Dirk Arnold
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The concept of oligometastatic disease – and role of ablative treatments in mCRC
Disclosures

• Participate on Advisory Board with:
  Bayer, Merck, Roche, Lilly, sanofi, Servier, Sirtex, Terumo

• Speaker and Chairman for educational events with:
  Bayer, Merck, Lilly, Servier, Terumo

• Investigator and researcher in data generating activities, (partly) supported and sponsored by
  Bayer, Roche, Mologen
What is oligometastatic disease?
Similar – but (likely) not the same

- **primarily local disease**
  - Prognosis determined by primary Local treatment

- **Metastatic disease**
  - Prognosis determined by metastases Systemic treatment

- **Oligometastatic disease**
  - Prognosis "intermediate" – because of biology (?) and the option for additional (local) treatment

- **diffuse metastatic disease**
  - Unfavourable biology, only systemic treatment

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**Prognosis**

- **Cure**
  - 70 yrs „tumour biology“
  - > 120,000 Publications

- **Chronic disease (potentially cure)**
  - → local (palliative) treatment
  - ca. 20 yrs
  - < 50 publications on „biology“

- **Palliation**
Mathematical-mechanistical hypotheses

Lethal tumor load

Baseline tumor load

Δ

PFS

Tumor shrinkage

No tumor shrinkage

Δ OS

PFS

Time under treatment
Cytoreduction: biological hypotheses

Goldie-Coldman Hypothesis:
less therapy-resistant clones with a smaller number of cells
- Goldie JH et al., Cancer Res. 1984
- Withers HR et al., Sem Radiat Oncol 2006

Norton-Simon Hypothesis:
kinetic resistance - poorer response to chemotherapy in small residuals
Norton L et al., Cancer Treat Rep 1986, Oncologist 2005

Gerlinger et al., NEJM 2012
Are there really biological characteristics existing, which may help us to distinguish between an oligometastatic and a whitespread pattern of metastazation?
Similar – but (likely) not the same

Local tumour → oligometastasation → diffuse mets. → terminal disease

continuum over time?

Paget et al., Lancet 1898; Halstead et al., Ann Surg 1907
Metastasation as an evolutorial process: The „SPECTRUM“ hypothesis

Adapted from: Hellman S., Karnofsky Memorial Lecture, J Clin Oncol 1994
Similar – but (likely) not the same

Local tumour → oligometastasation → diffuse mets. → terminal disease

Continuum over time?

„new biology“

Paget et al., Lancet 1898; Halstead et al., Ann Surg 1907
Hellman et al., 1994
Similar – but (likely) not the same

Local tumour → oligometastasation → diffuse mets. → terminal disease

Paget et al., Lancet 1898; Halstead et al., Ann Surg 1907
Hellman et al., 1994
Oligometastatic vs. Disseminated Disease

Adapted from: Reyes et al., Oncotarget 2015
Oligometastatic vs. Disseminated Disease

Adapted from: Reyes et al., Oncotarget 2015
A comparison of migrants, diaspora, and the spectrum of cancer metastases

<table>
<thead>
<tr>
<th>Trading Post Diaspora → Oligometastasis</th>
<th>Imperial Diaspora → Cancer metastasis</th>
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<tbody>
<tr>
<td>Migrated from primary cancer in passive manner</td>
<td>Dispersed from a primary cancer in an active manner</td>
</tr>
<tr>
<td>Mild hypoxia and unlimited nutrients; Home niche conditions do not cause evolutionary clonal pressure</td>
<td>Hypoxia and lack of nutrients cause pressure to leave primary; Evolving home niche conditions cause undifferentiated, aggressive clones.</td>
</tr>
<tr>
<td>Target organ may or may not be receptive</td>
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<tr>
<td>Pathologists can identify where a cancer cell originated</td>
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<tr>
<td>Few distinct metastases</td>
<td>Multiple metastases as distinct masses</td>
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<td>Immune system may not see a threat</td>
<td>Immune system tries to destroy the cancer cells</td>
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<tr>
<td>Limited need for outside resources from homeland; fewer cells trafficking</td>
<td>Multiple cell-type trafficking, trafficking of resources/info</td>
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</table>

tumor mets capabilities: migration

environmental adverse “pressure”

environmental “hospitality”: tissue

environmental “hospitality”: immunogenicity

adapted from: Pieta et al., Clin Cancer Res 2013
The Colorectal Cancer Subtyping Consortium (CRCSC) identifies a network of molecular subtypes.
Molecular classification of CRC

Dienstmann et al., WCGC / ESMO GI 2016
Biology and oligometastasation: What is do we need to know clinically?

• Prognostic information
  – How „ambitious“ should our treatment be?

• Predictive information
  – E.g. selection of a (primary) local-ablative treatment (e.g. SBRT) vs. systemic treatment

→ Biology: not ready for prime time!
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

ESMO Consensus 2016: What is meant by „oligometatstatic disease“?

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

• Generally...may be characterised by the existence of metastases at up to 2 or occasionally 3 sites and 5 (or sometimes more) lesions, predominantly visceral....
ESMO Consensus 2016:
What is not meant by „oligometastatic 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, LAT... are only used to prevent immediate complications.

