



Annual

**Advances and Innovations in Endoscopic Oncology
and Multidisciplinary Gastrointestinal Cancer Care**

Precision Radiotherapy for Organ Preservation: The Rectum and Beyond

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Disclosures

- Consultant for XRad Therapeutics.
- On the Speakers Bureau for Varian Medical Systems.
- Grant support from Beyond Spring Pharmaceuticals, Nektar Therapeutics
- This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Language access services, patient navigation, and culturally humble shared decision-making to ensure equitable understanding and adherence to organ preservation surveillance protocols for diverse rectal and esophageal cancer patients.
- How oncologists' implicit racial and ethnic biases can undermine patient-centered communication and treatment recommendations, contributing to disparities in who is offered nonoperative management.

Defining Organ Preservation

Four Requirements:

- Oncologic control
- Anatomic preservation
- Functional preservation
- Salvageability

Precise and effective radiotherapy changed the role of surgery for various cancers

A historical progression

- Head and Neck cancer
- Anal Cancer
- Early-stage lung cancer
- Rectal cancer

Why rectal preservation matters

What TME provides

- Excellent local control
- Definitive removal of residual disease
- Pathologic staging

What are the potential costs

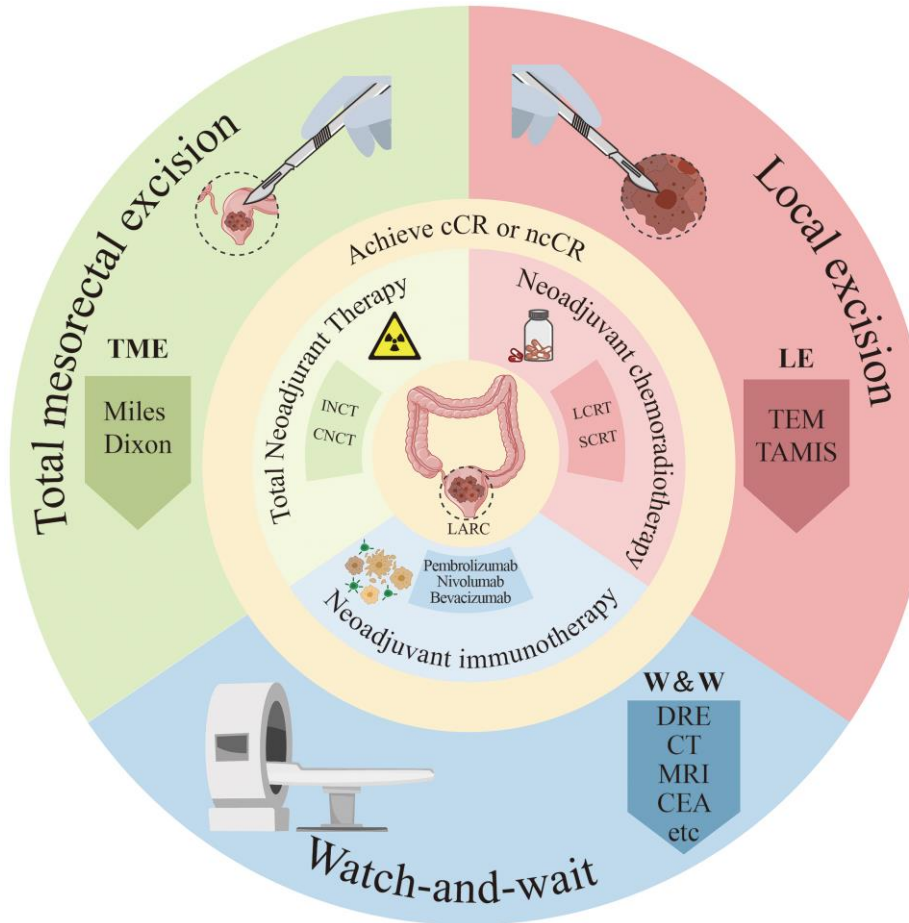
- Permanent or temporary stoma
- Low anterior resection syndrome
- Urinary and sexual dysfunction
- Operative morbidity

