Young-onset Colorectal Cancer Virtual Patient Conference
What is New in Young-onset Rectal Cancer

Outline

- Goal of Treatment in Rectal Cancer
- Categorizing Rectal Cancer for Treatment Planning
- Personalizing Treatment For Optimal Outcome
What is New in Young-onset Rectal Cancer

Goals of Treatment in Rectal Cancer

Survival

Local control

Quality of life

Optimal surgery = Backbone but not enough & major change in quality of life
What is New in Young-onset Rectal Cancer
Categorizing Rectal Cancer for Treatment Planning

• At diagnosis
  • What is “Early” or “Locally-advanced”?

• At follow-up
  • Scanxiety: New tools for prognosis / surveillance?
What is New in Young-onset Rectal Cancer
Categorizing Rectal Cancer for Treatment Planning
What is New in Young-onset Rectal Cancer

Categorizing Rectal Cancer for Treatment Planning

Scanxiety: Better tools?

MSKCC Nomogram; MDACC Conditional Survival Calculator
MD Anderson

What is New in Young-onset Rectal Cancer
Categorizing Rectal Cancer for Treatment Planning

Scanxiety: Better tools?

ctDNA?
What is New in Young-onset Rectal Cancer
Personalizing Treatment For Optimal Outcome

Principles of Surgery For Optimal Local Control

Total Mesorectal Excision
Circumferential Resection Margin (CRM)
Regional Lymphadenectomy
What is New in Young-onset Rectal Cancer
Personalizing Treatment For Optimal Outcome
Impact on functions and quality of life

Low Anterior Resection Syndrome

**Symptoms**
- Variable, unpredictable bowel function
- Altered stool consistency
- Increased stool frequency
- Repeated painful stools
- Emptying difficulties
- Urgency
- Incontinence
- Soiling

**Consequences**
- Toilet dependence
- Preoccupation with bowel function
- Dissatisfaction with bowels
- Strategies and compromises
- Mental and emotional wellbeing
- Social and daily activities
- Relationships and intimacy
- Roles, commitments and responsibilities

Impact on:
- Mental and emotional wellbeing
- Social and daily activities
- Relationships and intimacy
- Roles, commitments and responsibilities
What is New in Young-onset Rectal Cancer
Personalizing Treatment For Optimal Outcome

Local excision of Rectal Cancer: When is it safe to not remove more rectum or lymph nodes?

- Early T1
- Favorable features
What is New in Young-onset Rectal Cancer
Personalizing Treatment For Optimal Outcome

Local excision of Rectal Cancer: Can we “convert” some tumors to be “safe”?

- ACOSOG Z6041
Let’s make the surgery experience better!

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Personalizing Treatment For Optimal Outcome
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Goals of treatment of Locally Advanced Rectal Cancer

• Prevent distant (metastatic) recurrence

• Prevent Local-regional (pelvic) recurrence

• Individualize therapy
  • Omission of surgery
  • Omission of radiation
  • Biomarker driven approach: dMMR/MSI
What is New in Young-onset Rectal Cancer

Individualizing Therapy in Locally Advanced Rectal Cancer

Omission of radiation

• Do all locally advanced rectal cancers need to be radiated
  
  • Location matters
  
  • Response to systemic therapy matters (biomarker driven intensification of therapy)
What is New in Young-onset Rectal Cancer

Individualizing Therapy in Locally Advanced Rectal Cancer

Omission of radiation

• WHY?

Associated with significant short and long term toxicity
--bowel, bladder, sexual dysfunction, infertility
What is New in Young-onset Rectal Cancer

Individualizing Therapy in Locally Advanced Rectal Cancer

Omission of radiation

- Historical data supports benefit of RT for local pelvic control, no survival benefit
- Data from metastatic disease notable for significant responses to chemotherapy in primary, without need for surgery or RT

Gastrointestinal Tumor Study Group, 1985; Fisher et al., 1988; Krook et al., 1991; Tepper et al., 1997; Wolmark et al., 1993, Sauer et al., 2004, Kapiteijn et al., 2001, Poultsides JCO 2009
Neoadjuvant Chemotherapy Without Routine Use of Radiation Therapy for Patients With Locally Advanced Rectal Cancer: A Pilot Trial

