Adjuvant Chemotherapy for Rectal Cancer: Are we making progress?

Hagen Kennecke, MD, MHA, FRCPC
Division Of Medical Oncology
British Columbia Cancer Agency
October 25, 2008
Objectives

- Review milestones of rectal cancer therapy
- Review multimodality therapy for locally advanced and low rectal cancer
- Discuss optimal pre-operative and post-operative chemotherapy
Question #1: Chemoradiation for rectal cancer is most effective and least toxic when given:

- 4-6 weeks prior to TME surgery
- 4-6 weeks after TME surgery
- Either pre or post-operatively, as long as sufficient time between surgery and chemoradiation
Question #2: Postoperative chemotherapy is recommended to reduce the risk of distant recurrence for patients with:

- Stage $\geq$ I (any invasive cancer)
- Stage $\geq$ II (tumor invasion through the muscularis propria, node negative)
- Stage III only (node positive)
Question #3: Pre-operative downstaging chemoradiation has been shown to increase sphincter sparing surgery.

- True
- False
Rectal Cancer: Definitions

- Adenocarcinoma
- Defined by distance from Tumor located <16 cm from anal verge
  - 0-5 low
  - >5-10 mid
  - >10-15 high

- Staging: the SAME as colon cancer:
  - Stage I: T1/T2,N0
  - Stage II: T3/T4, N0
  - Stage III: T any, N positive
  - Stage IV: metastatic
Staging

- CT abdomen/pelvis
- CXR or CT chest
- CEA!
- Imaging of primary tumor: Endorectal US or pelvic MRI
  - T stage: Invasion through muscularis propria?
  - N stage: Nodes approaching the mesorectum?
Surgical Therapy of Rectal Cancer: DIFFERENT than colon cancer

- Total Mesorectal Excision (TME) –
  - “Sharp dissection along mesorectal plain to achieve *en bloc* resection of tumor”
  - Superior surgical technique results in significant reduction in loco-regional recurrence

- TME is done as part of:
  - Anterior Resection – sphincter sparing, or
  - Anterior-Perineal Resection (APR) – non sphincter sparing
Purpose of Adjuvant Therapy

- Reduce loco-regional recurrence
- Reduce distant metastasis
Adjuvant Therapy for Rectal Cancer: Milestones

- **1990**: New Standard: Combined Postoperative chemotherapy and radiation therapy is recommended in stage II and III rectal cancer and results in improved local control and survival. (NIH Consensus Statement)

- **1994**: Infusional 5-FU with radiation is superior to bolus 5FU with radiation in terms of Disease Free and Overall Survival (US)

- **1997**: Pre-op short course radiation reduces Local Recurrence (HR=0.4) improves Overall Survival (Swedish)
United Nations Milestones

- **2001**: Pre-op short course XRT with Total Mesorectal Excision reduces Local Recurrence (HR=0.3) but not Overall Survival (Dutch)

- **2004**: PRE-OP infusional 5-FU-radiation is more effective in terms of Local recurrence (HR=0.46) and less toxic (HR=0.6) than the same therapy given POST-OPERATIVELY (German)

- **2006**: 5-FU based chemotherapy added Pre- or Post-Operatively to Radiation and Surgery improves local recurrence but not survival (EORTC)
Outcomes of Rectal and Colon Cancer in BC: 1990 -2002

- Population based study of patients referred to BCCA, GI-ASCO 2008

**HYPOTHESES:**

- **#1:** On a population basis, due to advances in local and systemic therapy, outcomes have improved for both rectal and colon cancer.

- **#2:** Due to advances in therapy specific to rectal cancer, rectal cancer outcomes have improved to a greater degree than colon cancer outcomes.
Methods

- Patients with resected, pathological stage II or III colorectal cancer referred to BCCA in 1990, 1995/96, and 2001/02 were included.

- **1990**: guidelines recommending adjuvant chemotherapy for colon and rectal cancer first released.

- **1995/96**: time period prior to widespread adoption of TME.

