Locally Advanced Rectal Cancer

Historical Treatment Paradigms and a review of the NEOTERIC trial.

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Making Cancer History

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Let's take a moment to imagine...

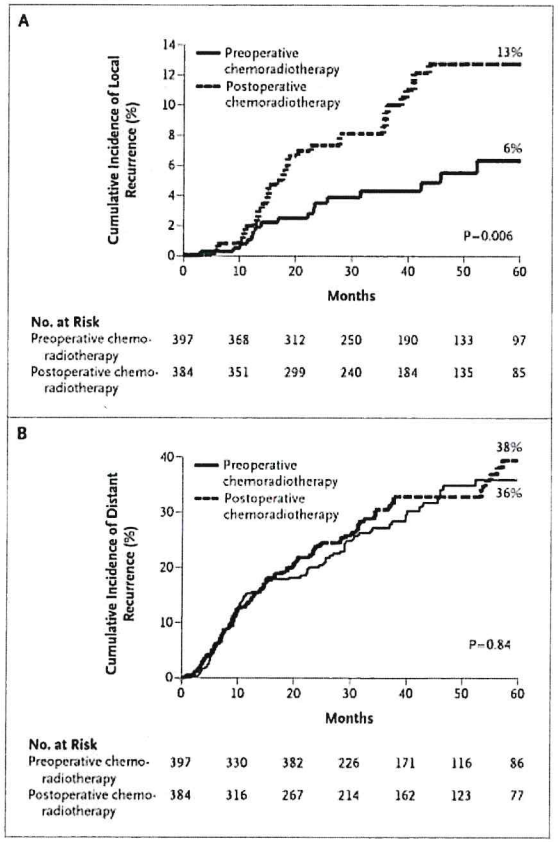
- 37-year -old woman presents for evaluation of hematochezia (previously attributed to hemorrhoids) and left lower quadrant abdominal pain.
- Colonoscopy demonstrates a mass of the anterior rectal wall, measuring 3.5cm from the anal verge.
- Biopsy confirms rectal adenocarcinoma.
- Pelvic MRI demonstrates tumor that infiltrates through the muscularis propria cT3 with involvement of at least 4 lymph nodes cN2. Systemic imaging demonstrates no distant metastatic disease. cT3N2M0 (Stage III) rectal adenocarcinoma.

The Landscape of Colorectal Cancer in the United States

- Rates of colorectal cancer are rising in patients under the age of 65.
  - This rise is being primarily driven by cancers in the distal colon and the rectum.
- Rectal cancer now makes up 32% of colorectal cancer diagnoses, compared to 27% in the mid-2000s.
- For adults under 50, colorectal cancer is now the leading cause of cancer mortality.

Establishing Neoadjuvant ChemoRT

- **CAO/ARO/AIO-94 trial** (Sauer et al., *NEJM* 2004.
  - Randomized 823 patients with clinical stage T3, T4 or node positive disease (Stage II or Stage III rectal cancer) to receive either neo-adjuvant chemoRT -->TME --> adjuvant 5-FU x 4 cycles OR chemoRT adjuvantly.
    - One month after surgery patients received four five day cycles of 5-FU.
  - 5 year cumulative relapse was 6% for patients assigned to neo-adjuvant chemotherapy and 13% for those who received adjuvant therapy.
  - Conclusions of this study: neo-adjuvant therapy improved local recurrence and toxicity, however did not improve overall survival.



The Addition of Oxaliplatin

- **CAO/ARO/AIO-04 trial:**
  - Investigated the addition of oxaliplatin to the 5-FU based regimen detailed in the AIO-94 trial.
  - cT3, T4 disease or any nodal disease. Groups randomized to receive Standard 5-FU combined modality therapy, or neoadjuvant oxaliplatin +5FU + radiation followed by surgery and adjuvant therapy with 8 cycles.
  - The oxaliplatin containing regimens improved 3-year disease free survival 75.9% vs. 71.2% and **increased pCR.**
  - No overall survival benefit.

