size > 5 cm; d) N+ve primary CRC; e) CEA > 200 ng/ml





- ✓ Subtypes with MSI-independent immune activation: most favourable survival
- ✓ Adverse outcomes: a) VEGFA amplification; b) stromal, mesenchimal and angiogenic signature; c) NOTCH1 and PIK3C2B mutations with E2F/MYC activation

Pitroda SP et al; Nature Commun 2018

nature COMMUNICATIONS

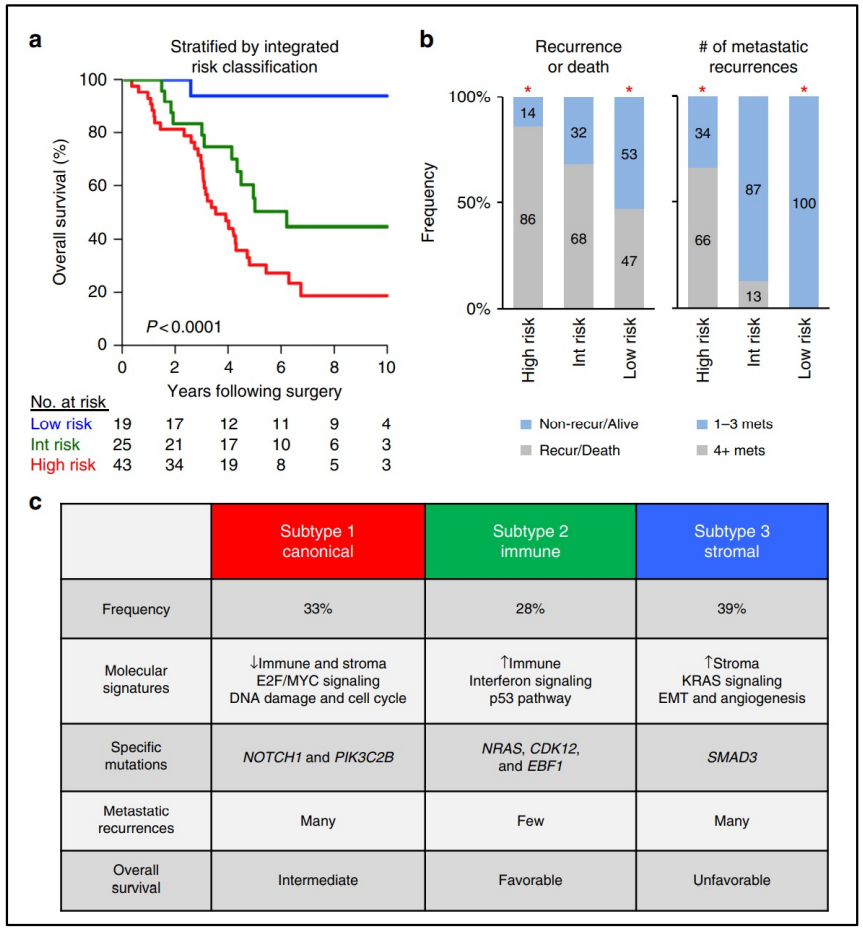
Corrected: Author correction

ARTICLE

DOI: 10.1038/s41467-018-04278-6 OPEN

Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis

Sean P. Pitroda[1,2], Nikolai N. Khodarev[1,2], Lei Huang[3], Abhineet Uppal[4], Sean C. Wightman[4], Sabha Ganai[5], Nora Joseph[6], Jason Pitt[7], Miguel Brown[7], Martin Forde[7], Kathy Mangold[6], Lai Xue[4], Christopher Weber[8], Jeremy P. Segal[8], Sabah Kadri[8], Melinda E. Stack[4], Sajid Khan[9], Philip Paty[10], Karen Kaul[6], Jorge Andrade[3], Kevin P. White[7,11], Mark Talamonti[12], Mitchell C. Posner[4], Samuel Hellman[1,2] & Ralph R. Weichselbaum[1,2]

