Chemotherapy in carcinoma rectum

Dr. Mahadevan.R,
MD (RT), DNB (RT), DMRT.
Professor of Radiotherapy
Medical College, Thrissur.
Progress in *multimodal therapy* is one of the best examples of success stories of Clinical Research in the last 2 decades.
Carcinoma rectum

- From 1975 to 1989, postoperative pelvic RT combined with FU-based chemotherapy (CT) was evaluated in the United States in patients with Dukes’ B and C rectal cancer. The combined therapy resulted in a significant benefit for local control, distant metastases, and survival compared with surgery alone.

Local-Regional Failure

**local-regional failure is the only or 1st site of recurrence in patients with curative resected rectal cancer**

- Stage I 5% to 10%
- Stage II up to 25% to 30%
- Stage III up to 50% or higher

*NIH Consensus Conference on Adjuvant Therapy for Patients with Colon and Rectal Cancer, JAMA, Sept. 19, 1990*
Carcinoma rectum

From 1975 to 1989, postoperative pelvic RT combined with FU-based chemotherapy (CT) was evaluated in the United States in patients with Dukes’ B and C rectal cancer. The combined therapy resulted in a significant benefit for local control, distant metastases, and survival compared with surgery alone.


Seiwert TY et al. (2007) The concurrent chemoradiation paradigm—general principles
Nat Clin Pract Oncol 4: 86–100 doi:10.1038/ncponc0714

Rationale for adding chemotherapy to radiation
Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation

Seiwert TY et al. (2007) The concurrent chemoradiation paradigm—general principles
Nat Clin Pract Oncol 4: 86–100 doi:10.1038/ncponc0714
Carcinoma rectum

In 1989, NIH Consensus Conference stated that postoperative chemo radiotherapy (RT-CT) should be regarded as standard treatment for patients with stage II and III rectal cancer.

*National Institutes of Health: NIH Consensus Conference: Adjuvant therapy for patients with colon and rectal cancer.*

JAMA 264:1444-1450, 1990
Carcinoma rectum

- *preoperative (preop) RT alone, demonstrated its value on local control and, on survival.*
- Swedish scheme delivered 25 Gy in 5 fractions over 1 week immediately followed by surgery, and conventional schemes delivered 40 to 50 Gy in 20 to 25 fractions over 4 to 5 weeks followed 3 to 4 weeks later by surgery.

*Compared with surgery alone, preop RT halved the local failure rates, irrespective of the scheme.*
## Long course Vs Short course

<table>
<thead>
<tr>
<th>Long course</th>
<th>Short course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better down staging</td>
<td>Patient convenience</td>
</tr>
<tr>
<td>Sphincter preservation</td>
<td>Lower cost</td>
</tr>
<tr>
<td>Decreased morbidity</td>
<td>T1-T3, Nx</td>
</tr>
<tr>
<td>Combine chemo along with it</td>
<td>T3/T4, N+</td>
</tr>
</tbody>
</table>
Short Course (25 Gy/5 fr)

- Surgery within 1 wk
- Sphinter preservation - not the end point
- No Chemo along with RT
- Only in Resectable rectal cancer
Conventional schedule (45 Gy/25 fr+/-boost)

Proper Counseling

- It increases operability and sphincter presentation
- Decreases tumor seeding
- Decreases A/c toxicity
- Increases radio sensitivity due to better oxygenation
- Surgery done after 4-8 wks
- Chemo increases pCR
Conventional Pre – OP RT

✓ 12 RCT
✓ 2 meta analysis
✓ Increased Sphincter preservation
✓ Increased Tumor down staging
Preoperative Radiotherapy for Resectable Rectal Cancer
A Meta-analysis

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>P=0.54</td>
</tr>
<tr>
<td>OS</td>
<td>P=.03</td>
</tr>
</tbody>
</table>

JAMA. 2000;284:1008-1015
In early 1990s, it became clear that preop RT-CT was a relevant issue for clinical research.

The European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Group demonstrated that an FU dose of 350 mg/m2/d could be safely administrated in combination with a leucovorin (LV) dose of 20 mg/m2/d delivered the first and fifth weeks of a 45-Gy dose of pelvic RT in patients with unresectable or locally recurrent rectal cancer.

Carcinoma rectum

In 1993, the EORTC initiated a four-arm randomized trial (EORTC 22921) to examine the value of pre op RT-CT versus pre op RT alone and the value of additional CT versus none with respect to overall survival and progression-free survival in the same patient group.
Enhanced Tumorocidal Effect of Chemotherapy With Preoperative Radiotherapy for Rectal Cancer: Preliminary Results—EORTC 22921

Jean-François Bossé, Gilles Calais, Laurent Mineur, Philippe Maitiong, Ljiljana Radosevic-Jelic, Alain Daban, Etienne Bardet, Alexander Beny, Antoine Briffaux, and Laurence Collette

Diagram:

1. Screen for eligibility
2. Randomly assigned
3. Pre-op RT → Surgery
4. Pre-op RT-CT → Surgery
5. Pre-op RT → Surgery
6. Pre-op RT-CT → Post-op CT
Carcinoma rectum

- Pre op RT-CT has been previously recommended after the observation that patients with a pathologic tumour response had a favourable outcome.