- **2001/2002**: increased adoption of TME, preoperative radiation therapy, and adjuvant 5-FU based chemotherapy. Prior to introduction of oxaliplatin based therapy.
Methods

- Data was collected through the BCCA colorectal cancer outcomes database
- The higher of clinical or pathological stage was used if long course preoperative chemo/radiation was given
- Kaplan Meier method was used for survival analysis
Results

1851 patients were included in the analysis

The median follow up time was:

15.7 years [1990]
10.8 years [1995/96]
5.3 years [2001/02]
<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>1995/96</th>
<th>2001/02</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>140</td>
<td>223</td>
</tr>
<tr>
<td>Median Age</td>
<td>65y</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Sex</td>
<td>67%</td>
<td>49</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 1: Patient Characteristics
<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>1995/96</th>
<th>2001/02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage II (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>30</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Colon</td>
<td>70</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td><strong>Stage III (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Adjuvant chemotherapy for rectal and colon cancer
Figure 2: Radiation therapy for rectal cancer

![Bar chart showing radiation therapy for rectal cancer from 1990 to 2001/02. The chart compares pre-operative radiation therapy (yellow bars) and any radiation therapy (red bars).](chart.png)
Figure 3: Rates of total mesorectal excision (TME) for rectal cancer

- 1990
- 1995/96
- 2001/02

P < 0.001
Table 3: 5 year overall survival for rectal and colon cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>5 Y Survival (%) Rectal Cancer</th>
<th>5 Y Survival (%) Colon Cancer</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>236</td>
<td>44</td>
<td>54</td>
<td>0.0969</td>
</tr>
<tr>
<td>1995-96</td>
<td>563</td>
<td>59</td>
<td>62</td>
<td>0.5607</td>
</tr>
<tr>
<td>2001-02</td>
<td>1052</td>
<td>64</td>
<td>66</td>
<td>0.4543</td>
</tr>
</tbody>
</table>
Kaplan Meier Plot of Overall Survival by Cohort for Rectal Cancer Patients

- 1989-90 Cohort
- 1995-96 Cohort
- 2001-2002 Cohort

Log-rank p=0.0003
Kaplan Meier Plot of Overall Survival by Cohort for Colon Cancer Patients

Overall Survival vs Years Since Diagnosis

- 1988-90 Cohort
- 1995-96 Cohort
- 2001-2002 Cohort

Log-rank p = 0.0248
Conclusions

- Between 1990 and 2001/02 the use of adjuvant chemotherapy increased significantly for rectal cancer from 14.7% to 68.5% (p<0.001) and for colon cancer from 32.9% to 54% (p<0.001)

- The use of preoperative radiation therapy (p<0.001) and TME (p<0.001) in rectal cancer also significantly increased
Conclusions

- In this population based study, 5 year OS for stage II/III rectal (p<0.001) and colon cancer (p=0.025) significantly improved between 1990 and 2001/02.

- Similar outcomes are now apparent for both rectal cancer and colon cancer.
Conclusions

- With respect to rectal cancer, improved outcomes are likely related to increased use of TME technique, preoperative RT and adjuvant chemotherapy

- Improved outcomes for colon cancer likely reflect increased use of adjuvant chemotherapy
Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?
Chemorads for Rectal Cancer

- Pre-operative combined with radiation
  - Bolus 5-FU
  - Infusional 5-FU
  - Capecitabine
  - Multiagent chemotherapy with oxaliplatin in phase II/III trials
5-FU Based Therapy with XRT

- **Standard** is 5-FU based therapy
- **Multiple regimens:**
  - Continuous throughout Radiation
  - Continuous week 1 and 5 of radiation
  - Bolus
  - Oral in the form of Capecitabine

- Able to induce a PATHOLOGICAL COMPLETE RESPONSE (pCR) in 10-15% of cases.
# pCR with 5-FU and with Capecitabine

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Therapy</th>
<th>pCR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sauer 2004</td>
<td>363</td>
<td>50.4 GY, 2 x 5d 5-FU CI</td>
<td>8</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>400</td>
<td>45 GY, 2 x 5d 5-FU, LV bolus</td>
<td>14</td>
</tr>
<tr>
<td>DePaoli 2006</td>
<td>53</td>
<td>50.4 Gy, Cap 825 m2 bid</td>
<td>24</td>
</tr>
<tr>
<td>Lin 2005</td>
<td>53</td>
<td>52.5 GY, Cap 825 m2 bid</td>
<td>17</td>
</tr>
<tr>
<td>Shen ASCO 04</td>
<td>71</td>
<td>60 GY, Cap 825 m2 bid</td>
<td>15</td>
</tr>
<tr>
<td>Kocakova ASCO 04</td>
<td>43</td>
<td>50.4 GY, Cap 825 m2 bid</td>
<td>21</td>
</tr>
<tr>
<td>Dupuis ASCO 04</td>
<td>51</td>
<td>45 Gy, Cap 825 m2 bid</td>
<td></td>
</tr>
<tr>
<td>Chau GI ASCO 05</td>
<td>68</td>
<td>50.4 GY, Cap 825 m2 bid</td>
<td>24</td>
</tr>
</tbody>
</table>
Chemotherapy beyond 5-FU: can we improve pre-op therapy?