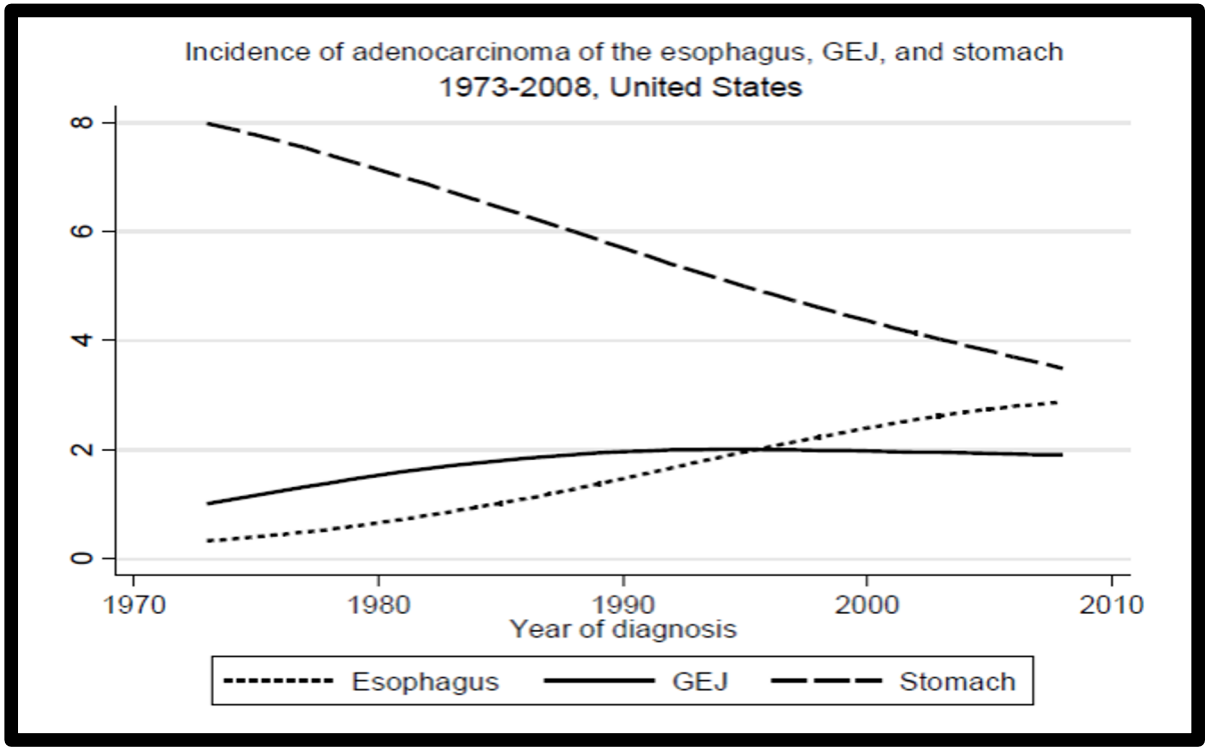


c

	Subtype 1 canonical	Subtype 2 immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	↓Immune and stroma E2F/MYC signaling DNA damage and cell cycle	↑Immune Interferon signaling p53 pathway	↑Stroma KRAS signaling EMT and angiogenesis
Specific mutations	*NOTCH1* and *PIK3C2B*	*NRAS*, *CDK12*, and *EBF1*	*SMAD3*
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

Pitroda SP et al; Nature Commun 2018

Esophageal cancer



Buas et al; Semin Radiat Oncol 2013

SCC- ESO-Shanghai 2 trial: a prospective phase II trial

Inclusion criteria

- ✓ Histologically proven ESCC
- ✓ Primary tumor treated definitively with no progression within 3 months from accrual
- ✓ ≤ 3 metastatic lesions on any distribution in ≤ 2 anatomic sites, with ≤ 5 cm diameter
- ✓ All mets amenable to SBRT
- ✓ Age ≥ 18; ECOG PS ≤ 2
- ✓ All mets naive of local therapies (surgery, RT, RF)