Stage II/III rectal cancer
cT3N0/N+
Candidates for LAR

Ineligible:
T4 unresectable

Schrag D., Saltz L., JCO 2014
Neoadjuvant Chemotherapy Without Routine Use of Radiation Therapy for Patients With Locally Advanced Rectal Cancer: A Pilot Trial

N= 32 patients

- 22 Node +

30 completed neoadjuvant therapy

3 recurred, lung mets

Table 1. Summary of Study Outcomes With Mean of 53 Months of Follow-Up Since Enrollment

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<th>Study Outcome</th>
<th>No.</th>
<th>%</th>
<th>95% CI</th>
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<td>R0 resection rate</td>
<td>32</td>
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<td>89 to 100</td>
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<td>Pathologic complete response rate</td>
<td>8</td>
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<td>Completion of neoadjuvant FOLFOX/bevacizumab</td>
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<td>1 to 21</td>
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<td>Postoperative radiation</td>
<td>1</td>
<td>3.1</td>
<td>1 to 16</td>
</tr>
<tr>
<td>4-year local recurrence rate</td>
<td>0</td>
<td>0</td>
<td>0 to 11</td>
</tr>
<tr>
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<td>27</td>
<td>84</td>
<td>67 to 94</td>
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Abbreviation: FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.

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Schrag D., Saltz L., JCO 2013
PROSPECT

- N= 1100
- Rectal adeno
- T21 T3N0-2
- Candidate for sphincter sparing surgery

**Primary Objective:**
- R0 resection, noninferiority TLR
- DFS

**Secondary Objectives:**
- TLR rates
- pCR rates
- OS

![Diagram of treatment options]

- **Randomize 1:1**

  - Response ≥ 20%
    - FOLFOX x 6
    - Re-stage
    - ChemoRT
    - TME
    - FOLFOX x 6
  - Response < 20%
    - FOLFOX x 4
    - ChemoRT
    - TME
    - FOLFOX x 8
Data will be presented at ASCO 2023!!
Individualizing Therapy in Locally Advanced Rectal Cancer

- Do all locally advanced rectal cancers \textit{need} to be radiated
  - Location matters
  - Response to systemic therapy matters
  - Biomarker driven therapy can improve neoadjuvant responses
Locally Advanced Mismatch Repair Deficient Rectal Cancer

- About 5-10% of all rectal cancers
- Less sensitive to chemotherapy
  - Adjuvant therapy
  - Neoadjuvant rectal - TNT
- Checkpoint blockade is highly effective in metastatic mismatch repair-deficient cancers with a complete response rate ~10%

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<th>Outcome</th>
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<th>pMMR</th>
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<tr>
<td>FOLFOX as initial treatment</td>
<td>n = 21</td>
<td>n = 63</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>6 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Response or stable disease</td>
<td>15 (71)</td>
<td>63 (100)</td>
</tr>
<tr>
<td>Chemoradiation as initial treatment</td>
<td>n = 16</td>
<td>n = 48</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Complete pathologic response</td>
<td>2 (13)</td>
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Phase II study of neoadjuvant PD-1 blockade in MMRd locally advanced rectal cancer

**Patient population:** Stage II and III mismatch repair-deficient rectal cancer

**Target Enrollment:** 30 subjects

**Study Design:** Simon’s 2-stage minimax design

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Cercek et al, NEJM 2022

NCT04165772.
Responses
patients who completed dostarlimab N=23

Cercek et al, NEJM 2022; JSMO 2023
Conclusion

Treatment of locally advanced rectal cancer should be individualized

Selective omission of radiation is feasible depending on tumor location response to neoadjuvant chemotherapy

Biomarker driven neoadjuvant therapy such as PD-1 blockade in mismatch repair deficient tumors can improve responses and potentially replace chemotherapy, radiation and surgery
What is New in Young-onset Rectal Cancer
Personalizing Treatment For Optimal Outcome
When There is A Complete Clinical Response ….

When is it safe to Watch & Wait, Maximizing Response, Follow-up, Salvage

- Digital Rectal Exam
- MRI
- Endoscopy
Young-onset Colorectal Cancer Virtual Patient Conference

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Thank You!!