OLIGOMETASTATIC COLORECTAL CANCER: WHAT TO KNOW ABOUT AND HOW TO TREAT IT

Erika Martinelli
Associate Professor of Medical Oncology
Department of Precision Medicine, Naples
Università degli Studi della Campania L. Vanvitelli

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OUTLINE

- Biological Background
  - Definition of OMD according to ESMO guidelines
- Endpoints
- Conversion therapy:
  a. doublet + targeted agents
  b. triplet + bevacizumab
- Future perspectives
  a. triplet + anti-EGFR
  b. the importance of biology
**THE FIRST HISTORICAL DIASPORA**

Mass dispersions

<table>
<thead>
<tr>
<th>Social demography</th>
<th>Cancer demography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diaspora communities</strong></td>
<td><strong>Cancer metastasis</strong></td>
</tr>
<tr>
<td>Dispersed from a single homeland</td>
<td>Dispersed from a primary cancer</td>
</tr>
<tr>
<td>Pushed from homeland</td>
<td>Hypoxia and lack of nutrients causes pressure to leave primary</td>
</tr>
<tr>
<td>Host country may or may not be receptive</td>
<td>Target organ receptive</td>
</tr>
<tr>
<td>Group maintains collective memory of their homeland and culture</td>
<td>Pathologists can identify where a cancer cell originated</td>
</tr>
<tr>
<td>They wish to survive as a distinct community</td>
<td>Metastases as distinct masses</td>
</tr>
<tr>
<td>Relationship with host country is complicated and uneasy</td>
<td>Immune system tries to destroy the cancer cells</td>
</tr>
<tr>
<td>They are tied to their homeland at many levels – exchange of resources (economic, sociopolitical)</td>
<td>Multiple cell-type trafficking, trafficking of resources/info</td>
</tr>
</tbody>
</table>
Paget’s "seed and soil" theory explained the nonrandom pattern of cancer metastasis in 1889 when he postulated that factors within the metastatic site promoted growth in the same way that fertile soil allows the successful growth of seeds.

James Ewing proposed in 1928 that cancer cells were directed to that site by the direction of lymphatic and circulatory systems.
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ESMO consensus guidelines for the management of patients with metastatic colorectal cancer


Oligometastatic disease

OMD is characterised by the localisation of the disease to a few sites and lesions and is associated with the option to use LAT approaches in patient treatment strategies with a view to improving disease control and therefore clinical outcome in these patients.

Generally, OMD may be characterised by the existence of metastases at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, predominantly visceral and occasionally lymphnodal. Typically, these are the primary, and other involved sites such as the liver, lung, peritoneum, nodes and ovary. Patients with disease at other sites, such as multiple lesions in the bones and the brain, may also be treated using a local ablative approach, but as these patients are associated with an unfavourable prognosis, local ablative treatment strategies are only used to prevent immediate complications. This latter group of patients should be excluded from a classification of OMD. On the other hand, a patient with one or two resectable liver metastases, and a single bone lesion, should be classified as having OMD, because for a patient with this disease profile, locally ablative treatment strategies could be used and meaningfully contribute to their prognosis.

Thus, treatment strategies for patients with OMD should be based on the possibility of achieving complete ablation of all tumour masses, using surgical R0 resection (complete resection with clear resection margins and no evidence of microscopic residual tumour) and/or LAT, either initially or possibly after induction treatment with systemic therapy, for both the primary tumour and metastases.
liver metastases and surgical resection

For patients with colorectal liver metastases (CLM), the treatment strategy should be directed towards complete resection whenever possible, with both 'oncological' (prognostic) and 'technical' (surgical) criteria being considered when evaluating patients for surgery [148]. However, prospective evaluations do not exist either for 'oncological' or for 'technical' criteria, and for many of these, there is no (international) consensus.

Radical (R0: negative margins) liver resection can be curative in selected cases.65

The number of liver metastasis is not related to a worse prognosis if the surgeon is an expert and the surgery is radical.

Liver resection in borderline resectable disease must be considered after tumour shrinkage is achieved with chemotherapy.

Liver

• Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.6
• Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.7
• The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.8-11 Having a plan for a debulking resection (less than an R0 resection) is not recommended.7
Resectable
or
Not resectable?
My decision is...

Our decision is..
Modern Multidisciplinary consensus defines resectable CRC liver mets as tumours completely resectable, leaving adequate liver remnant.

