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 $\leq$ 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