REVIEW ON THE ESMO CONSENSUS ON ADVANCED COLORECTAL CANCER

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Disclosures

Consulting and advisory services, speaking or writing engagements, public presenations:

Servier, Merck Serono, Amgen, Roche, Lilly, Bayer, Novartiis, Takeda, Beigene

Direct research support to the responsible project lead:

Servier, Roche, Genentech, Bayer, Janssen, Merck Serono, Medimmune

Strategic changes in the treatment of mCRC

- Changes in clinical presentation due to follow up after primary resection and earlier detection of metastatic disease
- Improvement in systemic therapies
- Integration of surgery and ablative therapies in a multidisciplinary team approach
- “Continuum of care” treatment

ESMO Guidelines

special article

Annals of Oncology 23: 2479–2516, 2012
doi:10.1093/annonc/mds236

ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

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ESMO GUIDELINES

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014
doi:10.1093/annonc/mdu260
Published online 4 September 2014

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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

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Ann Oncol 2016 Ann Oncol. 2016 Jul 5. pii: mdw235. [Epub ahead of print]

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ESMO consensus on mCRC 2015

Chairs:	Co-Chairs of working groups	
E Van Cutsem	A Sobrero	Advanced mCRC
D Arnold	R Adam	Local and ablative treatment, oligometastasis
A Cervantes	H Van Krieken	Molecular Pathology and Biomarkers

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Consensus report: Methodology

- An international group of experts from **a range of disciplines**, was convened in December 2014 to update the existing ESMO consensus guidelines for the management of patients with mCRC
- A set of **pre-formulated topics** was prepared and **3 working groups** convened in the areas of ***molecular pathology and biomarkers***, ***local and ablative treatment (including surgery)*** and ***treatment of advanced/metastatic disease*****.**
- The experts in each group were invited to **submit their recommendations in advance** to structure the on-site discussions.
- On-site discussions within each of the working groups resulted in a set of recommendations being presented to all participants and a **final set of consensus recommendations** being formulated.
- Levels of evidence and grades of recommendation: assigned by the meeting chairpersons.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America—United States Public Health Coding System[a] [4])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, …) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America.


Condition
Fit
Unfit
Goal
Molecular testing
Disease Control
Molecular testing
text

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Molecular Pathology and Biomarkers

Recommendation 1: Tissue handling

Recommendation 2: Selection of specimens for biomarker testing

Recommendation 3: Tissue selection

Molecular Pathology and Biomarkers

Recommendation: RAS testing

- ***RAS* is a predictive biomarker for therapeutic choices** involving EGFR antibody therapies in the metastatic disease setting [1, A].
- ***RAS* testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab [1, A].
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*).
- ***RAS* analysis** should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for *RAS* testing** (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

Molecular Pathology and Biomarkers

Recommendation 5: BRAF testing

- Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B]

Recommendation 6: MSI testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B]
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [II, B]

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Molecular Pathology and Biomarkers

Recommendation 9: emerging technologies

- Although CTC number correlates with prognosis in patientswith mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].
- Whole genome, whole exome and whole transcriptome analysis should be carried out only in a research setting [V, D].