- 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....locally ablative treatment strategies could be used and meaningfully contribute...

ESMO Consensus Guidelines mCRC., Ann Oncol 2016
ESMO Consensus 2016: Recommendation 10

• For patients with OMD, **systemic therapy is the standard of care** and should be **considered as the initial part of every treatment strategy** (exception: patients with single/few liver or lung lesions).
Contemporary mCRC algorithm

**Induction**

- chemotherapy + antibody

**Post induction**

- "best maintenance"
  - De-escalation?
  - pause?
  - other compound?

- "best ablation"
  - resection
  - "ablation toolbox"

- several manifestations, "palliative"

- Oligometastastatic disease "ablative"
Induction chemotherapy + antibody

where? response?

post induction

several manifestations, "palliative"

"best maintenance"
De-escalation?
apause?
other compound?

"best ablation"
resection
"ablation toolbox"

Oligometastastastic disease
"ablative"
ESMO Consensus 2016: Recommendation 10

• For patients with OMD, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions).

• ....should be selected from a ‘toolbox’ of procedures according to localisation, treatment goal (‘the more curative the more surgery’/higher importance of local/complete control), treatment-related morbidity, local expertise and availability, and patient-related factors such as comorbidity/ies and age [IV, B].
Best systemic treatment in terms of induction of response

Evaluation at 6–8 weeks
At time of "best response" also evaluate use of best treatment strategies available (patient-/expertise-dependent)

"Toolbox" instruments for local ablative treatment (surgery, invasive local ablation [RFA, microwave], precision radiotherapy [SBRT], embolisation techniques [any particles/beads, SIRT])

Consider (recommended) re-uptake of systemic treatment, but limit treatment duration to a total of 6 months
Toolbox of ablative treatments

Local treatments
- Thermal devices
  - Radiofrequency ablation or cryoablation
  - Microwave ablation
- Non-thermal devices
  - Brachytherapy electroporation
  - External Body Radiotherapy with high-precision RT

Locoregional treatments
- Embolic devices
  - Radioembolisation SIRT
  - Chemoembolisation TACE/Beads
- Local chemotherapy
Therapeutic concepts -
What do we know?
Supporting evidence for an „early palliative ablation“ strategy: News 2015

• EORTC CLOCC Trial
  – Phase II, small sample size
  – Early „palliative“ RFTA plus chemo vs. chemo alone
  – OS improved

• Y90 Radioembolisation: SIRFLOX trial
  – Phase III
  – Y90 radioembolisation + FOLFOX vs. FOLFOX alone, 1st line
  – „all“ PFS not better, Liver PFS improved, OS pending

Ruers et al., ASCO 2015; Van Hazel et al., J Clin Oncol 2016
CT brachy therapy:
Liver, Lung, retroperitoneal, mesenterial, ...
LOCAL RESPONSE AND IMPACT ON SURVIVAL AFTER LOCAL ABLATION OF LIVER METASTASES FROM COLORECTAL CARCINOMA BY COMPUTED TOMOGRAPHY–GUIDED HIGH-DOSE-RATE BRACHYTHERAPY

Jens Ricke, M.D.,* Konrad Mohnike, M.D.,* Maciej Pech, M.D.,* Max Seidensticker, M.D.,* Ricarda Rühl, M.D.,* Gero Wieners, M.D.,* Gunnar Gaffke, M.D.,* Siegfried Kropf, Ph.D.,† Roland Felix, M.D.,‡ and Peter Wust, M.D.‡

- Prospective randomised dose finding
- Primary endpoint: local tumor control: 93%
  - Secondary endpoint: overall survival, ...
- Tumors 5 – 15cm
  - FFLP >90% after 12mo (>20Gy single fraction)
SBRT in oligometatic mCRC
Radiosensitivity differences between liver mets and primary histology

Kamran et al., Int J of Rad Oncol Biol Phys 2016
Where are the limitations...?
Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983


EORTC Headquarters, Brussels, Belgium
Department of Surgery, Centre Hospitalier Universitaire Ambroise Pare, Assistance Publique Hopitaux de Paris, Boulogne-Billancourt, France
Department of Statistics, EORTC Headquarters, Brussels, Belgium
Department of Oncology, Haukeland University Hospital, Bergen, Norway
Department of Surgery, The Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands
Department of Surgery, Medical University Vienna, Vienna, Austria
Department of Surgery, Robert-Roessle-Klinik, Humboldt-Universitat Berlin, Berlin, Germany
### Table 4
Follow-up and first progressions.

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<td>Median fluorouracil (FU) from RFA/surgery</td>
<td>4.7 years</td>
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<td>Reurrences</td>
<td>38 (69.1%)</td>
<td>48 (59.3%)</td>
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<td>Local recurrence per patient treated (LR)*</td>
<td>8/55 (14.5%)</td>
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*Includes for RFA: three treated patients with combined non-local liver recurrences.
*Includes for RES: one patient with a combined extra-hepatic recurrences.