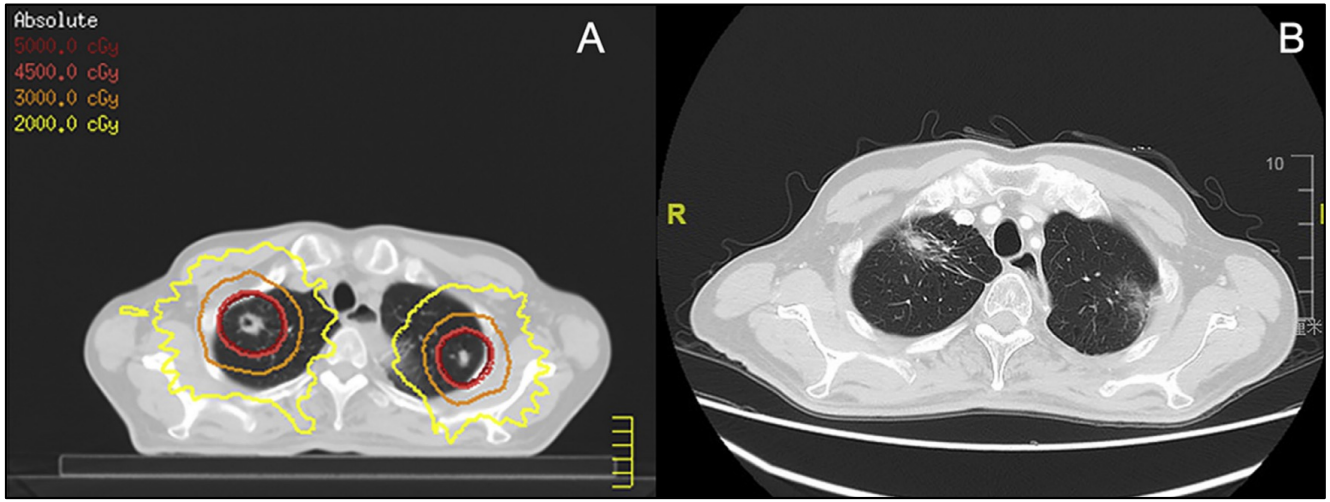
Exclusion criteria

- ✓ Progressive primary tumor
- ✓ Brain mets
- ✓ Metastatic disease invading GI tract
- ✓ Systemic therapy at diagnosis of oligometatastasis

Oligometastastic disease

- ✓ Synchronous oligometastasis: oligomets diagnosed between 3 and 6 months of definitve treatment of primary tumor
- ✓ Metachronous oligorecurrence: no history of metastastic disease who received a diagnosis > 6 months after diagnosis of primary tumor
- ✓ Repeat oligorecurrence: prior history of metastastic disease before current diagnosis

Liu et al, IJROBP 2020



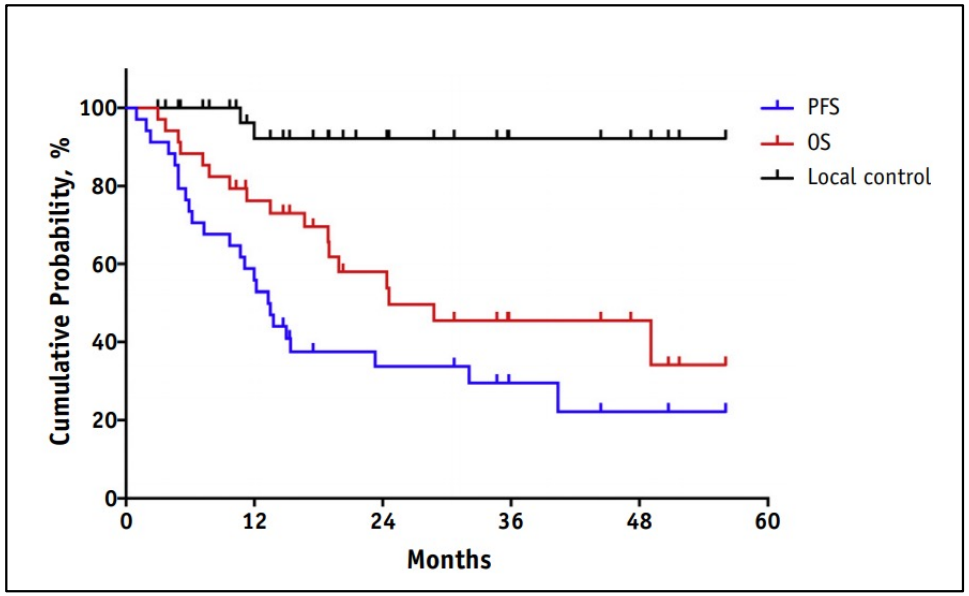
- ✓ Most common schedule: 48 Gy/6 fractions (24 targets)
- ✓ BED_{tumor} < 80 Gy in 4 pts to respect normal tissue dose constraints