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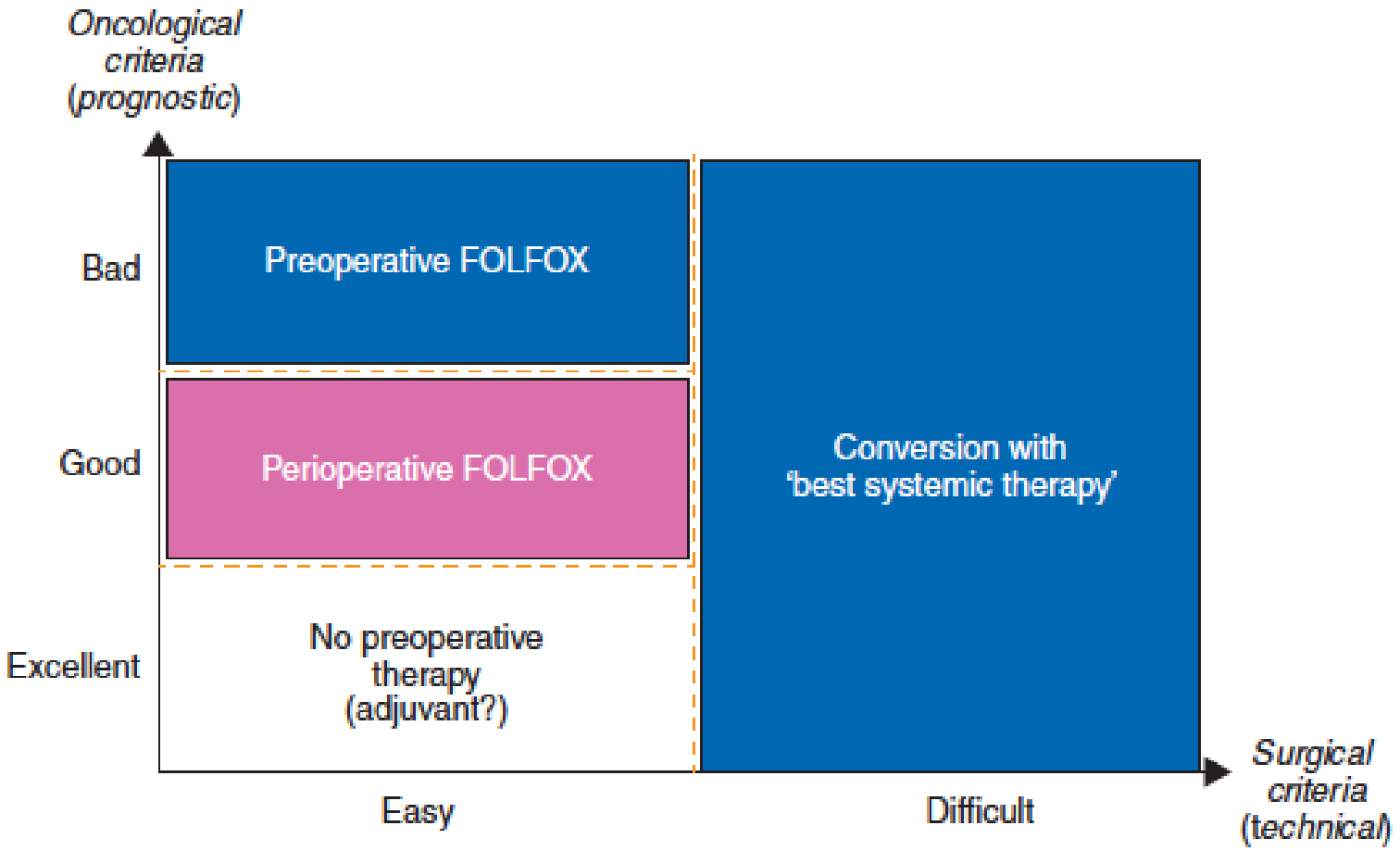

Figure 2. Categorisation of patients according to technical and oncological criteria. FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin.

Local and ablative treatment (including surgery)

Recommendation 13: conversion therapy.

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or a large tumour size reduction (shrinkage) is recommended [II, A].
- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
  - ✓ In patients with RAS wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A].
  - ✓ In patients with RAS-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab [II, A].
- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

