Neoadjuvant Radiation Therapy for Rectal Cancer: Is mo’ betta’?

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Background

- Mostly adenocarcinoma (scc possible, but treated like anal cancer)
- 39, 220 cases annually
- Primary treatment: surgery
- Radiation or chemo or both
  - Neo adjuvant vs. adjuvant
  - Early vs. late stages
Treatment

- Surgery is the primary treatment in curative patients

Surgical Management

- Superficial invasive cancer may be candidate for limited surgical procedure if small.
- Upper and middle third of rectum
  - Low Anterior Resection (LAR)
    - Coloanal anastomosis and preservation of anal sphincter
    - Total Mesorectal Excision (TME)
- Lower third of rectum (within 5-6 cm of anal verge)
  - APR
  - Permanent colostomy
    - high incidence of sexual and urinary dysfunction
Tri modality therapy: later stages

- Surgery
  - with or without Radiation and/or Chemotherapy

- Neo adjuvant vs. adjuvant radiation and/or chemo

- Neo adjuvant radiation:
  - Allows for tumor regression and possible sphincter preservation
  - Short course vs. long course
Neo adjuvant Therapy

- Neo adjuvant chemo/radiation
  - Definite indication:
    - T3 or T4 tumors (will require adjuvant chemo/xrt any way)
  - Relative indication:
    - Node + T1 or T2 tumors
    - Distal tumor that requires APR (for better sphincter preservation in 39% vs. 19% in German trial preop vs. post op)
    - Mesorectal fascia involvement or “threat” of involvement on pre op imaging

3D plan:
prone with 3 fields, 45+5.4 Gy
Treatment field: AP

Treatment field: Lateral
Options for Neo adjuvant therapy

- **Long course vs. short course**
  - Concurrent 5FU + 50.4 Gy (5 ½ weeks) vs. 25 Gy (1 week) without chemo

- **USA**
  - Long course preferred with chemo
  - Especially for T4 or bulky tumors
  - In extramural extension >5 mm on MRI (higher node +)
  - Short course in selected cases
  - Prior to surgery in the metastatic setting to prevent delays in initiation of chemo

- **Outside USA**
  - Short course favored
  - Cheaper and faster for patients
  - Toxicity?
Comparison of long course vs. short course: Radiobiological Dose

<table>
<thead>
<tr>
<th></th>
<th>5040 cGY in 28 fractions</th>
<th>2500 cGY in 5 fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BED$_{eq}$ (biological equivalent dose)</td>
<td>5947 cGY (also with chemo)</td>
<td>3750 cGY</td>
</tr>
<tr>
<td>Total time</td>
<td>5 1/2 weeks</td>
<td>1 week</td>
</tr>
<tr>
<td>Dose per fraction *</td>
<td>180 cGy</td>
<td>500 cGy</td>
</tr>
<tr>
<td>Cost</td>
<td>$5$$</td>
<td>$2$</td>
</tr>
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*Large fraction size => higher risk of late toxicity
Small fraction size, especially with chemo to reduce toxicity

Basis for Neo adjuvant Long course

- German Rectal Cancer Study
  - 823 patients
  - T3/T4 or node positive (5% node + with T1 or T2)
  - Preop chemo/xrt vs. post op chemo/xrt
    - 50.4 Gy in 28 fractions to pelvis
    - Concurrent infusional 5 FU for 5 days (week 1 &5)
    - Surgery: TME
    - Additional 5FU
German Rectal Cancer Study: Results

Median follow up: 46 months

<table>
<thead>
<tr>
<th>Preop chemo/xrt</th>
<th>Post op chemo/xrt</th>
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<tbody>
<tr>
<td>Pelvic relapse @ 5 yrs</td>
<td>6 %</td>
</tr>
<tr>
<td>@ 10 yrs</td>
<td>7 %</td>
</tr>
<tr>
<td>DFS @ 5 years:</td>
<td>68 %</td>
</tr>
<tr>
<td>OS @ 5 year:</td>
<td>76 %</td>
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<tr>
<td>Sphincter preserving</td>
<td>39%</td>
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NSABP R-03

long course

- Preop chemo/xrt vs. post op chemo/xrt
- Closed early
- 267 patients enrolled
- p CR after preop: 15%
- Locoregional recurrence: 11% in both arms
- DFS @ 5 years: 65% vs. 53% p=sig
- OS @ 5 years: 75% vs. 66% p=.065 trend
Basis for Neo adjuvant Short course

