Latest Advances in Colorectal Cancer

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Disclosure of potential conflicts of interests:

1. Consultant activities:
   - Amgen, Bayer, Celgene, Merck, Roche

2. Honoraries as invited speaker:
   - Amgen, Bayer, Celgene, Ebewe, Fresenius, Pfizer, Merck, Roche, Sanofi-Aventis

5. Any other financial relationships:
   - none
The most important advances in colorectal cancer treatment:

(1) Availability & use of novel agents

The most important advances in colorectal cancer treatment:

(2) Adoption of the interdisciplinary patient management
The most important advances in colorectal cancer treatment:

(3) Optimal timing of treatment, secondary liver resection

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Median survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>65.3 mos</td>
<td>55%</td>
</tr>
<tr>
<td>Non-resected</td>
<td>26.7 mos</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

The most important advances in colorectal cancer treatment:

(4) Identification of prognostic & therapeutic relevant biomarkers in the tumour tissue

- KRAS mutational status in metastatic colorectal cancer:
  - Which targeted therapy?

- Microsatellite instability:
  - Postoperative chemotherapy necessary?
Indications for chemotherapy in colorectal cancer:

- Postoperative (adjuvant)
- Preoperative (neoadjuvant)
- Palliative (metastatic disease)
In patients with locally advanced, resected tumours the likelihood of recurrence can be reduced, i.e., the chance for definitive cure can be improved.
Postoperative adjuvant chemotherapy?

Decision depends on (1) tumour stage

- **Stage I**
  - T1  N0  M0
  - T2  N0  M0

- **Stage II**
  - T3  N0  M0
  - T4  N0  M0

- **Stage III**
  - T1-4 N 1-3 M0 (lymph nodes involved)
Postoperative adjuvant chemotherapy?

depends on (2) histopathological risk factors

- Obstruction or perforation at the time of initial surgery
- Depth of tumour infiltration of the bowel wall (T1-3 vs T4)
- Number of involved or analysed lymph nodes (± 12 !)
- Histologic differentiation (grading 1,2 vs. 3)
- Infiltration of lymph- or blood vessels
Postoperative adjuvant chemotherapy?

depends on (3) individual patient characteristics

- Biological age
- Comorbidities
- Risk of toxicities
- Social & psychological background
- Patient’s choice
Recent advances in postop. adjuvant chemo:

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>3-years tumour-recurrence free</th>
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</thead>
<tbody>
<tr>
<td>Moertel</td>
<td>Observation</td>
<td>52%</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Observation</td>
<td>44%</td>
</tr>
<tr>
<td>IMPACT</td>
<td>5FU/LV</td>
<td>62%</td>
</tr>
<tr>
<td>Punt</td>
<td>5FU/LV</td>
<td>65%</td>
</tr>
<tr>
<td>Fields</td>
<td>5FU/LV</td>
<td>67%</td>
</tr>
<tr>
<td>André</td>
<td>5FU/LV</td>
<td>61%</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>5FU/LV</td>
<td>65%</td>
</tr>
<tr>
<td>X-ACT</td>
<td>Capecitabine</td>
<td>64%</td>
</tr>
<tr>
<td>MOSAIC</td>
<td>FOLFOX4</td>
<td>72%</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>FLOX</td>
<td>72%</td>
</tr>
<tr>
<td>XELOXA</td>
<td>XELOX</td>
<td>71%</td>
</tr>
</tbody>
</table>
ESMO 2012 adjuvant treatment recommendations in colon cancer

Patients having undergone colon cancer surgery in good general condition

Stage III

In patients >70 years:
- Assessment for co-morbidities
- Social & psychological background
- Patients’ choice
- Ability to tolerate systemic chemotherapy

Adjuvant chemotherapy

Oxaliplatin based adjuvant chemotherapy

Capecitabine (5-FU/LV)

No high risk features

Stage II

Observation alone

Adjuvant chemotherapy

MSI status ?!

Capecitabine (5-FU/LV) ± oxaliplatin

No routine role for any adjuvant biological agents
Adjuvant chemotherapy & “optimale timing”

A meta-analysis of the impact of time to adjuvant chemotherapy (TTAC) on survival (14,357 patients from 9 clinical studies)

12% increase in the risk of death for each 4 weeks of chemo delay! Still some benefit after a 3 months delay…..