Liu et al, IJROBP 2020

Table 1 Baseline characteristics (n = 34)

Characteristic	n (%)
Age, y	
Median (IQR)	63.5 (59.5-67.0)
Sex	
Male	30 (88)
Female	4 (12)
ECOG score	
1	24 (71)
2	10 (30)
Primary histology	
Squamous cell carcinoma	34 (100)
Location of primary tumor	
Cervical	1 (3)
Upper thoracic	5 (15)
Middle thoracic	15 (44)
Lower thoracic	11 (32)
Multiple primary	2 (6)
No. of metastases	
1	28 (82)
2	6 (18)
No. of involved organs	
1	32 (94)
2	2 (6)
Location of metastases (n = 40)	
Lung	23 (58)
Liver	1 (3)
Adrenal glands	1 (3)
Abdominal lymph nodes	15 (38)
Combined chemotherapy	
No	17 (50)
Yes	17 (50)
Classification of oligometastasis	
SO	4 (12)
MO	21 (62)
RO	9 (26)
Previous therapy for primary tumor	
S	10 (29)
S + adjuvant RT/cCRT	5 (15)
cCRT	19 (56)
Previous chemotherapy	
0 regimens	3 (9)
1 regimen	24 (70)
2 regimens	4 (12)
3 regimens	3 (9)
Time from the end of last therapy, mo	
Median (IQR)	7.5 (4.5-15)
SO	1.5 (1.0-3.5)
MO	8.0 (6.0-17.5)
RO	9.0 (3.5-11.5)
Time from initial diagnosis, mo	
Median (IQR)	15.0 (8-26)
SO	4.0 (3.3-4.8)
MO	13.0 (8-24.5)
RO	24.0 (16.0-47.0)

Abbreviations: cCRT = concurrent chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MO = metachronous oligorecurrence; RO = repeat oligorecurrence; RT = radiation therapy; S = surgery; SO = synchronous oligometastasis.



- ✓ 34 pts
- ✓ Median FU 18.2 months
- ✓ Median PFS 13.3 months
- ✓ Median OS 24.6 months
- ✓ 1- and 2-year LC rate: 92.1%
- ✓ 1- and 2-year PFS: 55.9% and 33.8%
- ✓ 1- and 2-year OS: 76.2% and 58%

Age, gender, n° mets, n° involved organs, nodal vs visceral, combined CT, time to last therapy and time to diagnosis, classification of oligomets – no effect on PFS nor OS