The Advent of Total Neoadjuvant Therapy

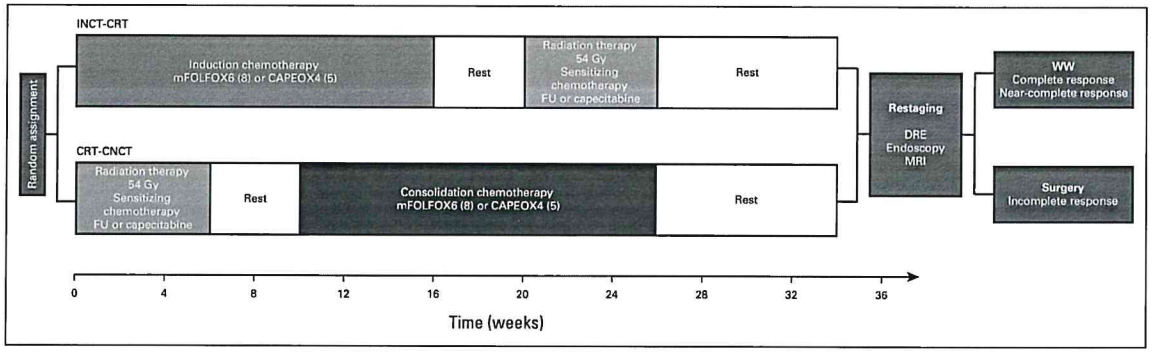
- **RAPIDO Trial:**
  - A phase 3 randomized multi-center trial that enrolled 920 patients from 54 centers in Europe and the United States.
  - Experimental arm: Short course radiation. 5 x 5gy followed by consolidation 6 cycles of CAPOX or 9 cycles of FOLFOX.
  - Standard arm: Long course chemoRT, followed by surgery and then **optional** adjuvant chemotherapy (~42% received).
  - Primary results:
    - Lower 3 year probability of of disease- related treatment failure.
    - Increased pCR.
    - At follow up, had a statistically **significant increase in locoregional recurrence.**
  - Remains in the NCCN guidelines.

- **PRODIGE 23 TRIAL:**
  - Landmark Phase III Trial that established total neo-adjuvant therapy with mFOLFIRINOX as the optimal approach to treatment for locally advanced rectal cancer.
  - 461 patients across 35 French centers. From June 2012-2017. Enrolled biopsy proved cT3 or cT4, M0, located <15cm of the anal verge, age 18-75 years, with WHO performance status of 0-1.
  - Experimental Arm: 6 cycles of mFOLFIRINOX --> chemoRT --> TME --> 3 months of adjuvant chemotherapy (mFOLFOX or capecitabine).
  - Standard arm: chemoradiotherapy --> surgery --> 6 months adjuvant chemotherapy.
  - Primary end point was disease free survival at 3 years.
    - Initial analysis of 46.5 months- 3 year disease free survival was 76% in experimetal arm vs. 69% in the standard arm, favoring TNT.
  - Long term follow up data demonstrated an overall survival benefit with 7 year OS of 81.9% vs. 76.1% with P value of 0.033.

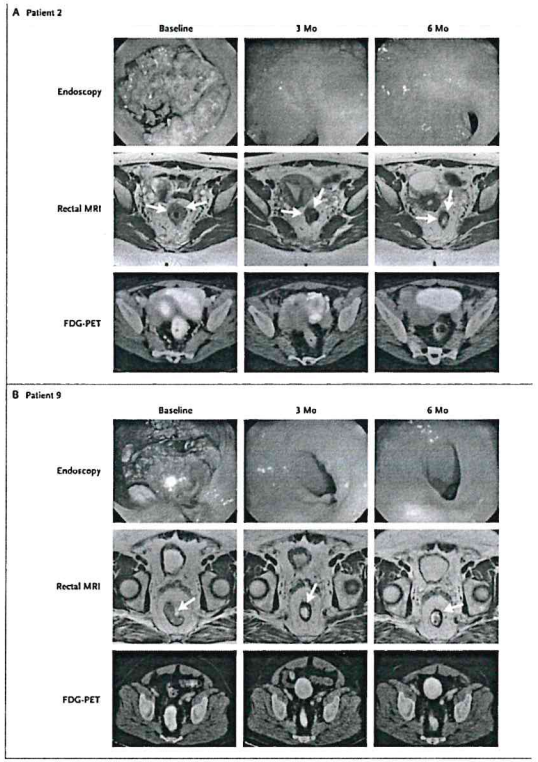
What about organ preservation?