MDT IMPORTANT WHEN ASSESSING RESECTABILITY

- Retrospective blinded evaluation of (potential) resectability of 448 patients in FIRE 3 trial
- Central Independent Review (assessment by 8 surgeons and 3 oncologists)
- Resection rate significantly associated with treatment setting (university hospital vs hospital/practice)

Modest et al Eur J Cancer 2018

97/448 baseline rectable (initially 16%, after MTD 22%)

238/ 448 resectable at best response (53%)
THE IMPACT OF RESECTABILITY ON OS

OS overall population:
- resectable/surgery=51.3 mo vs resectable/no surgery=30.8 mo vs not resectable=18.6 mo

Modest et al Eur J Cancer 2018
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EFFICACY ENDPOINTS

Early Tumor shrinkage (ETS)

Recist-based response criteria are insufficient predictors of survival (OS)

- Early tumour shrinkage (ETS) is a novel instrument to predict high sensitivity to treatment
- ETS may be viewed as a predictor of potential Depth of response (DpR)
- DpR correlates with post progression survival (PPS) and overall survival (OS)
- Volume-based measurement may be more accurate than longitudinal assessment according to RECIST

Heinemann V. et al.  Lancet Oncology  2014
EFFICACY ENDPOINTS

Early Tumor shrinkage (ETS)

ETS predicts sensitivity to treatment
ETS predicts deepness of response
Deepness of response correlates with PPS

Heinemann V. et al. Lancet Oncology 2014
CONVERSION TREATMENT

Safety concerns

**OXALIPLATIN**
- Hepatic sinusoidal abnormalities (sinusoidal obstruction syndrome)
- Non cirrhotic portal hypertension

**IRINOTECAN**
- Steatohepatitis (associated with >BMI)

**BEVACIZUMAB**
- Due to long half-life (20 days), commonly recommended to wait at least 28 days after last administration (preferably six to eight weeks)
- Possible impaired wound healing and impaires hepatic regeneration (if performed too soon after bevacizumab administration).
- Stroke and arterial thromboembolic events, bowel perforation, and bleeding
The ‘oncological’ criteria provide prognostic information that predict a longer DFS or a higher likelihood of cure. These include:

- the number of lesions
- the presence (or suspicion) of extrahepatic disease
- the criteria used in numerous retrospective evaluations and in the FONG score (including margins, extrahepatic mets, N+ primitive, DFI < 12 mo, N liver mets, >5cm liver mets, CEA >200 ng/mL)

ESMO RECOMMENDATION 12
Liver metastasis technical RESECTABLE up front

- In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [I, C; consensus >75%].

- In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (FOLFOX or CAPOX) should be administered [I, B; consensus >75%].

- Targeted agents should not be used in resectable patients where the indication for perioperative treatment is prognostic in nature [II, E].

- In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [IV, B]. Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.

- In patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from adjuvant treatment [III, B].

- In patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX or CAPOX is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy) [IV, B].

- Decision-making should include patients’ characteristics and preferences [IV, B].

**Conversion therapy:**
- Systemic therapy given to rendering technically unresectable CRC metastases resectable
- Response to systemic therapy is a strong prognostic indicator but is also unpredictable.

ESMO RECOMMENDATION 13
Potentially resectable CRC liver metastases: ‘conversion’ is a strategic treatment goal

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or tumour size reduction (shrinkage) is recommended (IIA).
  - 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 (IIA).
  - In patients with RAS-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab (IIA).

- Recommended regular radiological assessment, in order to prevent the overtreatment of resectable patients. The maximal response is expected after 12–16 weeks of therapy.

IMPLEMENTATION OF RECOMMENDATION ACCORDING TO SIDEDNESS
Pan-Asian adapted ESMO consensus guidelines

<table>
<thead>
<tr>
<th>Primary tumour location</th>
<th>Fit Cytoreduction</th>
<th>Fit Cytoreduction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>RAS/BRAF wt</td>
<td>BRAF mt</td>
</tr>
<tr>
<td>Left-sided</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doublet + anti-EGFR</td>
<td>Triplet + bev</td>
</tr>
<tr>
<td></td>
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<td>Triplet + bev</td>
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</tr>
<tr>
<td></td>
<td>Doublet + anti-EGFR</td>
<td>Triplet + bev</td>
</tr>
<tr>
<td>Right-sided**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triplet ± bev</td>
<td>Triplet + bev</td>
</tr>
<tr>
<td></td>
<td>Triplet ± bev</td>
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# Conversion Therapy Approach in Patients with Liver-Limited Disease

Doublet with anti-EGFR or anti-angiogenic drugs in RT

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Treatment</th>
<th>Number</th>
<th>Endpoints</th>
<th>RR%</th>
<th>R0 resection%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELIM¹</td>
<td>FOLFOX+cetuximab vs FOLFIRI+cetuximab</td>
<td>106</td>
<td>ORR</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>*BELIEF²</td>
<td>FOLFOX/FOLFIRI+cetuximab vs FOLFOX/FOLFIRI</td>
<td>138</td>
<td>R0 resection rate</td>
<td>57 vs 29</td>
<td>26.7 vs 6.3</td>
</tr>
<tr>
<td>*BECOME³</td>
<td>FOLFOX+bevacizumab vs FOLFOX</td>
<td>240</td>
<td>R0 resection rate</td>
<td>54.5 vs 36.7</td>
<td>22.3 vs 5.8</td>
</tr>
</tbody>
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CONVERSION THERAPY APPROACH IN PATIENTS WITH LIVER-LIMITED DISEASE