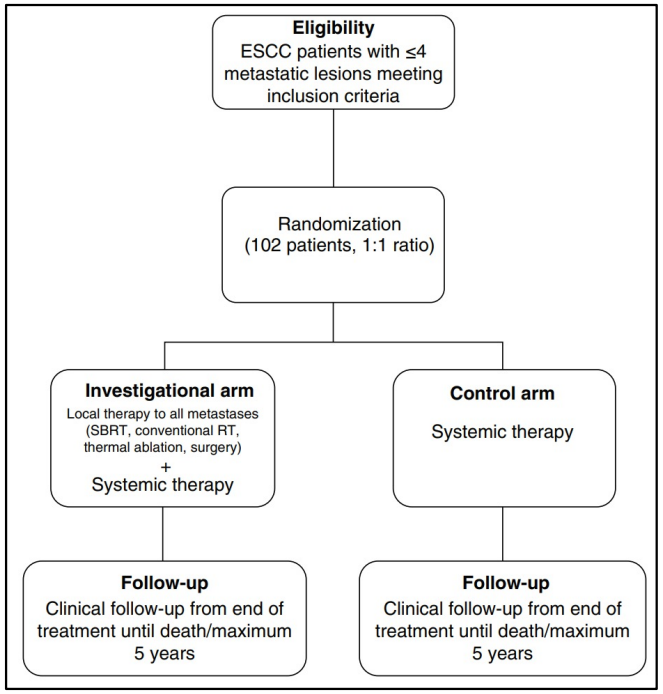
Liu et al, IJROBP 2020

Result of second-line therapy for metastastic or recurrent esophageal cancer

Author	Year	N°	Regimen	Setting	Median survival (mo)	Median PFS (mo)	1-year OS (%)
Kato et al	2011	53	CT	Metastatic or recurrent EC	10.4	3.9	NA
Kojima et al	2019	209 210	CT Nivolumab	Metastatic or recurrent ESCC	8.4 10.9	3.4 1.7	34 47
Kato et al	2019	314 314	CT Pembrolizumab	Metastatic or recurrent EC	7.1 7.1	3.4 2.1	24 32
Ohkura et al	2020	109	Resection ± CT/CRT	Oligometastatic EC	NA	NA	64.3 (3-yr)
Liu et al	2020	34	SBRT ± CT	Oligometastatic ESCC	24.6	13.3	76.2

CRT: chemoradiation; CT: chemotherapy; ES: esophageal cancer; ESCC: esophageal squamous cell carcinoma; OS: overall survival; PFS: progression-free survival; SBRT: stereotactic body radiation therapy

ESO-Shanghai 13 trial schema



Recommended dose and fractionation of stereotactic body radiation therapy by site

Location	Description	Recommended dose
Lung (central)	>1cm from CW and > 2 cm from the mediastinum, pericardium and brachial plexus	50Gy/5fractions
Lung (peripheral)	Abutting CW o ≤ 1 cm or within 2 cm of mediastinum or brachial plexus	48Gy/6fractions
Liver		48Gy/6fractions
Adrenal gland		48Gy/6fractions
Abdominal lymphnode		48Gy/6fractions
Bone/vertebral body	Any bone except femur	30 Gy/3fractions

Primary endpoint: PFS; secondary endpoints: OS, LC, toxicity, adverse events, QoL (EORTC QLQC30 + QLQ-OES18)

Liu et al, Future Oncol 2021

ESO-Shanghai 13 eligibility criteria

- ✓ Mts definition:
  - ✓ Distant organ mts
  - ✓ Nonregional lymphnodes
  - ✓ Distant organ/nonregional nodes + regional nodes
  - ✓ Excluded: regional mets only or anastomotic recurrence
- ✓ Oligometastastic disease:
  - ✓ Synchronous oligometastasis
  - ✓ Metachronous oligometastasis
  - ✓ Repeat oligometastasis
    - ✓ New oligometastasis in a pt with a previous metastastic diagnosis
    - ✓ Previous lesion regrowth after diagnosis of oligomeatstasis followed by treatment and systemic therapy free interval

- ✓ Primary tumor controlled
- ✓ All mets amenable to local therapy
- ✓ Total number of mets ≤ 4
- ✓ Number of mets per single organ ≤ 3
- ✓ Maximum diameter ≤ 5 cm
- ✓ If regional recurrence: all adjacent regional nodes are counted together as one lesion
- ✓ Nonregional nodes: adjacent metastastic lymphnodes can be treated as one lesion
- ✓ Synchronous oligometastasis: controlled primary + regional nodes are counted toward the number of 4
- ✓ Prior chemotherapy > 3 months
- ✓ Measurable lesion determined based on RECIST 1.1 assessment