OPRA Trial:

- A phase II clinical trial that compared:
  - Induction therapy followed by ChemoRT
  - ChemoRT followed by consolidation therapy.
- Patients who obtained a complete response or near complete response were offered a watch and wait approach.
- Patients who had an incomplete response were offered surgery.
- Primary end point was disease free survival.
- Secondary end point was TME free survival.
- Study demonstrated that for patients with complete or near complete response, that DFS was similar in patients who underwent TME after restaging vs. Those who waited for regrowth.
- Long term follow up demonstrates organ preservation in half of patients treated with TNT who entered watch and wait.



- **Cercek et al. 2022:**
  - Groundbreaking (and news making) prospective phase II trial that investigated utilization of PD-1 blockade in MMR deficient rectal cancer.
  - Stage II or Stage III patients. Received single agent dostarlimab every 3 weeks for 6 months.
    - All 12 patients had a complete clinical response.
  - **Of note, there is some concern that this is not reproducible.
- **Cercek et al. 2025:**
  - Extended enrollment to 117 patients, enrolled a cohort of agnostic diagnosis patients.
  - All 49 patients with rectal cancer achieved clinical CR and elected for non-operative management.
- The larger AZUR-1 trial is enrolling.



Immunotherapy in pMMR Rectal Cancer

- **TORCH Trial:**
  - Randomized prospective multi-center phase II trial evaluating short course radiotherapy with immunotherapy as a treatment paradigm for TNT.
  - There was **no** comparator with a non-immunotherapy regimen.
  - Primarily compared induction vs. Consolidation strategy.
    - SCRT --> 6 cycles of CAPEOX + toripalimab.
    - 2 cycles of CAPEOX + toripalimab --> SCRT --> 4 cycles of CAPEOX + toripalimab.
  - Both arms achieved significant pCR.

- **SPRING-O1:**
  - Single center open-label phase II trial that investigated addition of anti-PD1 antibody sintilimab to short course radiotherapy plus CAPEOX as total neoadjuvant therapy.
  - 98 patients at Shandong Provincial Hospital in China with treatment naïve locally advanced rectal cancer.
  - Primary endpoint was pathologic complete response.
    - 59.2% in the sintilimab + CAPEOX group compared to 32.7% in the chemotherapy alone group.
    - Response more pronounced in those with tumors >5cm from the anal verge.

- Randomized parallel group phase II study.
  - Took place at 5 cancer centers across China.
- Enrolled patients with cT3N+M0 or T4anyM0 rectal cancer.
  - All patients had pMMR/MSI-stable tumors with 90.9% having clinical stage III disease.
- All patients first received long course neoadjuvant chemoradiotherapy.
  - 45-50.4 Gy in 25-28 fractions with concurrent capecitabine.
- After neoadjuvant therapy, patients were then randomized 1:1 to receive 3 cycles of either.
  - Atezolizumab 1200mg + tiragolumab 600mg (n=28)
  - Atezolizumab 1200 mg alone.
  - A safety run in of three patients received the combination.