Tanis et al., Eur J Cancer 2014
Local control following resection / RFTA

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Tanis et al., Eur J Cancer 2014
SIRFLOX study: Y90 radioembolisation in parallel to 1st line FOLFOX

Liver-failure free survival

Progression free survival
CELIM trial: Irresectable CLM

Disease free survival after resection

- All patients
- < 5 metastases
- 5-10 metastases
- > 10 metastases

DFS 9.9 [95% CI: 5.8-14.0] months

Comparison between groups:
\[ p < 0.001 \]

Folprecht et al, Ann Oncol 2014
CELIM: Survival according to completeness of resection

- Progression free survival
- Overall survival

**R0 resected patients**
**R1 resection / ablation**
**Not resected patients**

OS
- R0 resected: 53.9 mo. [95% CI: 35.9-71.9]
- Not resected: 21.9 mo. [95% CI: 17.1-26.7]
HR 0.29 [0.17-0.50], p < 0.001

PFS
- R0 resected: 15.4 mo. [95% CI: 11.4-19.5]
- Not resected: 6.9 mo. [95% CI: 5.9-8.0]
HR 0.31 [0.19-0.50], p < 0.001

R0 resection vs. no resection: HR 0.42 [95% CI: 0.21-0.86], p=0.021

Patients with PR/CR, only

Folprecht et al, ASCO 2013
Local ablative treatments: For whom?

(Potential) criteria:

• Good selection before treatment – on prognostic factors
• Molecular characterisation before treatment
Local ablative treatments: For whom?

(Potential) criteria:

• Good selection before treatment – on prognostic factors
• Molecular characterisation before treatment
• Clinical information during treatment (e.g. „only responders“)
Response to systemic treatment – key factor for selection?

Example: „early tumour shrinkage“

- Cetuximab + FOLFIRI
  - ≥20%* (n=184)
  - <20%* (n=115)
  - mOS 30.0 mo
  - HR 0.53
  - p<0.001

- Cetuximab + FOLFOX4
  - ≥20%* (n=54)
  - <20%* (n=24)
  - mOS 26.0 mo
  - HR 0.43
  - p=0.006

- Probability of OS

- med. follow-up: 3.5 Jahre
- new mets: 42%
- new mets: 67%

Piessevaux et al., J Clin Oncol 2013
Local ablative treatments: For whom?

(Potential) criteria:

• Good selection before treatment – on prognostic factors
• Molecular characterisation before treatment
• Clinical information during treatment (e.g. “only responders“)
• (New translational parameter,s like cfDNA during treatment?)
Evaluation of response to treatment in mCRC


Slide kindly provided by Clara Montagut, Barcelona
Evaluation of response to treatment in mCRC

- CEA: Carbohydrate-Excretion Assay
- ctDNA: Circulating Tumor DNA
- RECIST: Response Evaluation Criteria in Solid Tumors

Response by RECIST (CT scan)
Molecular response by liquid biopsy
Tumor burden

Blood draws (ctDNA) vs. cycles of chemotherapy

Slide kindly provided by Clara Montagut, Barcelona
Do we need a „proof of concept“ – in randomised trials?
Draft: Randomized „strategy“ trial

non progressive, non resectable, oligometastatic (up to 3 sites/5 lesions) after any chemo for 3-6 months

Optimal SBRT (to be determined)
Resume for total of 6 months

Continuation of CT until PD

Progression
CLM: Surgery and retrospective series
Initially non-resectable liver metastases

Adam et al., J Clin Oncol 2009
Evaluating the feasibility and efficacy of local tumor destruction in combination with immunotherapy in patients with unresectable colorectal liver metastases
I_LOCC: Study design

**Randomize**

- Chemo + local tx. + anti CTLA 4 + anti PD1
- Chemo + anti CTLA 4 + anti PD1
- local tx. (twice) + anti CTLA 4 + anti PD1

**non-operable**

- CRC liver mets
- At least stable disease

*+/- limited extrahepatic

# RFA/microwave/radiotherapy for at least volume of 250 cm³
Rationale for combination regimen

Combining anti-PD-L1 with radiotherapy or chemotherapy may improve anti-tumor effects of immunotherapy

- by overcoming parts of immunosuppression
- by enhancing cross-presentation of tumor antigens
- by supporting better penetration of immune cells in tumor core

Apetoh et al, Ann Oncol 2015
Melanoma plus anti CTLA4 + RT

Twyman-Saint Victor et al., Nature 2015
# Limited mCRC: Considerations

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<td>2016 ff.</td>
<td>Concept of oligometastatic disease</td>
<td>New methods / multidisciplinarity</td>
<td>25% liver mets only</td>
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<td>Integration of ablative treatments</td>
<td>New strategic goals</td>
<td>About 60% with „any oligometastatic disease“</td>
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Integration of ablative treatment into the overall strategy in patients with oligometastatic CRC

- "Time without symptoms & treatment" (→ QoL?)
- Prolongation of "TFS" (→ Prolongation of OS?)
- No development of resistant clones against active treatment? (→ Impact on OS?)
Obrigado pela sua atenção