Case Conference

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Neoadjuvant versus Adjuvant Radiation Therapy in Rectal Carcinoma
Epidemiology

American Cancer Society statistics for 2002:
147,500 newly diagnosed cases of colorectal cancer
42,000 of these rectal cancer (approx. 30%)
74,700 deaths from colorectal cancer
Table 1: American Joint Committee on Cancer TNM Staging System for Colorectal Cancer

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intramucosal or invasion of the lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into the subserosa or nonperitonealized pericolicentral tissue</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades other organs or structures and/or perforates visceral peritoneum</td>
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<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)*</th>
<th>Description</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in one to three lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in four or more lymph nodes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Dukes</th>
<th>MAC*</th>
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<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B2</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>T1-T2</td>
<td>N1</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
</tr>
<tr>
<td></td>
<td>T3-T4</td>
<td>N1</td>
<td>M0</td>
<td>C</td>
<td>C2/C3</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
<td>C</td>
<td>C1/C2/C3</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

*A tumor nodule in the pericolicentral adipose tissue without histologic evidence of residual lymph node in the nodule is classified as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also be coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident) because there is a strong likelihood that it represents venous invasion.

*Modified Astle-Collet classification.

Treatment of rectal cancer

Surgical resection is the cornerstone of curative therapy; 5 year survival rates s/p curative resection:

- Stage 1 80 – 90%
- Stage 2 50 – 60%
- Stage 3 30 – 40%

Prognosis clearly related to degree of tumor penetration through bowel wall and LN involvement

Surgery alone is curative for only early stage cancer
Surgical therapy

Local excision - reserved for superficially invasive (T1) tumors with low likelihood of LN metastases
- should be considered a total biopsy, with further treatment based on pathology
- with unfavorable pathology patient should undergo total mesorectal excision with or without sphincter-preservation:
  positive margin (or <2 mm), lymphovascular invasion, poorly differentiated tumors, T2 lesion
Surgical therapy

Low Anterior Resection
-for tumors in upper/mid rectum;
allows preservation of anal sphincter
Surgical therapy

Abdominoperineal resection
- for tumors of distal rectum with distal edge up to 6 cm from anal verge
- associated with permanent colostomy and high incidence of sexual and genitourinary dysfunction

-sphincter-sparing options:
1. Local excision for T1-2 offers local control and survival comparable to APR
2. Neoadjuvant CT/RT to convert to LAR
Surgical therapy

Total mesorectal excision
- local failures are most often due to inadequate surgical clearance of radial margins
- conventional resection violates the mesorectal circumference during blunt dissection, leaving residual mesorectum
- TME involves precise dissection and removal of the entire rectal mesentery as an intact unit
- local recurrence with conventional surgery averages approx. 25-30% vs. TME 4-7% by several groups (although several series have higher recurrence)
Treatment of rectal cancer

Adjuvant therapy (postoperative)

Neoadjuvant therapy (preoperative)

Stage 2 and 3 patients are at high risk for local and systemic relapse

The addition of chemotherapy and radiation is to improve on surgical results

Perioperative RT has greater impact in rectal than colon ca because of the greater tendency for first failure in locoregional sites (even distribution of local and distant failure vs. colon ca failure mainly due to distant metastases)
Adjuvant radiation therapy

Several randomized trials have compared postop radiation versus surgery alone for stage 2 and 3; adjuvant RT associated with:
- better local control rates
- significant increase until time to local failure
- survival benefit has not been shown in any trial using conventional fractionation radiation
Adjuvant radiation therapy

Colorectal Cancer Collaborative Group (Lancet 10/01)

- meta-analysis of 2157 patients from 8 randomized trials of surgery with or without postop radiation
- 5 year risk of local recurrence significantly less in surgery + radiation group (15% vs. 23%)
- 5 year mortality rate not significantly different postop radiation vs. surgery alone (58% vs. 59%)
Adjuvant chemoradiotherapy

Postop combined modality RT plus CT (with 5-FU based regimen) for Stage 2 or 3 rectal ca appears to confer a survival advantage

The efficacy of this approach established by prospective randomized trials in 1980s and 1990s
- The Gastrointestinal Tumor Study Group (GITSG)
- North Central Cancer Treatment Group (NCCTG)
- National Surgical Adjuvant Breast and Bowel Project trial R-01 (NSABP)
Adjuvant chemoradiotherapy

The Gastrointestinal Tumor Study Group (GITSG) (NEJM, 1985)