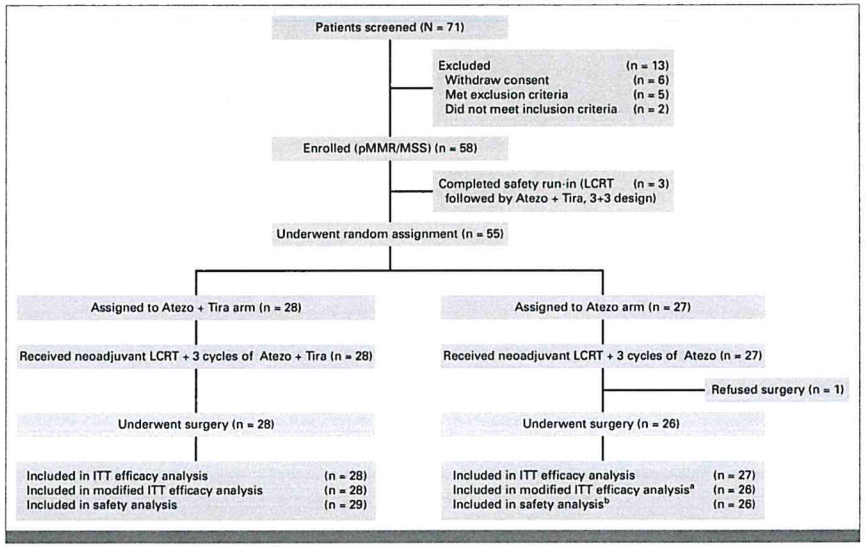


Fig 1. CONSORT diagram. [a]Due to one patient in the Atezo arm declined surgery and was excluded from the mITT population, resulting in 28 patients in the Atezo + Tira arm and 26 patients in the Atezo arm. [b]Due to a protocol deviation, one patient assigned to the Atezo arm received Atezo + Tira. As a result, the safety analysis set comprised 29 patients in the Atezo + Tira arm and 26 in the Atezo arm. Atezo, atezolizumab; LCRT, long-course chemoradiotherapy; mITT, modified intention-to-treat;

Tiragolumab

- A human monoclonal antibody drug targeting TIGIT a co-inhibitory receptor expressed on T cells and natural killer cells.
  - When tiragolumab binds to TIGIT it inhibits the interaction with poliovirus receptor (PVR) or CD155. In normal circumstances TIGIT is an inhibitory checkpoint receptor that inhibits tumor suppression response.
  - TIGIT promotes immune system evasion in many cancers.
- When combined with other immunotherapy agents, seems to have a synergistic response with enhanced anti-tumor responses by promoting T cell and NK-T cell activity.
- Previously investigated in the phaseII CITYSCAPE study which investigated treatment naïve PD-L1 positive patients with recurrent or metastatic NSCLC.

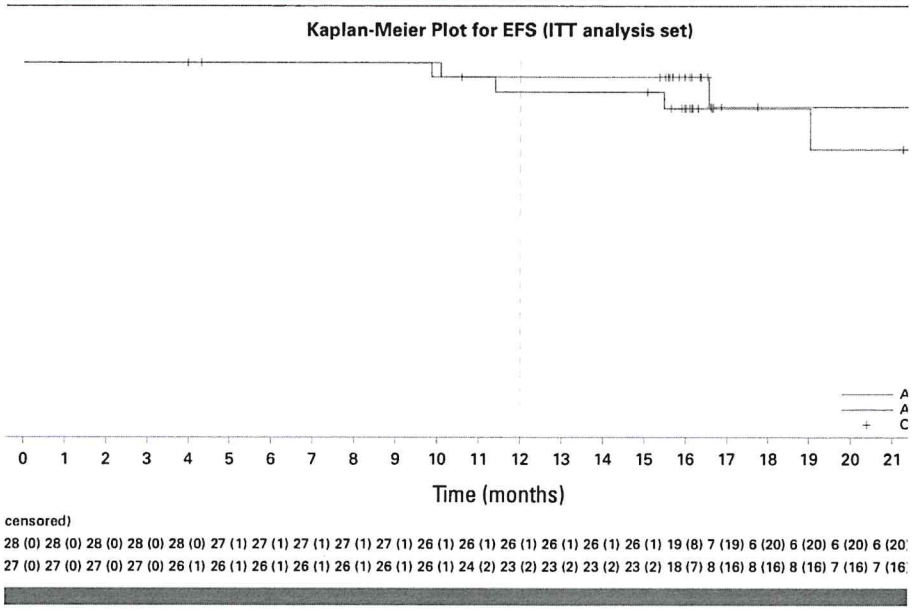
PD-L1 expression, median (IQR)	2% (1%-5%)	2% (0%-5%)
TIGIT expression, median (IQR)	5% (2%-10%)	4% (1%-6.5%)
PVR expression, median (IQR)	98% (95%-100%)	98% (92.5%-100%)

COLLAPSE

Abbreviation: ECOG, Eastern Cooperative Oncology Group; PVR, poliovirus receptor.