Triplet with anti-angiogenic drugs

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<th>Number</th>
<th>Endpoints</th>
<th>RR%</th>
<th>R0 resection%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLIVIA&lt;sup&gt;1&lt;/sup&gt;</td>
<td>FOLFOXIRI+ bevacizumab vs FOLFOX+bevacizumab</td>
<td>80</td>
<td>Overall resection rate (R0/R1/R2)</td>
<td>81 vs 62</td>
<td>49 vs 23</td>
</tr>
</tbody>
</table>

- Which is the impact of bevacizumab?
- What about the comparison with historical triplet treatment (TRIBE)?
POOLED ANALYSIS OF GONO TRIALS (TRIPLET+BEV)

FOIB (Ph2)  FOLFOXIRI bev (57)
TRIBE (Ph3)  FOLFOXIRI bev (252) / FOLFIRI bev
MOMA (Ph2)  FOLFOXIRI bev → BEV/ BEV+metroCT (232)

205*/541 (37.5%)
non resectable pts

62% = surgical
22% = oncological

*Liver-only disease

RR= 69%
Surgery = 91/205 (36%)
- R0 = 31%
- R1 = 5%

PFS

OS

Cremolini C et al. 2016 EJC
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## FUTURE PERSPECTIVE
Chemo-intensification: Triplet + anti-EGFR

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Treatment</th>
<th>Number</th>
<th>Endpoints</th>
<th>RR%</th>
<th>R0 resection%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACBETH¹</td>
<td>FOLFOXIRI+cetuximab maintainance cetuximab vs FOLFOXIRI+cetuximab maintainance bevacizumab</td>
<td>116</td>
<td>10mPFS</td>
<td>71.6</td>
<td>50</td>
</tr>
<tr>
<td>VOLFI²</td>
<td>FOLFOXIRI+panitumumab vs FOLFOXIRI</td>
<td>96</td>
<td>ORR</td>
<td>87.3 vs 60.6</td>
<td>50 vs 27</td>
</tr>
</tbody>
</table>

FUTURE PERSPECTIVE

TRIPLETE: a randomised phase III study of modified FOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer.

Primary endpoint= ORR  
Secondary endpoint= safety profile, PFS, OS, centrally assessed ORR, ETS, DoR, R0 resection rate  

Borelli B, et al. ESMO Open 2018
LOCALIZED INTERVENTION (LAT) FOR OMD

Radiofrequency ablation
- Monopolar RFA
- Multipolar No touch RFA
- Advantages: Well evaluated treatment (reference)
  - Multibipolar mode: increases volume and predictibility (margin) of ablation zones
- Limitations: Thermal injury of adjacent structure
  - Heat sink effect (near major vessels)

Microwave ablation
- Active energy deposition: ≈ 1 cm
- Advantages: Higher and faster temperature picks reached than with RFA (less sensitive to heat sink effect than monopolar RFA)
- Limitations: No reliable end point to set the amount of energy deposition

Cryoablation
- Ice ball ≈ 1-3 cm
- Advantages: Easy monitoring with imaging of ice ball progression
- Limitations: Cryoshock with first device
  - Limited clinical data available with new devices

Irreversible electroporation
- Advantages: Limited risk of thermal injury to neighbouring critical structures
  - Unsensitive to heat sink effect
  - Advantage of multibipolar mode (no touch technique, predictability of margins)
- Limitations: Only preliminary clinical data
  - General anesthesia using curare and major anagastic drugs is mandatory

Nault et al. Journal of Hepatology 2018
LOCALIZED INTERVENTION (LAT) FOR OMD

Toolbox of ablative treatments

Local treatments
- Thermal devices
  - Radiofrequency ablation or cryoablation
  - Microwave ablation
- Non-thermal devices
  - Brachytherapy electroporation
- Embolic devices
  - Radioembolisation SIRT
  - Chemoembolisation TACE/Beads

Locoregional treatments

Toolbox of ablative treatments. SIRT, selective internal radiation therapy; RT, radiation therapy; TACE, transarterial chemoembolisation.

CONCLUSIONS

- The concept of oligometastases, intuitively known for many years, is known as validated in metastatic colorectal cancer (CRC).

- The MTD approach of metastatic CRC will consist to push the limits of the indications for aggressive metastasectomy with a curative intent, even in cases of difficult or at-risk presentations from a technical point of view.

- In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified.

- If conversion is the goal, a regimen leading to high RRs and/or tumour size reduction (shrinkage) is recommended.

- It is important to extend the indications for nonresectional techniques in patients with definitively unresectable disease with oligometastatic characteristics.

- For the future it would be important to evaluate candidate biomarkers in order to try and define an oligometastatic profile instead of establishing it on the demonstration of long-term survival or cure after metastases-directed therapy clinician.