-227 randomly assigned patients with completely resected Dukes B2 and C rectal carcinomas to one of four arms: observation, postop irradiation only (4000 or 4400 cGy), chemotherapy only (5-FU and semustine), or postop combined therapy

-trial terminated early after 227 of planned 500 patient because of observed outcome differences

-at 80 mo. median followup, combined Tx recurrence rate 33% vs. 55% surgery only

-postop chemoRT had significant survival benefit
Adjuvant chemoradiotherapy

Mayo Clinic/North Central Cancer Treatment Group (NCCTG) (NEJM, 1991)

- 204 Dukes B2/C patients randomly assigned to receive postop radiation alone (4500-5040 cGy) or combined chemo with 5-FU

- at median followup 7 years, combination therapy associated with: 46% decrease in local recurrence, 37% decrease distant metastases, 29% reduced mortality
Adjuvant chemoradiotherapy

National Surgical Adjuvant Breast and Bowel Project trial R-01 (NSABP) (Jnl NCI, 1988)

-largest randomized trial: 555 patient with resected Dukes B and C rectal ca assigned to observation, chemo only (5-FU, semustine, vincristine), or radiation only (400-4700 cGy)

-median 64 month followup

-postop RT had reduced local recurrence but no improved survival vs. surgery alone

-chemotherapy associated with improved disease-free survival but no overall survival advantage
Adjuvant chemotherapy

Subsequent studies have attempted to increase the survival benefit by improving radiation sensitization and by identifying optimal chemotherapeutic agents and delivery systems.
Adjuvant chemotherapy

Semustine (methyl-CCNU)
- all chemo regimens in GITSG, NSABP, and NCCTG contained semustine
- known risk factor for acute myeloid leukemia, with 6 year cumulative risk of developing AML 4%
- two subsequent randomized postop trials from GITSG and NCCTG showed semustine added no added benefit to adjuvant irradiation plus 5-FU
- no longer utilized in adjuvant chemo regimen for colorectal ca
Adjuvant chemotherapy

Intergroup 86-47-51 trial showed 10% improved overall survival with continuous infusion 5-FU (225mg/m²/day) throughout RT compared to bolus 5-FU (500mg/m² three injections in the 1st and 5th weeks of RT) (NEJM, 1994)

Intergroup trial 0114 showed no survival or local control benefit to the addition of Leucovorin (folinic acid), Levamisole, or both to postop 5-FU for Stage 2/3 rectal ca at median of 7.4 years
Adjuvant chemotherapy

Irinotecan (CPT-11)- topoisomerase-I inhibitor with a 10-20% partial response rate in metastatic rectal ca and in patients with worsening disease on 5-FU

Irinotecan Study Group (NEJM, 2000)
-compared 5-FU, leucovorin, CPT-11 with 5-FU, leucovorin alone, and CPT-11 alone in patients with rectal ca refractory to 5-FU
-combination Tx had time-to-tumor progression of 7.0 mos. vs. 4.3 mos.
-median survival was 14.8 mos. combination Tx and 12.6 mo. 5-FU arm
Adjuvant chemotherapy

Oxaliplatin - DNA damaging agent
-in combination with 5-FU for metastatic disease
was associated with median progression-free
survival of 5 mos. and median survival of 11 mos.
(J Clin Onc, 1999)

The safety and efficacy of 5-FU together with
irinotecan and/or oxaliplatin for Stage 4, as well as
earlier stage disease is under investigation
Participation in clinical trials is appropriate
Adjuvant chemoradiotherapy

Complications associated with adjuvant therapy:
- although improved local control and survival, acute and late morbidity are observed
- acute severe or life-threatening diarrhea (25%)
- chronic bowel injury (25%)
- long term quality of life changes: increased BM/day (median 7 with chemoRT vs. surgery alone), occasional incontinence (39% vs. 7%)
Adjuvant chemoradiotherapy

Avoiding bowel injury:
- small bowel fixed in pelvis at higher risk for radiation injury, therefore move SB out of pelvis:
  - reperitonealize pelvic floor
  - omental loop
  - retrovert uterus
  - place absorbable mesh sling
- these approaches most important s/p APR; with LAR, remaining rectum and colon prevent some SB from reaching deep pelvis
Adjuvant chemoradiotherapy

Avoiding bowel injury:
Improved radiation planning and techniques minimize treatment-related complications
- use of multiple pelvic fields
- prone positioning
- bladder distention
- visualization of SB with oral contrast
Neoadjuvant treatment