- Tumors were evaluated for PD-L1 expression, TGIT expression, and poliovirus receptor (pVR).

- Important findings:
  - Pathologic CR (primary endpoint) was 35.7% in the atezolizumab and tiragolumab arm vs. 22.2% in the atezolizumab arm alone.
  - Secondary endpoints included:
    - R0 resection rate
      - Both arms achieved R0 resection.
    - EFS:
      - The 1-year EFS rate was 96.3% (95% CI, 76.5 to 99.5) and 92.1% (95% CI, 72.1 to 98.0) in Atezo + Tira arm and Atezo arm, respectively



lan-Meier plot for EFS (ITT analysis set). EFS, event-free survival; ITT, intention-t

Safety:

- Due to a protocol deviation, one patient assigned to the Atezo-Tira arm received only Atezolizumab.
- All patients in both arms experienced at least one Treatment Emergent Adverse Event (TEAE).
- TEAEs related to RT or CT occurred in 89.7% of patients in the Atezo-Tira arm and 80.8% in the Atezo arm.
- Treatment related grade 3 and grade 4 adverse events occurred in 31% of the Atezo+ Tira arm and 26.9% in the Atezo arm.
- TEAEs leading to dose discontinuation or interruption occurred in 10.3% and 11.5% of patients, primarily during immunotherapy. No TEAEs resulted in treatment withdrawal in either arm. The most common grade ≥3 treatment-related AEs were decreased lymphocyte count (27.6% in the Atezo + Tira arm and 19.2% in the Atezo arm), increased aspartate aminotransferase (3.4% and 3.8%, respectively), and hyperglycemia (3.4% and 3.8%, respectively).

	Atezo + Tira (n = 29), No. (%)			Atezo (n = 26), No. (%)		
Event	Any Grade	Grade 1 to 2	Grade 3 to 4	Any Grade	Grade 1 to 2	Grade 3 to 4
Any TEAE	29 (100)	19 (65.5)	10 (34.5)	26 (100)	19 (73.1)	7 (26.9)
Anemia	16 (55.2)	16 (55.2)	0	14 (53.8)	13 (50.0)	1 (3.8)
Blood bilirubin increased	12 (41.4)	12 (41.4)	0	8 (30.8)	8 (30.8)	0
Lymphocyte count decreased	8 (27.6)	0	8 (27.6)	6 (23.1)	1 (3.8)	5 (19.2)
WBC count decreased	8 (27.6)	7 (24.1)	1 (3.4)	5 (19.2)	5 (19.2)	0
Proctalgia	7 (24.1)	7 (24.1)	0	7 (26.9)	7 (26.9)	0
Diarrhea	7 (24.1)	6 (20.7)	1 (3.4)	6 (23.1)	6 (23.1)	0
Leukopenia	6 (20.7)	6 (20.7)	0	6 (23.1)	6 (23.1)	0
ALT increased	6 (20.7)	5 (17.2)	1 (3.4)	6 (23.1)	6 (23.1)	0
Nausea	6 (20.7)	6 (20.7)	0	5 (19.2)	5 (19.2)	0
Hypoalbuminemia	6 (20.7)	6 (20.7)	0	5 (19.2)	5 (19.2)	0
Radiation proctitis	6 (20.7)	6 (20.7)	0	3 (11.5)	3 (11.5)	0
Proctitis	5 (17.2)	5 (17.2)	0	6 (23.1)	6 (23.1)	0
Fatigue	4 (13.8)	4 (13.8)	0	6 (23.1)	6 (23.1)	0
AST increased	4 (13.8)	3 (10.3)	1 (3.4)	4 (15.4)	3 (11.5)	1 (3.8)
Incision site pain	4 (13.8)	4 (13.8)	0	4 (15.4)	4 (15.4)	0
Pyrexia	4 (13.8)	4 (13.8)	0	2 (7.7)	2 (7.7)	0
Gamma-glutamyltransferase increased	4 (13.8)	4 (13.8)	0	1 (3.8)	1 (3.8)	0
Decreased appetite	4 (13.8)	4 (13.8)	0	1 (3.8)	1 (3.8)	0
Vomiting	3 (10.3)	3 (10.3)	0	2 (7.7)	2 (7.7)	0
Ileus	3 (10.3)	3 (10.3)	0	1 (3.8)	0	1 (3.8)
Hyperglycemia	3 (10.3)	2 (6.9)	1 (3.4)	2 (7.7)	1 (3.8)	1 (3.8)
Cystitis radiation	3 (10.3)	3 (10.3)	0	1 (3.8)	1 (3.8)	0
Neutrophil count decreased	3 (10.3)	3 (10.3)	0	0	0	0
Hypocalcemia	3 (10.3)	3 (10.3)	0	0	0	0
Interleukin level increased	2 (6.9)	2 (6.9)	0	3 (11.5)	3 (11.5)	0
Hyperuricemia	1 (3.4)	1 (3.4)	0	4 (15.4)	4 (15.4)	0
Hyponatremia	1 (3.4)	1 (3.4)	0	3 (11.5)	3 (11.5)	0

