Preoperative adjuvant radiotherapy

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The key question for the surgeon

Do you think that this tumour can be resected with clear margins?
Is it resectable with clear margins?

- If the answer is No, then preop treatment is indicated to try to reduce the size of the tumour.

- If Yes, is there an indication for preop radiotherapy?
To make the tumour smaller

- “Long course” radiotherapy over 4-6 weeks
  45Gy – 54Gy in 20-30 daily fractions
- Surgery delayed for 4-8 weeks after treatment to allow tumour to shrink and inflammation subside
- Concurrent chemotherapy - 5FU or capecitabine reduces pelvic recurrence
Radiotherapy volume

- Posterior pelvis which includes:
  - Primary tumour
  - Mesorectal nodes
  - Obturator nodes
  - Internal iliac nodes

- Avoid sphincter unless lower third tumour

- CT planned conformal treatment to minimise dose to adjacent tissues
Long course treatment

- Overall response rate depends on case mix
- Complete pathological response in 15-25% of patients
Long course treatment

Current questions

- What is the optimal radiation dose?
- Will more effective chemotherapy improve the results?
- Is short course treatment with delayed surgery as effective as long course treatment?
- What do you do when there is a complete clinical and radiological response?
Resectable tumours

- To treat or not to treat?
- Short course vs long course
- Preop vs post-op
Short course preop radiotherapy

- 25Gy in 5 daily fractions (5 x 5)
  - Biologically equivalent to 44Gy in 22 fractions
- Surgery follows within one week
  - ie before inflammatory reaction has developed
- No time for tumour to shrink
- Works by sterilising cells that may be left behind after resection
- Can’t add concurrent chemo – too toxic
Resectable rectal cancer: preop trials

**Swedish Trial** 1987-1990. 1168 patients. All stages. Non TME surgery +/- short course XRT

**Dutch Trial** 1996-1999. 1861 patients. All stages. TME +/- short course XRT

**German Trial** 1995-2002. 421 patients. cT3,T4 or Node + TME with either pre or postop long course chemoradiation

**Polish Trial** 1999-2002. 316 patients. T3,T4 palpable. TME with preop long or short course

**MRC UK Trial** 1998-2005. 1350 patients. All stages. TME with either short course pre-op or post-op long course if CRM ≤ 1mm
Resectable rectal cancer: preop trials

- **Swedish Trial**: Non TME surgery +/- short course XRT
  5 yr pelvic recurrence 11% vs 27% surgery alone

- **Dutch Trial**: TME +/- short course XRT
  6 yr pelvic recurrence 5.6% vs 10.9% surgery alone

- **German Trial**: TME with either pre or postop long course
  5 yr pelvic recurrence 6% preop vs 13% postop

- **Polish Trial**: TME with preop long or short course
  4 yr pelvic recurrence 9% short course vs 14% long course

- **MRC UK Trial**: TME + short course or selective post-op
  3 yr pelvic recurrence 4.4% preop vs 10.6% postop
Resectable rectal cancer: preop trials

- Short course XRT reduces pelvic recurrence by >50% regardless of surgical technique.
- Absolute benefit depends on quality of surgery.
- Increased survival only seen in Swedish trial where post-op recurrence rate was highest.
- Long course and short course schedules appear to be equally effective with similar toxicity.
- Preop more effective and less toxic than postop.
Resectable rectal cancer: preop trials
Sub group analyses

- **Swedish trial.**
  Local recurrence benefit all stages, not signif’t upper 1/3
  Survival benefit women more than men

- **Dutch trial**
  Benefit for middle third and Stage 3.

- **MRC trial.**
  Benefit for Stage 2 and 3. All levels.

- **German trial.**
  Fewer APRs after preop

- **Polish trial.**
  No significant difference in APR with short or long course, but more stomas in short course group for other reasons.
Resectable rectal cancer: preop trials
Circumferential resection margin

**Dutch trial**
APR 30% had +ve CRM
Ant resection 11% +ve CRM
Local recurrence 19.7% with XRT, 23.5% without.

**Polish trial**
12.9% after short course
  4.4% after long course

No difference in local recurrence
With modern surgery, the risk of pelvic recurrence is 10-15% which can be halved by preop radiotherapy.

It follows that more than 90% of patients are now irradiated without benefit and are exposed to the risk of significant side effects.
Acute side effects of preop radiation

- More with long course than short course, particularly with concurrent chemotherapy
- Increased perioperative mortality if >80yrs when surgery delayed more than 3 days
- Anastomotic leaks not increased
- Healing of perineal wound delayed
  - 29% vs 18% with surgery alone
- Occasional patient gets sacral nerve pain
Late effects of radiotherapy

- Small bowel
- Large bowel and anus
- Bladder
- Sacral nerves
- Second (pelvic) malignancy
Late effects of radiotherapy
Anal and rectal dysfunction

Swedish trial – completed 1990
>4 bowel movements/day: 20% vs 8%
Incontinence with loose stool: 50% vs 24%
solid stool: 20% vs 8%

Dutch trial found similar results

MRC trial found lower rates: 16% vs 6%
Not clear if this is due to smaller XRT volumes or shorter follow up
Late effects of radiotherapy
Bladder and sexual dysfunction

No increase in bladder problems with XRT

**Dutch trial**

Number of previously sexually active patients reduced after XRT

Males 67% vs 76%

Females 72% vs 90%
Late effects of radiotherapy

Caveats

- Longer term data drawn from trials that used outdated radiotherapy techniques
  - Very large volumes treating abdominal nodes and perineum
  - No CT planning

- Although most data is from Swedish and Dutch trials using short course treatment but the Polish trial found no difference between long and short course schedules
Summary

- TME substantially reduces pelvic recurrence
- Short course preop XRT reduces it further but that reduction comes with an increased risk of incontinence and rectal dysfunction
- Preop long course XRT/chemo
  - Reduces tumour bulk
  - May increase rate of sphincter preservation
  - Is less toxic than similar postop treatment
Future prospects

- Better selection of patients for treatment
  - Node positive
  - Lower 2/3
  - Carefully selected T3N0

- Optimal imaging is crucial