Adjuvant Treatment for Stage II Colorectal Cancer—Which patients to treat?

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Difference between colon and rectal cancer

- Adjuvant chemotherapy of rectal cancer is largely extrapolated from studies in colon cancer
- Rectal cancers have distinct gene expression, fewer BRAF mutations and less microsatellite instability
- Colon and rectal cancers have distinct embryological, anatomical and physiological characters
Rectal Cancer

• Controversy regarding the use of adjuvant chemo for rectal cancer following neo-adjuvant chemotherapy as chemotherapy is associated with significant systemic toxicity
• Nonetheless recommended by some guidelines
• Recent trials showed no benefit in survival and rate of metastases
• A personalized approach should be employed as not all patients benefit from adjuvant chemo
Rectal Cancer-recommendation

• Widespread use of neo adjuvant therapy
• National Comprehensive Cancer Network, ASCO, ESMO, National Institute of Clinical Excellence) recommend additional post operative chemo
Current: Postop chemo after neoadjuvant chemorad and surgery

- 5 European Trials: Chronicle (n=112), Quasar (n=948), Eortc 22921 (n=1011), Proctoscript (n=437), I Cnr-Rt (n=635) total n=3143, stage 2 and 3 patients
- Only Quasar showed borderline significant benefit of adjuvant chemo after neoadjuvant therapy. But only 21% of patients had radiotherapy.
- Meta-analysis of studies n=1196 showed no significant advantage (Breugom 2015)
Quasar

• “The only prospective RCT with OS benefit for adjuvant chemo in stage 2 CRC
• 5y recurrence rate 22.2% vs. 26.2%
  – relative risk 0.78, 95% CI 0.67-0.91; p= 0.001
• Analyzing the stage II alone, small absolute survival benefit 3.6% at 5 years, p= 0.04
Limitations of Quasar

• Under-staged population
  – Median LN harvested = 6
  – ~ 25% had > 12 LN harvested

  • suggesting that the stage II population was likely contaminated by stage III patients
Problems with these trials

- Poor adherence to post op chemo is widespread eg 25% in Eortc 22921 did not start adjuvant chemo and even more did not finish.
- Surgical standards have changed since 1990s when many trials started, TME was performed in only 36.8% in Eortc 22921.
- APR rate was 47.2% in the surgical arm of Chronicle study.
- No study used MRI for circumferential margin assessment nor PET or MRI for lymph nodes involvement.
Who might benefit from adjuvant chemo?

- Results are conflicting
- Suggestion that patients who respond to neoadjuvant may benefit
- Those who do not respond do not benefit
- But responders had 90% 5 y survival with/without adjuvant
- Adjuvant chemo potentially toxic and survival benefit transient and equalized after 10 years
Non responders

• May indicate unfavourable tumour biology
• Continued adjuvant therapy of no benefit
• What about the use of more aggressive adjuvant treatment? - This is a question for the medical oncologist
Heterogeneity

- All cancers esp rectal cancers are heterogenous
- Staging
- Grading
- Biomarkers – microsatellite instability, p53, Kras, BRAF, thymidylate synthase etc all shown to be useful in colon cancer
- But what about other factors- surgery and pathology
A Word on Colon Cancers

• The role of chemotherapy is not established for stage 2 colon cancer
• T staging, adequate lymph node assessment, lymphovascular invasion, bowel perforation, cancer cell differentiation, pre op CEA levels and microsatellite instability may indicate need for chemo post operatively
• But for those who do not have these markers chemo is controversial
Prognostic Gene Assays – Important Considerations

• None help predict benefit of chemotherapy

• Issues of cost, reproducibility, logistics, rapidity of turnover and whether other potential markers of outcome have been included in assessment

• Neither NCCN guidelines or ASCO recommendations for managing stage II colon cancer recommend the use of these assays eg oncotype DX Colon Ca Test, ColoPrint assay,
ASCO Guidelines: JCO 15 August 2004