Liu et al, Future Oncol 2021

Adenocarcinoma

- 6 studies involving 420 pts
- Metastasectomy for oligomets esophageal cancer
- Adenocarcinoma: 73.5%; SCC: 22.7%
- Synchronous oligomets - 73.5% underwent resection of primary tumor + mets
- Preo-op RT-CT: 66.7/; pre-op CT: 33.3%

Parameter	Relative rate (%)	95%CI
T0-T2	21.5	2.3-16.9
T3-T4	78.5	32.4-50.6
N0	13.6	10.0-18.2
N1	86.4	6.3-62.2
M1	100	NA

Metastastic site	Relative rate (%)	95%CI
Peritoneal	37.7	32.5-43.3
Multiple	20.5	16.3-2.5
Liver	16.8	13.1-21.5
Lung	6.2	4.0-9.7
Other	18.5	14.6-23.3

Schizas D et al, Inter CardioVasc Thor Surg 2021

Key question

What is the prognosis of patients undergoing surgery for oesophageal oligometastasis?

Key finding(s)

Mean overall survival was 24.5 months (95% CI: 14.4-34.6).

Take-home message

Locoregional control of oligometastatic disease appears to improve survival by at least 100%.

Patients Undergoing Surgery for Oligometastatic Oesophageal Cancer Survive for Over Two Years: Bootstrapping Systematic Review Data

Bootstrapping

1,000,000 repetitions per outcome

Mean overall survival

24.5 months (95% CI: 14.4-34.6)

Survival rates

One-year: 88.3% (95% CI: 85.6%-90.8%)
Three-year: 36.3% (95% CI: 15.3%-57.3%)
Five-year: 23.8% (95% CI: 12.0%-35.7%)

Schizas & Mylonas et al. Interactive CardioVascular and Thoracic Surgery. *2020*

Damanakis *et al. BMC Cancer* (2019) 19:1261
https://doi.org/10.1186/s12885-019-6448-9

BMC Cancer

RESEARCH ARTICLE Open Access

Proposal for a definition of "Oligometastatic disease in pancreatic cancer"

Alexander I. Damanakis[1*], Luisa Ostertag[1], Dirk Waldschmidt[2], Fabian Kütting[2], Alexander Quaas[3], Patrick Plum[1], Christiane J. Bruns[1], Florian Gebauer[1†] and Felix Popp[1†]

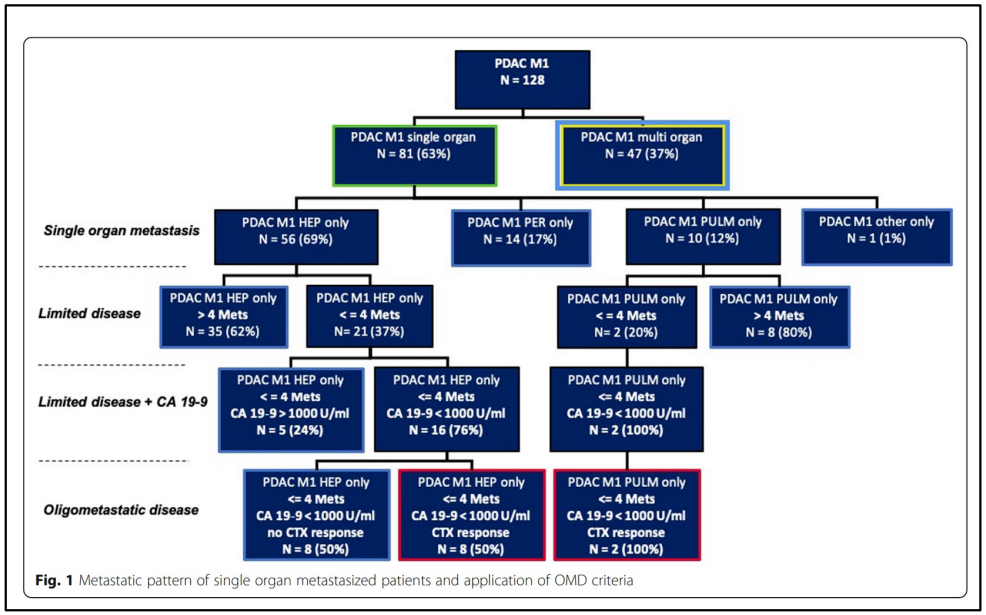


Fig. 1 Metastatic pattern of single organ metastasized patients and application of OMD criteria