- The randomized German study showed improved local control and reduced toxicity with pre op RT-CT compared with postoperative RT-CT.

Authors’ conclusions

Compared to preoperative RT alone, preoperative CRT enhances pathological response and improves local control in resectable stage II and III rectal cancer, but does not benefit disease free or overall survival. The effects of preoperative CRT on functional outcome and quality of life are incompletely understood and should be addressed in future trials.
RECTAL CARCINOMA – RECENT ADVANCES -- OVERALL

1. Sphincter saving procedures – from 15% to 50% -- no colostomy (improved qol)
2. Overall five year survival – up from 30% to 60%
3. Depth of invasion – decreased by 40%-60% with adjuvant treatment.
4. Lymph node status and rec. free survival - same
Pre OP Chemo RT Vs Post OP Chemo RT

- INT 0147
- NSABP-R-03
- German Trial CAO/ARO/AIO-94
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre OP RT</th>
<th>Post OP Chemo RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour down Staging</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Increased tumour resectability</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Increased sphinter preservation</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Increased compliance</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Less A/c and C/c toxicity</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Increased survival</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Treatment based on pathologic finding</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
## Compliance with Therapy

<table>
<thead>
<tr>
<th>Chemo RT</th>
<th>Pre-OP Chemo RT</th>
<th>Post OP Chemo RT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>92%</td>
<td>54%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D., Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D., Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D., Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D., Heinz Schmidberger, M.D., and Rudolf Raab, M.D., for the German Rectal Cancer Study Group* 

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial


Comment

Capecitabine in the treatment of rectal cancer
Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

Short-Course Radiation Versus Long-Course Chemoradiation for Rectal Cancer: Making Progress

Bruce D. Minsky, MD Anderson Cancer Center, Houston, TX
Median follow up 5.9 yrs
Short-Course Versus Standard Chemoradiation in T3 Rectal Cancer

Section Editor’s note: Locally advanced rectal cancer, in contrast to colon cancer, has a substantial risk for local recurrence. Two approaches of neoadjuvant therapy have been formally tested in multiple randomized trials. Short-course radiation therapy uses 1 week of radiation without chemotherapy (5 Gy × 5) followed by surgery the next week. In contrast, standard chemoradiation uses 45–50.4 Gy in 25–28 fractions with concurrent 5-FU chemotherapy followed by 4–8 weeks of rest before surgery. Short-course radiation therapy is not frequently used in the U.S. The pros and cons of short-course radiation therapy and standard chemoradiation are presented herein.
Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study

Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Suzana Stojanovic-Rundic, René-Jean Bensadoun, Etienne Bardet, Alexander Beny, Jean-Claude Ollier, Michel Bolla, Dominique Marchal, Jean-Luc Van Laethem, Vincent Klein, Jordi Giralt, Pierre Clavère, Christoph Glanzmann, Patrice Cellier, Laurence Collette, for the EORTC Radiation Oncology Group

Lancet Oncol 2014; 15: 184-90

Adjuvant chemotherapy for rectal cancer still controversial
Median follow up 10.4 yrs
Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine + oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: Early results of the PETACC 6 trial


For the EORTC GITCG, AIO, AGITG, EORTC ROG, BGDO, FFCD and PETACC

The future of cancer therapy
1. The addition of oxaliplatin to preoperative capecitabine-based chemo-radiation led to
   - decreased treatment compliance due to toxicity,
   - but did not improve R0 resection, pathological CR or sphincter preservation
   - in accordance with STAR, ACCORD/PRODIGE 2, NSABP R04, except CAO/ARO/AIO-04 favouring 5FU+oxaliplatin.

2. Interim results at a median follow up of 2.6 years indicate no DFS-benefit for the addition of oxaliplatin to pre-and post-op Capecitabine.
Conclusions

Patterns of relapse - different for rectal & colonic cancer

LR 5-50%

Adjuvant chemo RT improves survival

Post OP -5040 Gy/28 fr for along with Chemo 5 FU

No additional benefit with another agent

TME - LR is 10%

Short Course XRT increases survival (Swedish Trial)
Conclusions....

Better LCR ?OS

Proper counseling before long course RT

Addition of chemo increased pCR

German trial

- Decreased LR
- Decreased toxicity
- Increased sphincter preservation
- No diff in OS

Capecitabine is equivalent to 5 FU

No benefit by adding oxaliplatin and toxicity increased

Short course VS Long course- early results promising

Adjuvant Chemo- controversial
Chemotherapy forms an integral part in management of carcinoma rectum which has definite advantage in the concurrent setting.