- Local recurrence <10% for stage II/III with TME and Radiation
- But there are high risk groups:
  - Locally advanced presentation (T4,N2)
  - Low rectal Tumors
- Better “downstaging” required
- Ongoing Phase II/III trials
  - 5-FU/capecitabine + oxaliplatin
  - 5-FU/cape + oxali + biologics
NSABP R-04

Stratify
- T2 vs. T3
- M vs. F
- SP vs. APR

n=1460

Capecitabine (825 mg BID) 50.4 Gy

± Oxaliplatin

CI 5-FU (225 mg/m2/d) 50.4 Gy

± Oxaliplatin
Oxaliplatin with Radiation

- Oxaliplatin chemotherapy shown to improve survival in colon cancer
- Rationale:
  - Achieve better downstaging of locally advanced tumors
  - Better downstaging of low rectal cancers to reduce requirement for colostomy
  - Allow earlier systemic therapy to reduce risk of metastatic disease
Oxaliplatin with Radiation

- Multiple phase I/II trials of 5-FU/Capecitabine plus oxaliplatin
- Therapy effectiveness determined by pathological Complete Response rate (pCR):
  - The complete absence of tumor in the resected pathological specimen
- Therapy is safe and achieves high rates of pCR of 20-25%
Aim:

- Phase II trial is to evaluate the efficacy and safety of bevacizumab, capecitabine and oxaliplatin + XRT

- Multicenter: Vancouver, Edmonton, Calgary, Winnipeg, Toronto

Previous study: bevacizumab in combination with 5-FU chemoradiation followed by surgery did not result in dose-limiting toxicity in any of the evaluated patients.
Figure 1. Treatment schedule

Histologically proven locally advanced T3/T4 rectal carcinoma

-14  -8  1  8  15  22  29  35

Eligible for study

Day

Bevacizumab i.v. (5 mg/m²)

Oral capecitabine (twice daily)

Oxaliplatin i.v. (50 mg/m²)

Radiotherapy (1.8 Gy for 5 weeks + boost, total 50.4 Gy)

825 mg/m²  Rest  825 mg/m²

Surgery 7–9 weeks later
**Treatment**

- As of 31 December 2007, 10 evaluable patients have been enrolled.

- In total, there have been 5 cycles where dose reductions / interruptions / discontinuation (3/4/1) have occurred (4 of 8 patients); all were due to adverse events.

- All 10 of the patients that received protocol treatment have each completed a total dose of 50.4 Gy delivered to the tumor.
Pre-operative adverse events with bevacizumab, capecitabine, oxaliplatin and radiotherapy (n=10)
Post-operative adverse events with bevacizumab, capecitabine, oxaliplatin and radiotherapy (n=8)
Post-operative efficacy evaluation

- Post-operative information is available on 8 patients.
- A pCR was observed in 3 of 8 patients. Mild-Moderate regression was observed in 3 patients.
- 5 of 8 patients have had sphincter-sparing surgeries (local abdominal resection [LAR]) and 3 of 8 an abdominoperineal resection (APR).
- Complete tumor resection was possible in 7 of the 8 patients.
Conclusions: A-CORRECT study

- Interim safety analysis suggest that chemoradiation with bevacizumab, capecitabine and oxaliplatin is feasible.
- Full doses of planned radiation (50.4 Gy) were delivered to all patients.
- Accrual of a total of 55 patients
Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- What duration of therapy?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?
Post-Operative chemotherapy

- OPTIONS
  - Bolus 5-FU
  - Infusional 5-FU
  - Capecitabine
  - 5-FU and oxaliplatin *included in NCCN guidelines as adjuvant therapy for rectal cancer
  - 5-FU based, oxaliplatin and biologics in phase III trials
Evidence for Post-operative Chemo

- Distant recurrence risk significant
- Stage for stage, rectal risk at least equivalent to colon cancer
- 5-FU based chemo either pre-operatively with radiation or post-operatively reduces local recurrence (EORTC, NEJM ‘06)
- Evidence for chemo benefit difficult to estimate:
  - adjuvant chemotherapy variable in trials
  - compliance variable
  - path stage obscured by downstaging chemo-radiation therapy
  - DIFFERENT than colon cancer
Ongoing Adjuvant Chemotherapy trials for Rectal Cancer

- POST-OPERATIVE THERAPY:
  - E5204
    - Post-operative therapy
    - 12 cycles of FOLFOX +/- Bevacizumab

