Adjuvant Chemotherapy in Rectal Cancer Patients Receiving Chemo-radiation: A Moving Target

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CRC as worldwide health problem

- CRC Global Statistics:
  - 3rd highest incidence rate (~ 1,200,000/yr)
  - 4th highest mortality rate (~ 608,000/yr)

- CRC US Statistics:
  - 3rd highest incidence rate (~ 143,000/yr)
  - 2nd highest mortality rate (~ 51,500/yr)

Rectal Cancer

- Approximately 40,000 new cases per year in the USA
- Therapy is dictated by the extent of disease at presentation
  - Pretreatment (TNM) staging of rectal cancer with EUS and/or pelvic MRI (better) is mandatory
  - Surgical resection is the cornerstone of curative therapy
  - However, the majority of patients present with more deeply invasive tumors
  - Significant advances in local control with multimodality therapy
- Up to 25% of patients develop distant metastases
<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{is}$</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>$T_1$</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>$T_3$</td>
<td>Tumor invades through muscularis propria or subserosa</td>
</tr>
<tr>
<td>$T_4$</td>
<td>Tumor directly invades other organs or structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_0$</td>
</tr>
<tr>
<td>$N_1$</td>
</tr>
<tr>
<td>$N_2$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_0$</td>
</tr>
<tr>
<td>$M_1$</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer.
National Comprehensive Cancer Network (NCCN), 2008; Greene et al., 2002.

**TNM / AJCC v7 Effective Jan 2010**

- **T4a**: perf. visceral peritoneum
- **T4b**: invasion of organs
- **N1a**: 1 N+
- **N1b**: 2-3 N+
- **N2a**: 4-6 N+
- **N2b**: >7 N+
History Of Multimodality Therapy In Rectal Cancer

Peri-op XRT reduces LRR
(No impact on OS)

Total Mesorectal Excision (TME) established as superior surgical modality
Post-operative chemoradiation becomes standard

CRT better than RT
Preop CRT better than Post-op
Refinements on CT and RT

Preop Radiation reduces LRR even when TME is done.


CCCG, Lancet, 2001; O'Connell MJ NEJM 1994
Kapitejn NEJM 2001; Bosset NEJM 06;
Sauer NEJM 04
1. 5-FU Based Radiochemotherapy is Superior to Radiation Alone

Krook, NEJM, 324:709, 1991

- Improved local control, sphincter preservation (downstaging)
- Better compliance
- Decreased acute and chronic (anastomotic leak) toxicity
- No survival differences

3. Capecitabine vs. 5-FU in Rectal Cancer

- **German Trial**
  - 401 pts
  - Local recurrence: 6 vs. 7%
  - Distant metastases: 18% vs. 28%
  - 5-year OS: 75 vs 67%

- **ASCO GI 2014**: Preliminary report of NSABP R-04: Comparable rates of pCR (21 vs 18%), locoregional control (12 vs. 11% 3-year incidence of locoregional events) and OS (81 vs. 80%).

\(^1\)Hofheinz et al., Lancet Oncol 2012
4. Oxaliplatin in Neoadjuvant Radio-Chemotherapy for Rectal Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Chemo</th>
<th>RT</th>
<th>Grade 3-4 toxicity</th>
<th>Pathological CR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aschele (STAR)</td>
<td>379</td>
<td>5-FU 225 mg/m²/d</td>
<td>50.4 Gy in 28 fractions</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>368</td>
<td>5-FU 225 mg/m²/d + Oxaliplatin 60 mg/m²/w x 6</td>
<td>50.4 Gy in 28 fractions</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Gerard (ACCORD)</td>
<td>295</td>
<td>Capecitabine 800 mg/m² bid</td>
<td>45 Gy in 25 fractions</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>292</td>
<td>Capecitabine 800 mg/m² bid 5 of 7 d + Oxaliplatin 50 mg/m²/w</td>
<td>50 Gy in 25 fractions</td>
<td>25%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Aschele, JCO 2011; Gerard, JCO 2010.
### 5 x 5 Gy versus 5-FU CRT?

**Bujko et al., Br J Surg 2006**

<table>
<thead>
<tr>
<th>T3NxM0</th>
<th>5 x 5 Gy</th>
<th>5-FU CRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts.</td>
<td>163</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>3-year LR rates</td>
<td>7.5%</td>
<td>4.4%</td>
<td>0.24</td>
</tr>
<tr>
<td>5-year M1</td>
<td>27%</td>
<td>30%</td>
<td>0.92</td>
</tr>
<tr>
<td>5-year OS</td>
<td>74%</td>
<td>70%</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Ngan et al., JCO 2012**
Rectal Cancer: Indications for Neoadjuvant CRT

- **Definitive indication**
  - T3/4 tumors

- **Relative indications**
  - T1/2 and clinically node positive
  - Distal tumors (to achieve sphincter preservation)
  - Mesorectal fascia involvement (by TRUS or MRI)