Potential advantages of preop chemoradiation:
- ability to downstage tumors at time of resection, thereby facilitating resection
- distal rectal tumors may regress and convert APR to sphincter-preserving procedure
- unresectable disease may become resectable
- improved ability to achieve negative margins
- ability to perform anastomosis with non-irradiated colon
- initiation of chemo earlier in course to address micrometastatic disease
Neoadjuvant treatment

Staging

-patients considered for sphincter-sparing procedure must be accurately staged prior to treatment
-endoscopic US and endorectal coil MRI are more accurate for staging of tumor and LN status than CT scan
-CT scan is complimentary and used to evaluate liver and retroperitoneal LNs
Neoadjuvant treatment

- restaging after radiation, prior to planned resection does not predict the absence of disease at surgery

- series of 488 patients at MSK who had preop CT/RT followed by resection, clinical complete response rate was 19%, but only 10% had pathologic complete response (JACS 2/02)

- all acceptable-risk patients with diagnosis of primary rectal cancer should undergo resection, regardless of their response to preop therapy
Neoadjuvant radiotherapy

Several trials have compared preop radiation plus surgery to surgery alone
- at “moderate dose” irradiation (3450 cGy) local failure rates are reduced, but there was no improved survival in most studies

Swedish Rectal Cancer Trial (NEJM, 1997)
- randomly assigned 1168 patients to surgery alone vs. preop RT/surgery (2500 cGy)
- 5 year rates significantly improved for both local recurrence (11% vs. 27%) and overall survival (58% vs. 48%)
Neoadjuvant radiotherapy

A meta-analysis of 14 randomized controlled trials with 6426 resectable rectal cancer patients having surgery alone or RT/surgery (JAMA, 2000)

-neoadjuvant RT had significantly fewer local recurrences (odds ratio 0.49) and improved overall 5 year survival (odds ratio 0.84)

-RT/surgery group had significantly greater amount of sepsis (21% vs. 15%) and other complications (21% vs. 18%); preop RT was found to be more detrimental in patients receiving > 3000 cGy
Neoadjuvant radiotherapy

- separate meta-analysis by the Colorectal Cancer Collaborative Group (Lancet 10/01)
- 6350 patients in 14 randomized controlled trials found preop RT associated with significantly reduced positive LNs at resection (32% vs. 38%), significant decrease in absolute risk at 5 years of recurrence (46% vs. 53%) and local recurrence (13% vs. 22%)
- significantly fewer patients died from rectal cancer (45% vs. 50%) but 5 year overall survival equal (64% vs. 65%)
Neoadjuvant chemoradiotherapy

Preliminary data show tumor downstaging, however the significance of this is unclear; long term outcomes are pending for several studies.

- Pathological complete response for preop RT averages 6-12% while combined chemoRT have shown pCR 15-37%.

- 40 patients received preop RT (5000 cGy) and oxaliplatin, 5-FU, leucovorin (J Clin Onc, 2003). 6 cases had pCR (15%), 12 (30%) had only few residual cells detected.
Neoadjuvant vs. adjuvant chemotherapy

National Surgical Adjuvant Breast and Bowel Project trial R-03 (NSABP) (Proc Am Soc Clin Onc, 2001)

- 267 patients preop therapy (5-FU, leucovorin, RT, surgery, then postop 5-FU, leucovorin) or postop therapy (surgery, 5-FU, leucovorin, radiation)
- 23% clinical CR, of these 44% pathological CR
- 31% of preop group projected candidates for sphincter preservation, but 50% had LAR; in the adjuvant group the 33% projected was unchanged
- at 1 year preop group had 83% disease-free survival vs. 78% postop group (not statistically significant)
Neoadjuvant vs. adjuvant chemoradiotherapy

German Rectal Cancer Group (Colorectal Dis, 2003)
- 823 patients randomly assigned to preop or postop therapy (5040 cGy, 5-FU) and had surgery that included TME
- 43 mo. median FU, preop Tx had lower pelvic relapse rate (7% vs. 11%)
- disease free (59% vs. 55%) and overall survival rates (78% vs. 73%) were similar
- stage distribution suggested significant downstaging effects; stage distribution (1-4):
  preop (24,28,27,6%) vs. postop (18,29,39,7%)
Neoadjuvant vs. adjuvant chemoradiotherapy

Complications of neoadjuvant treatment:
Preop RT does not increase postop complications
-NSABP R-03 trial: postop complications were similar between groups, however grade 4 diarrhea was more common in preop group (24% vs. 12%)
-German Rectal Cancer group: incidence of grade 3 or 4 GI toxicity similar between groups, postop morbidity rates were not higher
-chronic anastomotic strictures were significantly less in the neoadjuvant group (2.7% vs. 8.5%)
Neoadjuvant vs. adjuvant chemotherapy