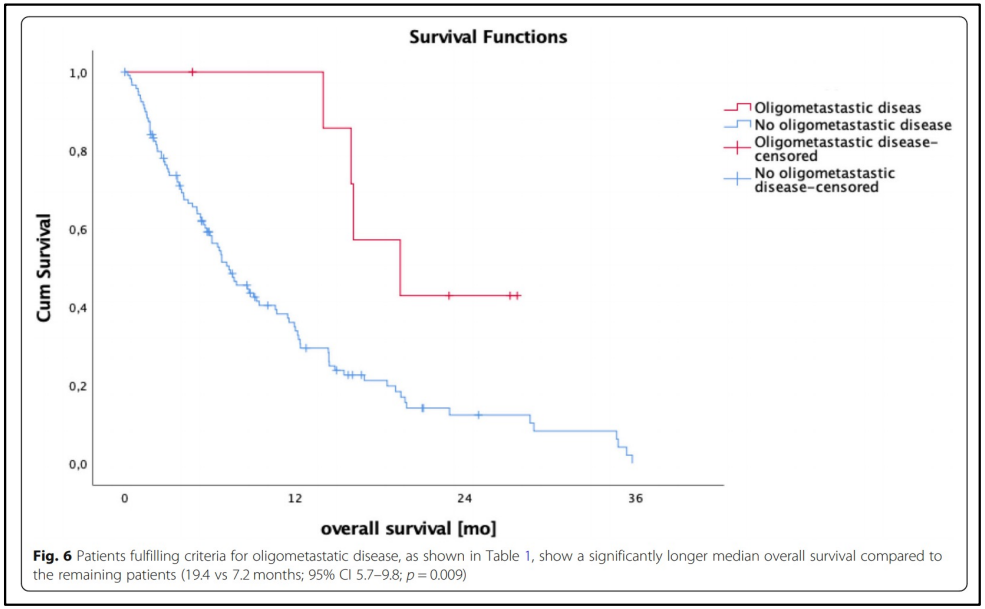
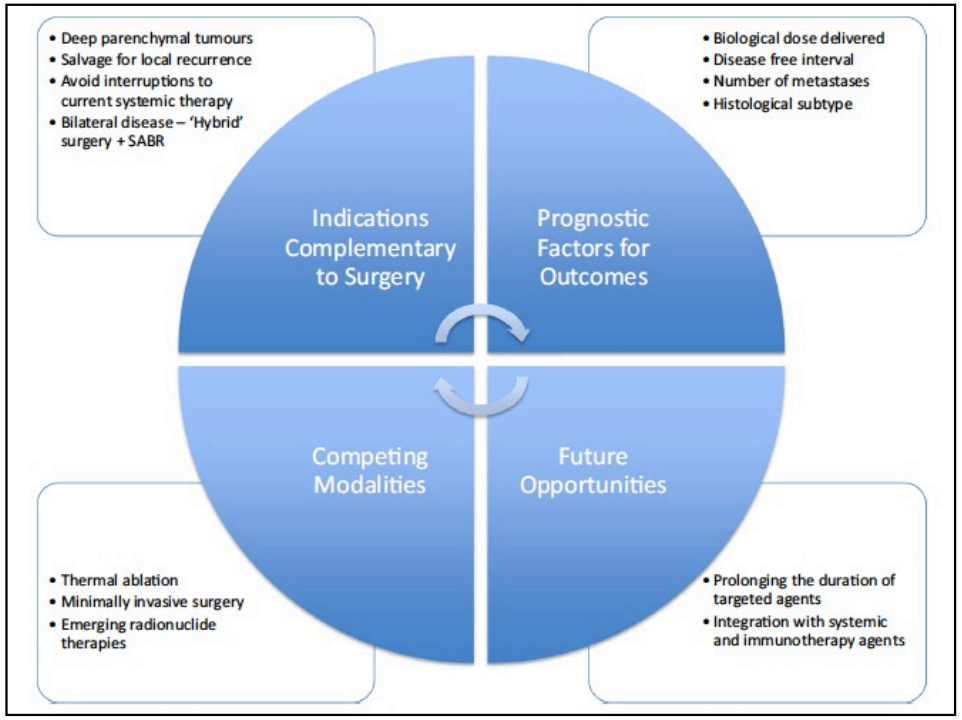