Willet C, Ryan DP. Uptodate 2014.
NCCN 2014: Dosing Schedules for Concurrent Chemotherapy/RT

- **XRT + continuous infusion 5-FU:**
  - 5-FU 225 mg/m² over 24 hours 5 or 7 days/week during XRT

- **XRT + 5-FU/leucovorin**
  - 5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

- **XRT + Capecitabine**
  - Capecitabine 825 mg/m² twice daily 5 days/week + XRT x 5 weeks
Multimodality Management of Rectal Cancer

- Pretreatment staging of rectal cancer with EUS and/or pelvic MRI (better) is mandatory
- Neoadjuvant radio-chemotherapy is standard of care in T3 Nx rectal cancers
  - Fluoropyrimidine alone (capecitabine or infusional 5-FU) as radiosensitizer
  - Addition of oxaliplatin did not improve short-term outcomes, but is more toxic
- Short-course radiation therapy alone (5x5 Gy) is non-inferior to neoadjuvant radio-chemotherapy
- Post-operative adjuvant therapy is guided by clinical staging before neoadjuvant therapy
Adjuvant Chemotherapy in Locally Advanced Rectal Cancer After Preoperative Chemoradiation?

... it’s complicated
Adjuvant chemotherapy in Rectal Cancer after CMT Yes or No?

- **US: NCCN** recommends that all pts receive postop chemotherapy even if they have a pCR to neoadjuvant therapy.

- **ESMO**: Similar to colon cancer (stage III and high risk stage II), adjuvant chemotherapy can be provided, even if scientific support for sufficient effect is less.

- **European Rectal Cancer Conference**: Insufficient evidence on the benefit of adjuvant chemotherapy after preop CMT to recommend its use.
CT regimens in the adjuvant setting (NCCN 2014)

- **mFOLFOX6 (Q 2 WEEKS):**
  - Oxaliplatin 85 mg/m2 IV over 2 hours, day 1,
  - leucovorin* 400 mg/m2 IV over 2 hours, day 1,
  - 5-FU 400 mg/m2 IV bolus on day 1,
  - 5-FU 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46-48 hrs)
  - Repeat every 2 weeks for a total of 6 months perioperative tx

- Simplified biweekly infusional 5-FU/LV (*sLV5FU2*)
  - Similar to above, without oxaliplatin

- **CAPECITABINE:** 1250 mg/m2 twice daily days 1-14 every 3 wks

- **CapeOx:**
  - Oxaliplatin 130 mg/m2 over 2 hours, day 1. Capecitabine 1000 mg/m2 twice daily days 1-14 every 3 weeks.
  - 5-FU 500 mg/m2 IV bolus weekly x 6 + leucovorin 500 mg/m2 IV weekly x 6, each 8-week cycle. Repeat every 8 weeks
Evidence supporting adjuvant chemotherapy

- Evidence to support adjuvant chemotx an extrapolation of postop adjuvant therapy with RT and chemo (in the era before CMT)

- Cochrane review (20 randomized trials)
  - 5FU based chemotherapy significantly reduced risk of death (HR 0.83, 95% CI 0.76-0.91)
  - Only 1 of 20 trials included preop chemoradiation
Evidence NOT Supporting Adjuvant Chemotherapy After Chemoradiation

- EORTC 22921\(^1\): Long term results
  - Preoperative CMT improved local control
  - Adjuvant 5FU provided no significant clinical benefit

- Italian Trial (Cionini et al)\(^2\): 655 pts
  - No difference in 10-year OS (63.4% vs. 63.0%)

- PROCTOR/SCRIPT trials \(^3\) (470 pts)
  - 5-year OS: 74% vs. 76%

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\(^1\) Bosset JF et al. Lancet Oncology. 15, 2. 2014.
\(^2\) Cionini et al. Radiother Oncol 2010; 96 (S113 ).
EORTC 22921: Adjuvant Fluorouracil based CT after preoperative CRT in rectal cancer

- **Long term follow up**
  - 10-year OS: 51.8% (95% CI 47-56.4) vs. 48.8 (95% CI 43.6-53)
  - 10-year DFS: 47% (95% CI 42.2-51.6) vs. 43.7 (95% CI 39.1-48.2)

- **90% of distant metastases occurred before 3 years of follow up**
  - At 10 years, distant metastases are 2.5 times more common than local relapses, in about one third of patients

Bosset JF et al. Lancet Oncology. 15, 2. 2014
Lessons from EORTC 22921\textsuperscript{1,2}

- Adherence to adjuvant chemotherapy was poor ( < 43% pts received planned dose)
  - More than 25% of pts could not start adjuvant chemotherapy due to postoperative complications, absence of tumor resection, PD, or pt refusal (similar to other studies: Italian, CAO/ARO/A10-04)