- there is conflicting data about improved survival benefit
- for distal rectal cancers not amenable to local excision, preop radiation with concurrent chemotherapy is recommended to permit sphincter-preserving surgery
### Table 4: Current Recommendations for Adjuvant Therapy for Colon Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No adjuvant therapy</td>
</tr>
<tr>
<td>IIA</td>
<td>Observation or clinical trial</td>
</tr>
<tr>
<td>IIA*</td>
<td>Consider 5-FU/leucovorin or clinical trial or observation</td>
</tr>
<tr>
<td>IIB</td>
<td>Consider 5-FU/leucovorin +/- radiation or clinical trial or observation</td>
</tr>
<tr>
<td>III</td>
<td>5-FU/leucovorin or clinical trial incorporating 5-FU/leucovorin</td>
</tr>
<tr>
<td>IV†</td>
<td>Colectomy and metastectomy followed by adjuvant 5-FU/leucovorin with or without either irinotecan or oxaliplatin or colectomy, neoadjuvant chemotherapy, staged resection, and adjuvant chemotherapy</td>
</tr>
<tr>
<td>IV‡</td>
<td>Palliative combination chemotherapy or clinical trial</td>
</tr>
</tbody>
</table>

*Patients with poor prognostic factors such as poorly or undifferentiated tumors, obstructing or perforated tumors, or tumors with lymphatic, vascular, or perineural invasion.

†Patients with resectable liver or lung metastases.

‡Patients with unresectable metastatic disease.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No adjuvant therapy.*</td>
</tr>
<tr>
<td>II/III</td>
<td>5-FU/leucovorin × 2 cycles, then concurrent 5-FU with radiation therapy, then 5-FU/leucovorin × 2 cycles or neoadjuvant concurrent 5-FU with radiation therapy, then surgery, then 5-FU/leucovorin × 4 cycles or clinical trial.</td>
</tr>
<tr>
<td>IV†</td>
<td>Resection of primary tumor and metastectomy followed by adjuvant 5-FU/leucovorin with or without either irinotecan or oxaliplatin or resection, neoadjuvant chemotherapy, staged resection, concurrent 5-FU with radiation therapy, then adjuvant chemotherapy.</td>
</tr>
<tr>
<td>IV‡</td>
<td>Palliative combination chemotherapy or concurrent 5-FU with radiation therapy, then palliative combination chemotherapy.</td>
</tr>
</tbody>
</table>

*For patients treated with a transanal excision and found to have a T1 lesion with positive margins, lymphovascular invasion, or poorly differentiated tumors or a T2 lesion requiring transabdominal resection or 5-FU with radiation therapy.

† Patients with resectable metastases.

‡ Patients with unresectable metastatic disease. Consider palliative resection or bypass surgery.
# Colorectal cancer surveillance following surgical resection

American Society of Clinical Oncology guidelines for surveillance following resection:

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
<td>Every 3-6 mo for 3yr, then annually</td>
</tr>
<tr>
<td>Serum CEA</td>
<td>Every 2-3 mo in stage 2/3 for ≥ 2 yrs</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 3 – 5 years</td>
</tr>
<tr>
<td>CXR</td>
<td>Not recommended (may consider in asymptomatic patient with ↑ CEA)</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>Not recommended</td>
</tr>
<tr>
<td>CBC</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Questions

Which of the following regarding rectal cancer is true?

A) Current screening recommendations for rectal ca include H+P, CEA, and colonoscopy

B) Techniques to avoid postop radiation induced bowel injury include reperitonealizing the pelvic floor and placing nonabsorbable

C) Adjuvant RT is indicated for Stage 2 colon and rectal ca

D) Following neoadjuvant therapy, patients with complete clinical response should not undergo resection

E) All of the above
Questions

Which of the following regarding the surgical management of rectal ca is true?

A) Because the local recurrence rates after TME are low, adjuvant RT is not indicated

B) Surgical options for T2N1 tumor of distal rectum include local excision or neoadjuvant Tx/LAR

C) 5 year survival rates s/p curative resection for Stage 3 rectal cancer is 30%

D) Neoadjuvant Tx plus resection has consistently been shown to improve survival

E) All of the above
Current chemotherapeutic regimens for rectal ca may include all of the following except:
A) 5-FU, leucovorin, and irinotecan
B) 5-FU, leucovorin
C) 5-FU
D) 5-FU, leucovorin, Semustine (methyl-CCNU)
E) All of the above