- PETTAC/EORTC:
  - Post-operative Capecitabine vs. Cap Oxaliplatin

- UK CHRONICLE STUDY:
  - Pre-Op chemo-radiation, Post-operative Observation vs. Cap Oxaliplatin
ECOG 5204 Phase III Trial
NCIC CRC.4

Stage II/II
Preop CRT
(Cape, FU)
-NSABP R04

IF preop oxali:
9 cycles mFOLFOX6 +
3 cycles 5FU/LV

mFOLFOX6 X 12

mFOLFOX6 + Bev
X 12
PETACC/EORTEC Phase III trial

R

1:1

R0-resectable
- RT 5 x 5 Gy
- XRT cap + 50 Gy
- RT 50 Gy

R0-resectability uncertain
- XRT cap + 50 Gy

All
- XRT 50 Gy cap + oxaliplatin

n=1090

Capecitabine 6#

TME

Capecitabine + oxaliplatin 6#
**CHRONICLE Phase III study**

**Pre-operative**
- Minimum 45 Gy RT
- Fluoropyrimidine-based CT
- No prior oxaliplatin
- n=800

**Post-operative**
- 6 x 3-weekly intervals (18 weeks)
  - Oxaliplatin 130 mg/m² infusion, day 1
  - Capecitabine (1000 mg/m² once daily on days 1–14)

**Follow-up only**

R0 excision
Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?
Clinical vs Pathologic Stage

- Pathologic stage usual standard determining adjuvant therapy in oncology
- Referred to as “Y stage” if previous tx:
  - Minimally affected by “short course” pre-operative radiation (25GY in 5)
  - Significantly affected by “long course” therapy (50.4GY in 25)

- Clinical stage in rectal less reliable
  - T stage 80-90% accurate with MRI, ERUS
  - N stage 60-80% accurate with MRI, ERUS
Pathologic CR

- 10-15% complete response with long course XRT and 5-FU/Cap
- **Prognostic:** 5Y DFS 86% in pts with pCR and 4 months Bolus 5-FU (German ‘04)
- **Predictive:** pT0-2 but not pT3 benefit from further adjuvant 5-FU chemotherapy (French, JCO 07)
- Thus, further chemo may be beneficial even if low Y stage
Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?
Low Rectal Cancer

- Low rectal tumors, any one of:
  - <5 cm
  - Palpable
  - Require abdominoperineal (APR) resection in surgeon's opinion
- Higher rate of circumferential margin positivity due to resection plane of APR
- Permanent colostomy highly undesirable
- Long course CXRT recommended for downstaging
Low Rectal Tumors

- Conflicting evidence that downstaging increases rate of sphincter sparing:
  - Pre-op CXRT 39% vs. Post-op 19% (German)
  - Short XRT 62% vs Long CXRT 58% (Polish)

- Why?
  - Low rate of complete path response 10-15%
  - Reluctance among surgeons to change surgery
LOW RECTAL CANCER

- BCCA recommendation: pre-op CXRT for low tumors
- Study opportunities:
  - Phase II trials of novel agents
  - Pre-op PETCT, ERUS to assess response
BCCA Guidelines: Stage II/III rectal cancer

LOCALLY ADVANCED AND LOW TUMORS

- Locally advanced define by:
  - T4
  - Clinically fixed/tethered
  - Nodes approaching the mesorectum

- Locally advanced
  - Pre-operative chemoradiation, 45 +5.4 GY
  - Post-operative chemo according to path stage
    - Stage II or less: 4 months of capecitabine
    - Stage III: 4 months of 5 FU/oxaliplatin
BCCA Guidelines

- **LOCALLY ADVANCED AND LOW TUMORS**
- Pre-operative chemoradiation, 45 +5.4 GY
  - Capecitabine 825mg/m2 bid daily
  - For duration of XRT
  - AM dose 1-2 hours prior to radiation

- Post-operative chemo according to path stage
  - Stage II or less: 4 months of capecitabine
  - Stage III: 4 months of 5 FU/oxaliplatin
BCCA Guidelines

- **RESECTABLE RECTAL CANCER**
  - Short course rads 25 GY over 5 days, surgery within 1 week
  - Limited downstaging due to short interval btw radiation and surgery so path stage likely reflects “true” stage
  - Post-operative chemo according to path stage
    - Stage II: 6 months of capecitabine
    - Stage III: 6 months of 5 FU/oxaliplatin
Conclusions

- Pre-operative staging and multidisciplinary care are essential in mmt of rectal cancer
- New systemic therapy options are available for patients with stage II and III rectal cancer
- Rectal cancer outcomes have significantly improved over past 20 years
- Areas for further improvement are:
  - More consistent pre-op staging
  - Locally advanced rectal cancer
  - Low rectal cancer