Fig. 6 Patients fulfilling criteria for oligometastatic disease, as shown in Table 1, show a significantly longer median overall survival compared to the remaining patients (19.4 vs 7.2 months; 95% CI 5.7–9.8; $p = 0.009$)

Damanachis AI et al, BMC Cancer 2019

Conclusion

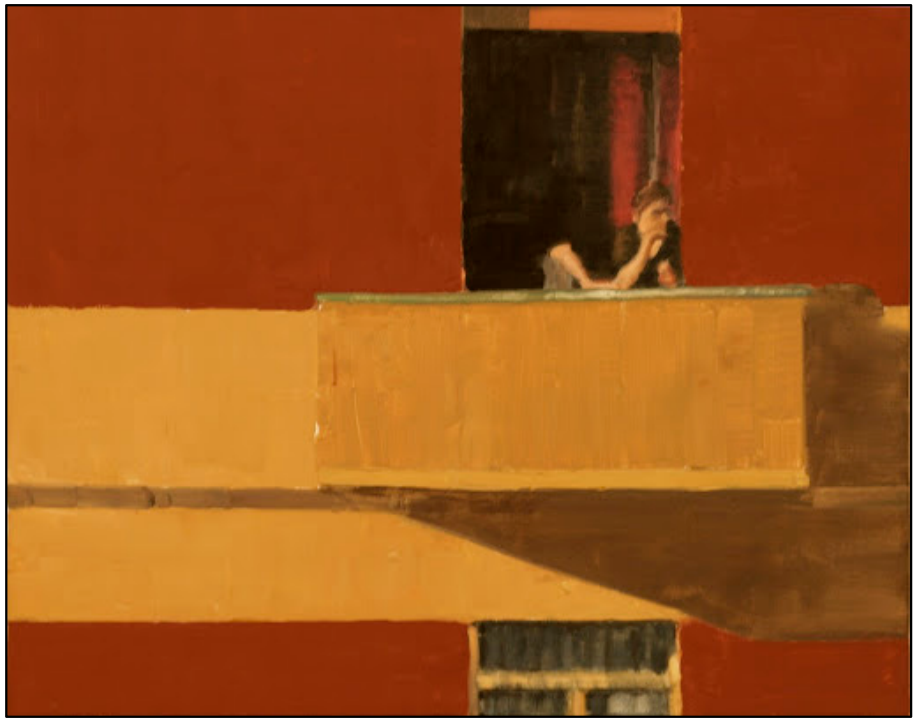
SBRT: evidence accumulated so far



- ✓ High local control rate from retrospective and prospective series
- ✓ Very low toxicity
- ✓ High feasibility
- ✓ PFS advantage confirmed in the first randomized trials across different settings
- ✓ Ideal candidate for the combination with targeted agents and immunotherapy?

Conclusion
Future perspective

- Improvements in diagnostics
- Improvements in SBRT technology
- Deeper knowledge in prognostic factors
- Advances in radiobiological knowledge on SBRT effects (and combination with systemic therapies)



Daniele Galliano, Senza Titolo 2013

Thanks for your attention

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Dipartimento di Radioterapia Oncologica, AOU 'Maggiore della Carità', Novara