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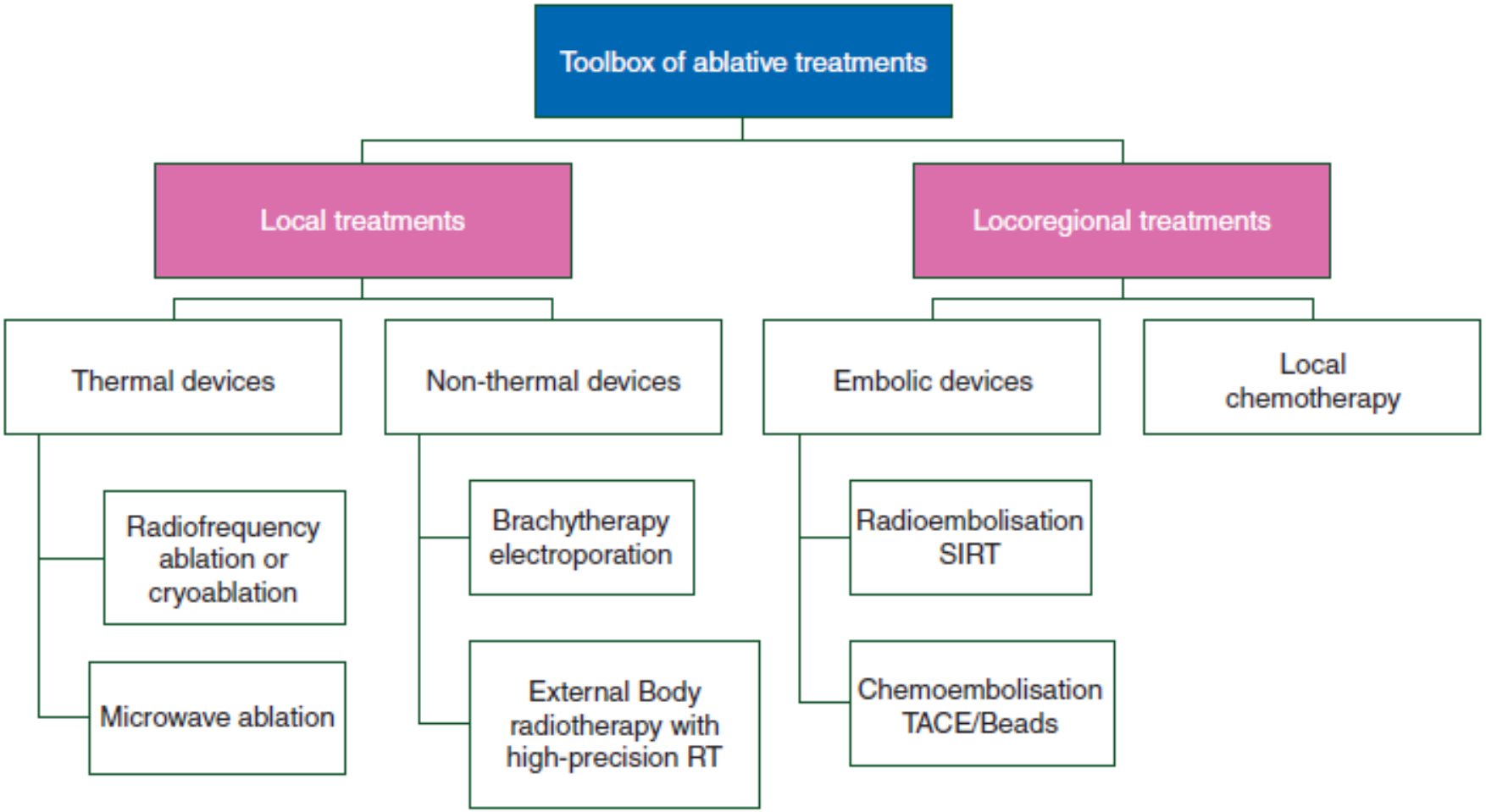
Figure 1: toolbox of ablative treatments



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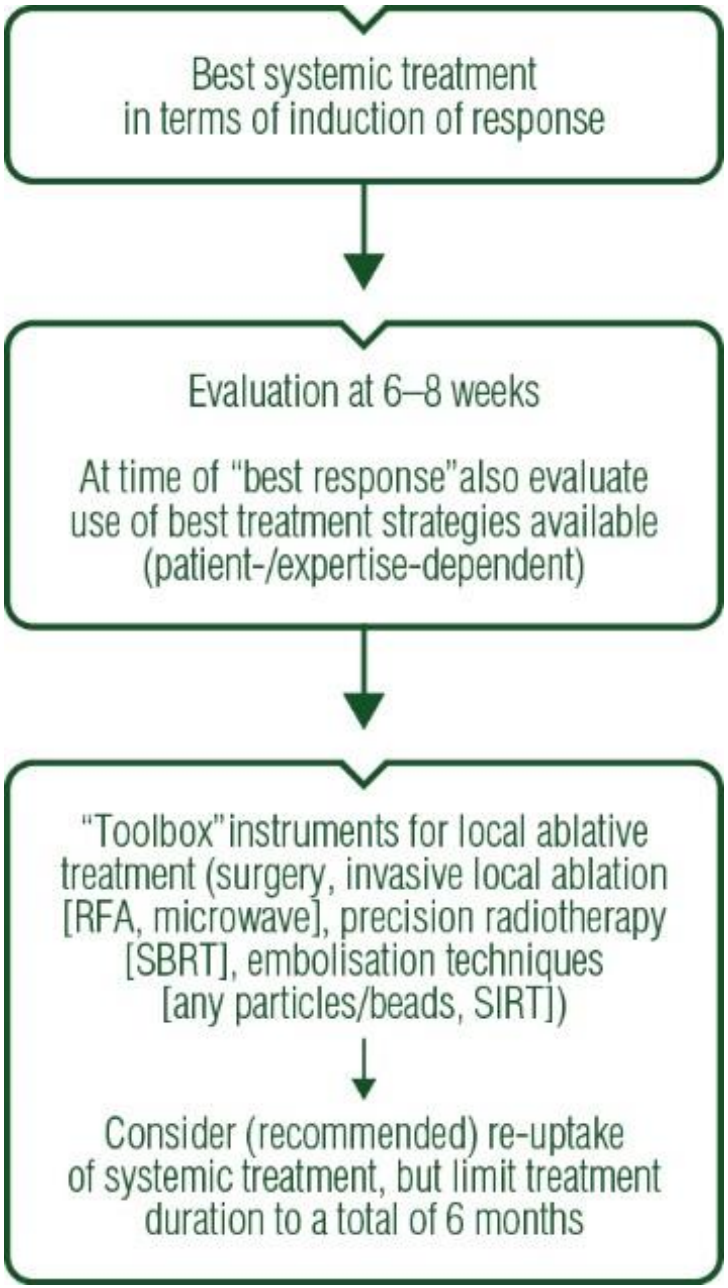