- Neoadjuvant radiation only (no chemo)
- 25 Gy in 5 fractions, one week prior to surgery vs. surgery alone for T1-3
- Trials:
  - Swedish Rectal Cancer trial (non TME)
  - Dutch trial (TME)
  - Medical Research Council trial

Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Swedish (5yr) n= 1168</th>
<th>Dutch (5yr)* n=1861</th>
<th>MRC (4 yr)* n= 1350</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>89 with xrt vs. 73%</td>
<td>94.4 vs. 89%</td>
<td>96 vs. 89 %</td>
</tr>
<tr>
<td>OS</td>
<td>58 vs. 48% (p=sig)</td>
<td>64% in both</td>
<td>80 vs. 79 (no diff)</td>
</tr>
<tr>
<td>(3 yr DFS: 78 vs. 72 sig)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>2-4 x with xrt</td>
<td>Fecal incontinence, pad wearing, bleeding, mucous discharge: more in radiation arm</td>
<td>Sexual dysfunction in radiation arm</td>
</tr>
</tbody>
</table>

- Dutch*
  - More perineal wound problems after APR (29 vs. 18%), fecal incontinence, anal blood loss, etc in xrt group
- MRC*
  - Selected pts with +margins or LN + got chemo/ additional xrt
  - Greater sexual dysfunction with preop xrt
  - High number of stage 1 pts.
Long course vs. short course

- **Polish trial**
  - n=316, T3/T4
  - Preop 5040 cGy (28 fx)+5FU/LV vs. 2500 cGy in 5 fractions
  - Results:
    - pCR: 16 vs. 1% favoring long course
    - Radial margin positivity: 4 vs. 13%
    - Sphincter preservation: 58 vs. 61% (no diff)
    - Early chemo/xrt toxicity: 18 vs. 3%
    - Local recurrence: 9 vs. 14% (p=ns)
    - DFS: 58 vs. 56% (p=ns)
    - Severe late toxicity: 10 vs. 7 % (p=ns)

- **Trans-Tasman Radiation Oncology Group**
  - n = 326, cT3 N any, short course vs. long course
  - Both arms received adjuvant chemo
  - Results:
    - pCR: 15 vs. 1 % favoring long course
    - no difference in margin positivity or sphincter preservation
    - No difference in Distant recurrence, RFS , OS, toxicity
    - Local recurrence @ 3 yrs: 4.4 (long) vs. 7.5 % p= ns
      5 yrs: 5.7 vs. 7.5 % p=ns
    - Subset analysis of 79 pts with distal tumors:
      - LR: 12.5% (short) vs. 0% (long)
    - Need longer term followup
Criticism of short course

- Lack of sphincter preservation
- Difficult to combine short course with adequate chemo which also has positive effect on local control
- Higher surgical complications
- Margin status does not change due to short interval between radiation and surgery
- Good for patients with limited metastasis, to allow earlier chemo after surgery

Ongoing trial

- Stockholm II
  - 1: Short course -> immediate surgery vs.
  - 2: Short course -> delayed surgery (4-8 weeks) vs.
  - 3: Long course -> delayed surgery
- Early report of 585 pts: arm 1 has the highest risk of post op complication.
PROSPECT study
Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery

- clinical stage T2Ni, T3No, and T3Ni upper and mid rectal cancer and no evidence of compromise of the mesorectal fascia
- Neoadjuvant chemotherapy followed by reevaluation and surgical resection, followed by adjuvant chemotherapy if, after three months of chemotherapy, there is a >20 percent clinical response;
- the control arm is standard long-course chemo radiation followed by surgery and subsequent adjuvant chemotherapy.
- The primary objectives of the study are the rates of complete (R0) resection and non-inferiority time to local recurrence in the experimental arm for the phase II component and to compare both groups in terms of time to local recurrence and disease-free survival for the phase III component of the study

Summary: Long vs. short course

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