Points of Discussion

- All patients were pMMR, which we know is the case for most of our patients.
  - Promising data from other phase II trials TORCH and SPRING-01.
- Statistical significance achieved in the Atezo + Tiga arm and not just the Tiga arm, to suggest benefit of dual ICI therapy.
- Are we targeting pathologic response?
  - Identified as a predictor of long term survival, but its role as a surrogate end point is still open to debate.

Points of Discussion

- Limitations of the study:
  - Surgery was performed 2 weeks after cessation of immunotherapy.
    - Is this enough time?
  - Non-operative management was not considered an option.
  - Post-operative follow up was relatively short.
  - Long term data needs to mature.
  - Small sample size.
  - Can this be generalized to our population?

To return to our patient...

- How would you counsel her regarding treatment if she walked into your office today?
- How do you think that will change in the next 3-5 years?
- When you will feel comfortable incorporated ICI or possible dual ICI into your treatment paradigm for rectal cancer?

Please feel free to reach out to me: rais-jessica@cooperhealth.edu

THANK YOU!

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In Kind Donation

- 2 Hextec 2 Qt saucepan estimated value $30 each (hex-tec.com)
- 2 Hextec 9" Fry Pans estimated value $40 each
- 1 Hextec 11" Sauté Pan estimated value $65
- 2 Hextec 5 Qt Stock Pot estimated value $85 each
- 2 Appetit Flatware 20 piece sets estimated value $59.99 each
- Classic 3 QT Crock Pot estimated value $30
- Iceman Personal Fridge 6 cans estimated value $58.01
- 2 George Foreman Indoor Panini Grill estimated value $41.99 each
- ECO & Chef Cold Brew 4 cup Coffee Maker estimated values $19.99
- Chefman two slice Toaster estimated value $24
- 2 Coffee Cup Sets by Mesmerizing Elegance estimated value $24 each
- Backyard Living Neck Fan estimated value $25
- 2 Rubbermaid 3 pack Produce Saver estimated value- $25 each
- Power House AM/FM Radio estimated value $25
- Parx Casino Cooler Backpack estimated value - $60
- Black and Decker Power Driver estimated value-$27
- Black and Decker 5" Orbit Sander estimated value -$44
- Prestige Garment/Duffle bag estimated value -$128 average price
- Pro Diamond4 stage knife sharpener- estimated value 9.99

Approximate value not including garmet/duffel bag – 999.95