RFA = radiofrequency ablation;
SBRT = stereotactic body radiation therapy
SIRT = selective internal radiation therapy

Figure 3. Standard treatment algorithm for patients with oligometastatic disease.

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Table 4.
Drivers for first-line treatment

Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation: Tumour burden Tumour localisation	Age	Toxicity profile
Tumour biology	Performance status	Flexibility of treatment administration
RAS mutation status	Organ function	Socio-economic factors
BRAF mutation status	Comorbidities, patient attitude, expectation and preference	Quality of life

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Metastatic colorectal cancer (mCRC) is not one disease

- Patient and tumor characteristics vary widely
- Tumor cell heterogeneity is what makes tumors challenging to treat:
  - Multiple molecular alterations occur during tumor progression
  - Various molecular signaling pathways are involved
- Development of drugs which target and inhibit key molecular pathways is an essential step towards personalized cancer care

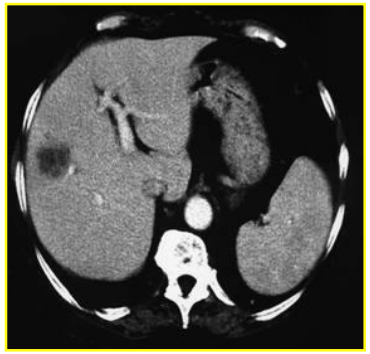
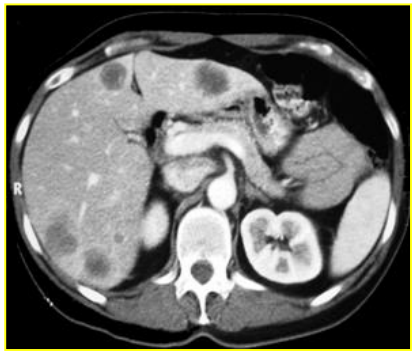
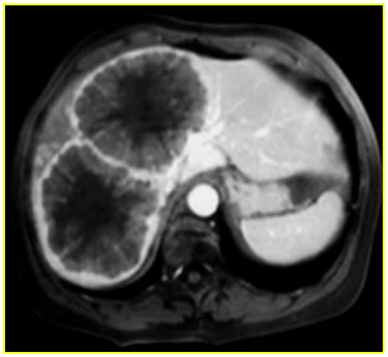
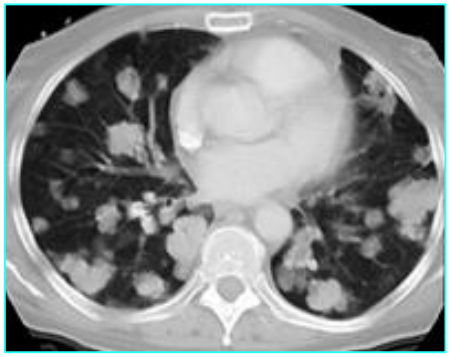

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Table 6.
Revised ESMO groups for treatment stratification of patients according to whether patients are ‘fit’ or ‘unfit’

Patient’s classification	‘Fit’ patients		‘Unfit’ patients
	Group 1	Group 2	
Clinical presentation	A. Conversion and achievement of NED B. Impending clinical threat, impending organ dysfunction and severe (disease-related) symptoms Treatment biomarker driven: *RAS* wt, *RAS* mt, *BRAF* mt patient subgroups	Asymptomatic patients No impending clinical threat Resection not an option Treatment biomarker driven: *RAS* wt, *RAS* mt, *BRAF* mt patient subgroups	Best supportive care
Treatment goal	A. Cytoreduction, followed by R0 resection; NED achieved by LAT B. Improvement of symptoms and hence avoidance of rapid evolution and prolonged survival	Disease control and hence prolonged survival	Palliative