Biagi JJ et al, Proc GI-ASCO 2011, abstr. 364
If the tumour can not be operated with curative intent, or only with a major surgical effort, chemotherapy is administered preoperatively.
Neoadjuvant chemotherapy - Rationale

- Minimise the extent of surgery
- Reduce the risk of operative complications
- Destruction of frequently coexistent micrometastases
- Identify the chemosensitivity of the tumour
- Identify aggressive, chemotherapy-resistant disease
- Avoid unnecessary surgical interventions
- Increase the likelihood of curative surgery
- Improve recurrence-free & overall survival
Neoadjuvant chemotherapy in colorectal cancer liver metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>&gt;50% ▼ size</th>
<th>Potential cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>64%</td>
<td>41%</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>71%</td>
<td>38%</td>
</tr>
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</table>
Neoadjuvant chemotherapy in locally advanced rectal cancer

Before combined radiochemotherapy

After completion of treatment, before surgery
Indications for chemotherapy in colorectal cancer:

- Adjuvant
- Neoadjuvant
- Palliative

Treatment Settings:
- Adjuvant
- Neoadjuvant
- Palliative
Palliative chemotherapy

Treatment goals in patients with metastases

- Cure
- Prolongation of survival
- Release of tumour-related symptoms
- Improve the quality of life
Palliative treatment scenario must be defined

- Aggressive tumour with metastases in inner organs and clinical symptoms
- Indolent tumours with metastases in organs, but without symptoms

Treatment goals
- Rapid reduction in tumour size
- Prolongation of survival
- Improvement or maintenance of a good quality in life

1) Therapy must be effective, tolerable, convenient, and should be conducted for an optimal duration.

2) Biological age, physical condition, comorbidities, toxicity profile & acceptance must be taken into consideration.
Anticancer drugs used in colorectal cancer

Conventional chemotherapeutic agents
- Oxaliplatin
- Irinotecan
- 5-Fluorouracil
- Capecitabine
- Uracil/Tegafur

Tumour-targeted agents ("biologicals")
- Bevacizumab
- Afiblercept
- Cetuximab
- Panitumumab
- Regorafenib

antiangiogenetic drugs
anti-EGFRs
Antiangiogenic drugs (e.g., Bevacizumab) mechanism of action

1. **Regression**
   - Decreases tumour size

2. **Normalisation**
   - Improves delivery of chemotherapy

3. **Inhibition**
   - Suppresses new vessel growth

**EARLY EFFECTS**

**CONTINUED EFFECTS**
Anti-epidermal growth factor (EGFR) drugs: mechanism of action

- Tumour growth
- Angiogenesis
- Tumour cell survival
- Metastatic spread

Receptor activation

Tumor

Blood vessel

Tumour growth

Anti-epidermal growth factor (EGFR) drugs: mechanism of action
Anti-EGFR drugs: correlation between skin reaction and tumour shrinkage

- **Grade 0**: 13%
- **Grade 1**: 42.2%
- **Grade 2**: 53.2%
- **Grade 3**: 66.7%
1991: A classical case of mCRC

- 3 months symptomatic therapy
- 4 months 5-FU/LV
- 2 months infusional 5-FU
- 2 months treatment break
- OS 11 months

Progression
The new principles of mCRC management

• Biologicals have definitively enriched our therapeutic armamentarium

• Exposure to multiple chemotherapy agents is associated with prolonged survival

• No need to continue chemo until progression: breaks / holidays or mild maintenance treatment ± reintroduction
2012: A classical case of mCRC

- 3 months symptomatic care
- 3 months rescue therapy
- 3 months third line
- 3 months break
- 4 months second line therapy
- 3 months reintroduction
- 6 months maintenance
- 5 months first-line therapy

OS 30 months
Advances in Colorectal Cancer: Conclusions

- Primary prevention
- Screening
- Better preoperative diagnostic means
- Better surgical techniques
- Superior oncological therapeutical armentarium
- Adoption of the interdisciplinary patient management
- Increasing knowledge about the optimal timing of available anticancer treatment strategies
SEKUNDÄRE HÄMOSTASE

INTRINSIK
FXII → FXIIa
FXI → FXIa
FX → FXa
FXIII → FXIIIa
FXIII → FXIIIa

EXTRINSIK
F VII → FVIIa

Fibrinogen
Fibrin
Protease

Plasminogen
Plasmin

NOCH FRAGEN?

Herzlichen Dank

www.rippenspreizer.de