- \textit{Pts were not stratified for prognostic factors (T or N stage)}

- Subgroup analysis of pts who underwent R0 resections and node negative:
  - Adjuvant chemotherapy improved OS in pts whose tumors were downstaged to ypT0-2, but not stage ypT3-4

- \textit{Better understanding of prognostic/predictive factors should help in the design of risk adapted therapy for rectal cancer patients.}

\textsuperscript{1}Bosset JF et al. Lancet Oncology. 15, 2.
Important questions regarding adjuvant CT in LARC

• Is Preoperative (clinical) staging reliable enough to dictate adjuvant therapy?
• Preoperative (clinical) or postoperative staging: which is a better predictor of DFS
• How do patients with cT3-4 or N+ tumors who are downstaged do?
  • ypT0, ypT1-2
  • Do they benefit from adjuvant CT?
• No randomized trials to answer these questions
Pathologic T and N stages independently predict for LR, DM and OS in rectal Ca pts treated with mesorectal excision and CRT

TABLE 5. Survival by Pathologic T and N Stages and Stage Groups

<table>
<thead>
<tr>
<th>Pathologic T stage</th>
<th>5-yr Freedom From LR (%)</th>
<th>5-yr Freedom From DM (%)</th>
<th>5-yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>96</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>Pathologic N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>94</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>1–2</td>
<td>81</td>
<td>66</td>
<td>69</td>
</tr>
<tr>
<td>Pathologic stage group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (T0–Tis, N0)</td>
<td>96</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>I (T1–T2, N0)</td>
<td>97</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>II (T3–T4, N0)</td>
<td>88</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>III (N1–N2)</td>
<td>81</td>
<td>66</td>
<td>70</td>
</tr>
</tbody>
</table>

LR, local recurrence; DM, distant metastasis; OS, overall survival.

N: 470 patients

Das, P, et al. AJCO. 29(3) 219-224. 2006
Pathologic stage is a better prognostic indicator of DFS in LARC patients after preoperative chemoradiation

N=342  (clinical Stage II/III: T3/4 and/or N1/2)

Quah HM et al. Cancer. 113(1) 57-64. 2008
Pathologic vs clinical stage is better prognostic indicator of DFS in LARC patients after preoperative chemoradiation.

(a) Disease-free survival for patients with clinical stage II rectal cancer, stratified by final pathologic stage. (b) Disease-free survival for patients with clinical stage III rectal cancer, stratified by final pathologic stage.

Quah HM et al. Cancer. 113(1) 57-64. 2008
Response To CRT As A Predictor Of Disease Free Survival

Quah HM et al. Cancer. 113(1) 57-64. 2008
Studies evaluating role of adjuvant chemotherapy after chemo radiation

- CAO-ARO-AIO-04: Neoadjuvant chemoradiotherapy and adjuvant chemotherapy with 5-FU and oxaliplatin vs 5-FU alone in rectal cancer
- NSABP R-04/E5204:
  - Preop XRT and CAPE with preop XRT and continuous IV infusion of 5-FU with or without OX in pts with operable carcinoma of the rectum
  - ECOG 5204: Intergroup Randomized Phase III Trial of Postop Oxaliplatin, 5-FU and Leucovorin vs. Oxaliplatin, 5-FU, Leucovorin and BEV for Stage II or III Rectal Cancer Receiving Preoperative Chemoradiation
- EORTC 40054-22062: Preop CRT and postop CT with CAP and OX vs. CAP alone in locally advanced rectal cancer (PETACC-6)

*The above studies do not have control (observation) arms*
Adjuvant therapy for rectal cancer pts after preoperative CRT: final considerations

- Discuss with patient advantages, disadvantages and gap in knowledge regarding adjuvant CT
  - Consider postoperative state, PS, age
- If patient does well after surgery (risk based decision)
  - Consider fluoropyrimidine based CT for patients who were downstaged or elderly patients
  - Consider oxaliplatin based regimens in patients with less tumor downstaging (ypT3-4 or N+)
- If patient has postop complications or poor PS:
  - Don’t feel bad about not giving adjuvant CT

Summary and Conclusions

• In conjunction with neoadjuvant radiation, chemotherapy has improved local control and increased rate of sphincter-sparing surgery

• Adjuvant chemotherapy for LARC patients after CRT?
  • There is no evidence from randomized trials that adjuvant 5FU based chemotherapy significantly prolongs DFS or OS
  • While we await current trials using modern adjuvant chemotherapy regimens, current practice (in the US) continues to be offering adjuvant chemotherapy
Conclusions

• Decisions on whether to give adjuvant CT or not after preoperative CRT should be individualized
• Consider patient’s postoperative and performance status
• Consider risk adapted decisions based on pT,N staging
• Ongoing trials are focusing on the integration of
  • new cytotoxic and targeted agents in the neoadjuvant and adjuvant treatment phase
• Development of molecular and clinical predictors of treatment efficacy and prognosis are urgently needed
Obrigado!!

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