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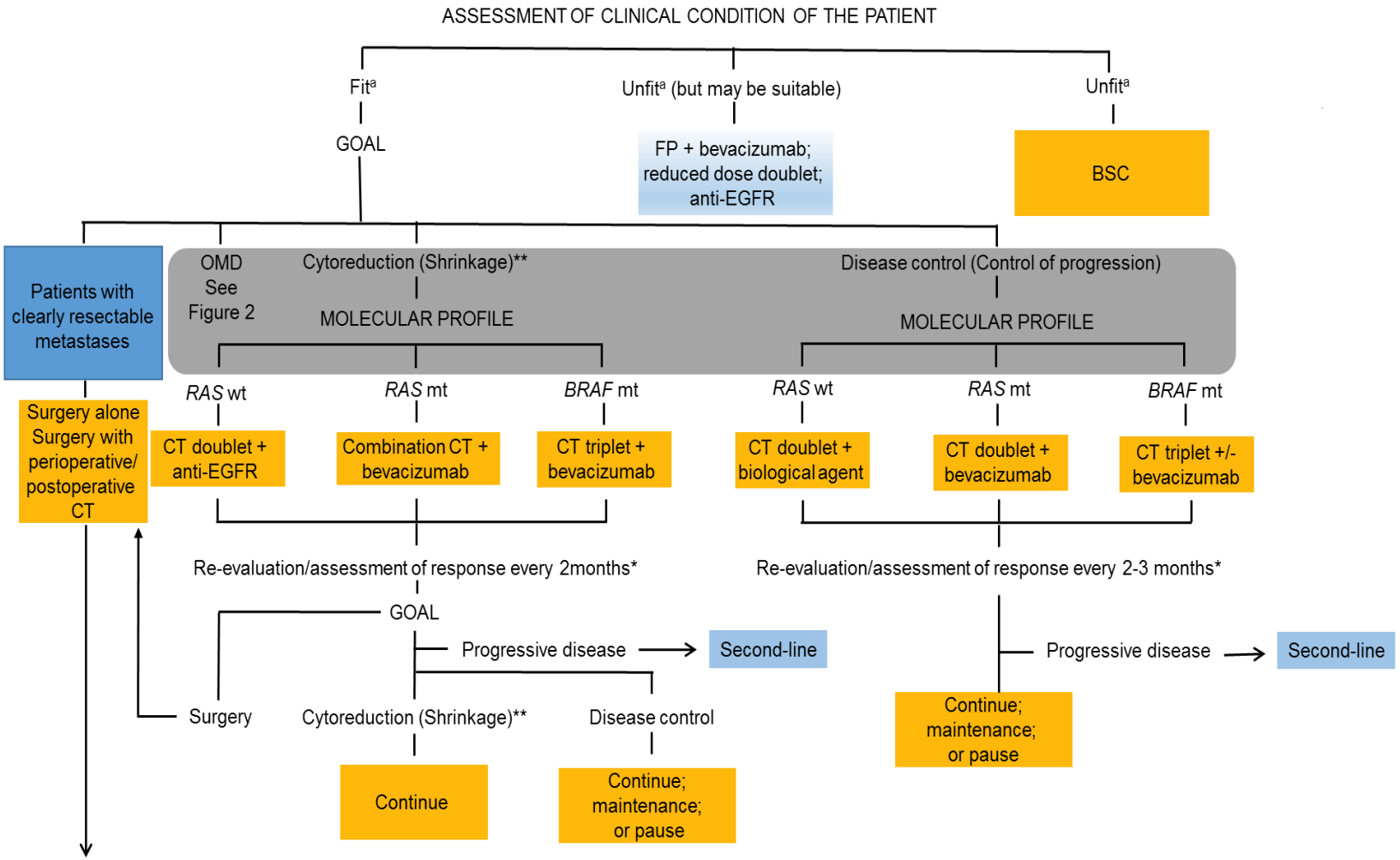
Treatment of metastatic disease



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Treatment of metastatic disease

Recommendation 18: First-line systemic therapy combinations according to targeted agent used

- **Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [I, A].**
- **The VEGF antibody bevacizumab should be used in combination with:**
  - The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI
  - The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal - and potentially also in fit patients with tumour BRAF mutations [II, B]
  - Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [I, B].
- **EGFR antibodies should be used in combination with:**
  - FOLFOX/FOLFIRI [I, A]
  - Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [I, E].

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