- Direct evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer.
- The ultimate clinical decision should be based on discussions with the patient.
<table>
<thead>
<tr>
<th>Study</th>
<th>Stage II</th>
<th>Abs Surv Benefit</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>NACCP randomized</td>
<td>463</td>
<td>8%</td>
<td>Small criticized study</td>
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<tr>
<td>QUASAR randomized</td>
<td>2900</td>
<td>4%</td>
<td>Contaminated by stage 3</td>
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<tr>
<td>MOSAIC randomized</td>
<td>900</td>
<td>Low risk: Ø</td>
<td>Only test of interaction positive</td>
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<td></td>
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<td>High risk: DFS ,</td>
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<td></td>
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<td>Ø OS</td>
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<tr>
<td>ACCENT database</td>
<td>6898</td>
<td>5% at 8 years</td>
<td>Relative benefit &gt;III; abs benefit same for high &amp; low risk</td>
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<tr>
<td>NSABP pooled analysis</td>
<td>1565</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Japanese meta-analysis</td>
<td>2300</td>
<td>3%</td>
<td>Relative benefit &gt;III</td>
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Evidence against adjuvant for stage II

- Subgroups of Randomized studies
  - NCCTG study
  - NSABP C-07
- Randomized studies
  - INT 0035 study
- MeAn
  - IMPACT B2 meta-analysis
  - SEER-Medicare data
  - Meta-analysis (Gill et al)
  - CCOPGI meta-analysis
  - ASCO-CCOPGI meta-analysis
Adjuvant chemotherapy - latest

- National Cancer Data Base - 1998-2006
- N=153,110 stage 2 colon cancer
- Predictors for chemo= <65 yr, male, non white, use of community treatment facility, non-medicare insurance and diagnosed before 2004.
- Improved overall survival in all patient groups regardless of cell differentiation, <12 nodes, positive resection margins, stage, age of chemo regimen.
- No difference between single or multi-agent regimens.

Casadaban L et al Cancer July 2016
Other Factors

- Better pathology
- Better surgery
- Better understanding of clinical trials
Better Pathology doubles proportion of Stage 3

Assessing 12 or more lymph nodes increases the proportion of stage III disease in colorectal cancer (CRC): Evidence from the Surveillance, Epidemiology and End Results (SEER) cancer registry Cai et al. ASCO 2007
A secondary analysis of INT-089: number of lymph nodes examined affects survival in stage 2 CRC

If <10 nodes examined lymph node involvement is under diagnosed
When > 10 LN: More ‘benign’ lymph nodes better?

Why surgery is different from medicine

• The effect of a particular medication is independent of the skills of the doctor as long as the right doses are taken at the right time.

• The effect of any particular surgery however is totally dependent on the operative technique of the surgeon.
Art and Science

• In medical trials there is no learning curve for the drug used
• In surgical trials with each additional patient the surgeon is learning
• Surgical aptitude, volume, training, personal preferences as well as frame of mind and health influences surgery.
• Surgeons must be cognizant of one’s own skills before he can advise his patients of his own expected results.
• Quoting the results of other surgeons will negate the achievements of a master surgeon and mask the danger of mediocrity in a unskilled surgeon

Koh & Seow ANZJ Surg 2006: 76: 286-7
Adjuvant therapy for rectal cancer cannot be based on the results of other surgeons

- Distant recurrence after curative surgery is a failure of staging
- Local recurrence is a failure of technique
- Technical ability varies widely with variation in surgical results
- Surgeons with high recurrence rates should consider retraining, adding routine adjuvant therapy or giving up the craft
- Surgeons with very low recurrence rates need to better individualize their patients for adjuvant therapy so as to treat only those who will need it.

Seow-Choen BJS 2002:89:946-7
Decision making

The ultimate decision should be arrived at together with the patient.
Conclusion

• The surgeon, the medical oncologist and the radiation oncologist must have a frank and truthful discussion with the patient.
• The oncologist must know what his drugs can achieve and what their toxicities are.
• The radiation oncologist must understand the benefits as well as the long term toxicities of his therapies.
• The surgeon must know his own results; excellent or poor and he must know his pathologist as well.