Total neoadjuvant therapy as the treatment platform

Historically

CRT → Surgery → chemo

Adjuvant chemo is often
Difficult to complete



Current paradigm

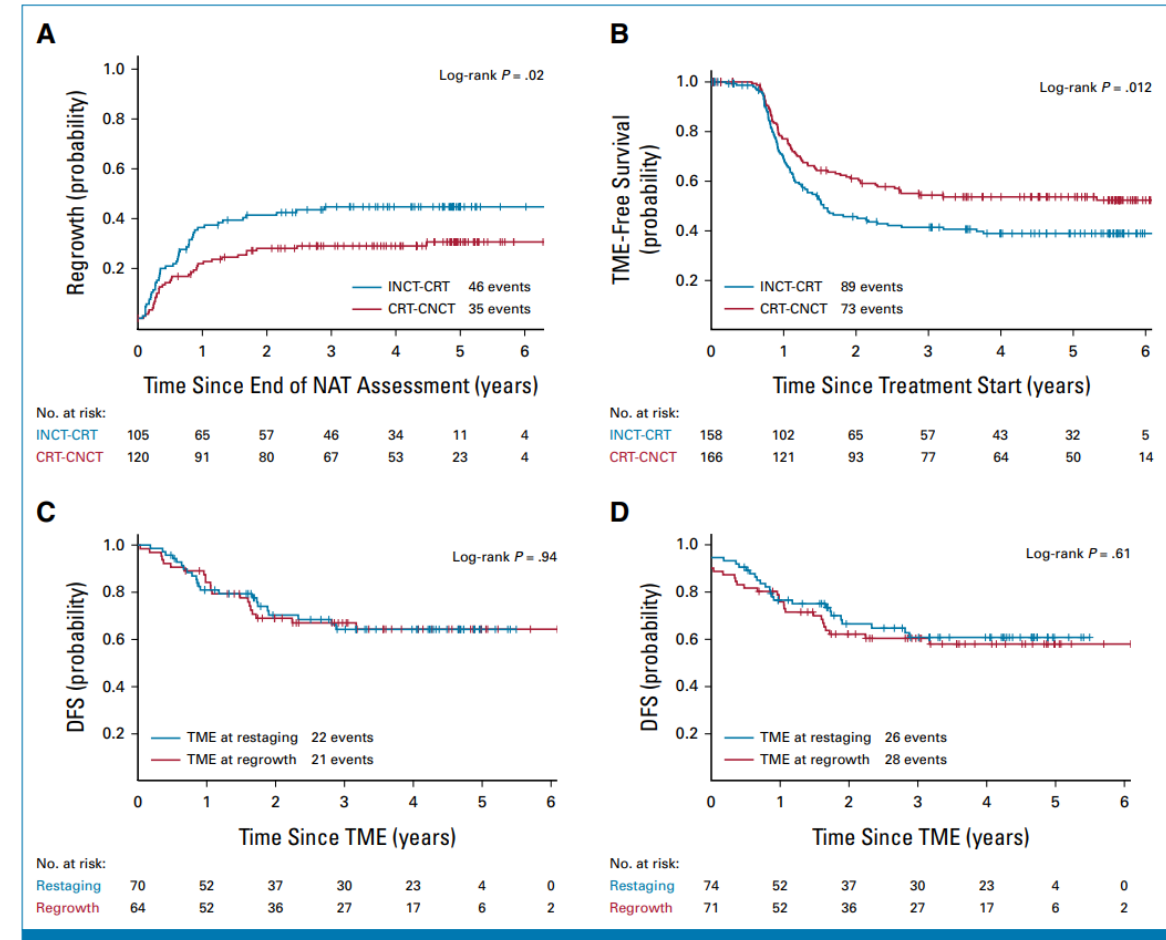
**CRT → chemo → Selective surgery
(OPRA, CAO/ARO/AIO-12)**

- 1) CRT followed by chemo allows tumor to continue to regress during chemo → better organ preservation
- 2) Higher risk locally advanced dz may require upfront chemo
- 3) Longer interval and more therapy to allow for tumor regression
- 4) Watchful waiting and selective surgery for residual / progressive disease

Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial

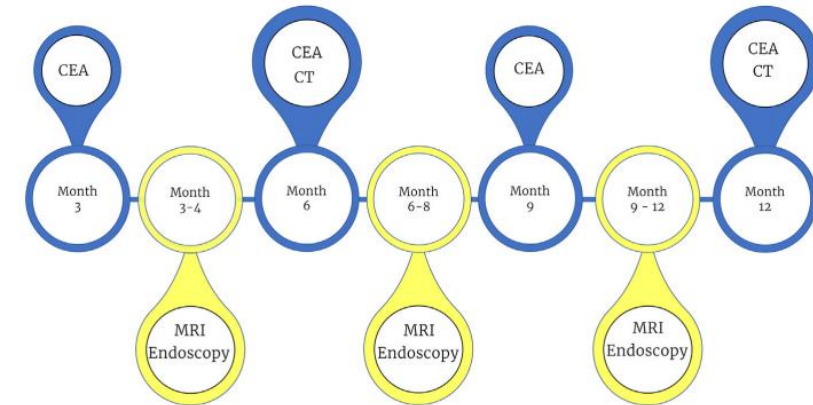
Verheij et al., JCO 2023

- Primary endpoint is DFS
- No differences in DFS, DMFS, LRFS
- Key differences are in TME-free survival (39% chemo-first vs 54% in CRT first)
- DFS similar in pts who had TME first after Neoadj therapy vs regrowth after WW (both 64%)
- In WW group, most tumor regrowth occurs within 2 years

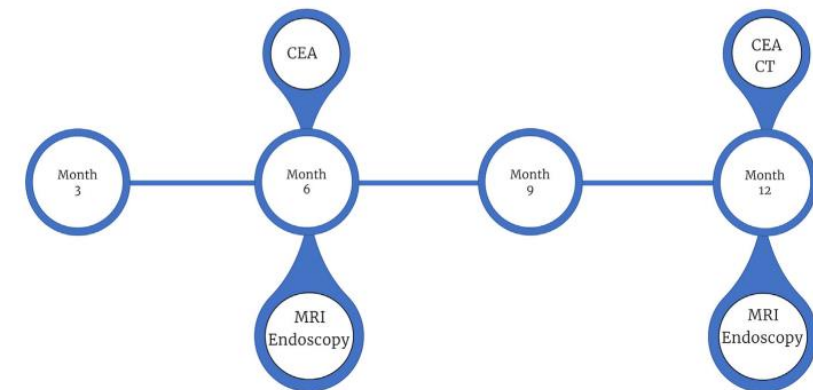


Watch-and-wait after cCR is active management

- Watch-and-wait approach requires intensive surveillance strategy, but the benefit outweighs the increased cost
- It is now an established and oncologically standard option for patients with cCR
- Long term survival is equivalent to primary rectal resection (85%), but QoL outcomes are superior in WW approach
- Tumor regrowth is 25-33% during WW, but patients are often salvageable (85-90%), with outcome equivalent to upfront surgery



Year 1 – 2



Year 3 – 5

Wyatt et al., Clin Oncol 2023

Response assessment is part of the treatment

Clinical complete response requires agreement among:

- Endoscopy
- Digital rectal examination
- MRI
- Serial reassessment

Precision Radiotherapy influences every aspect of organ preservation

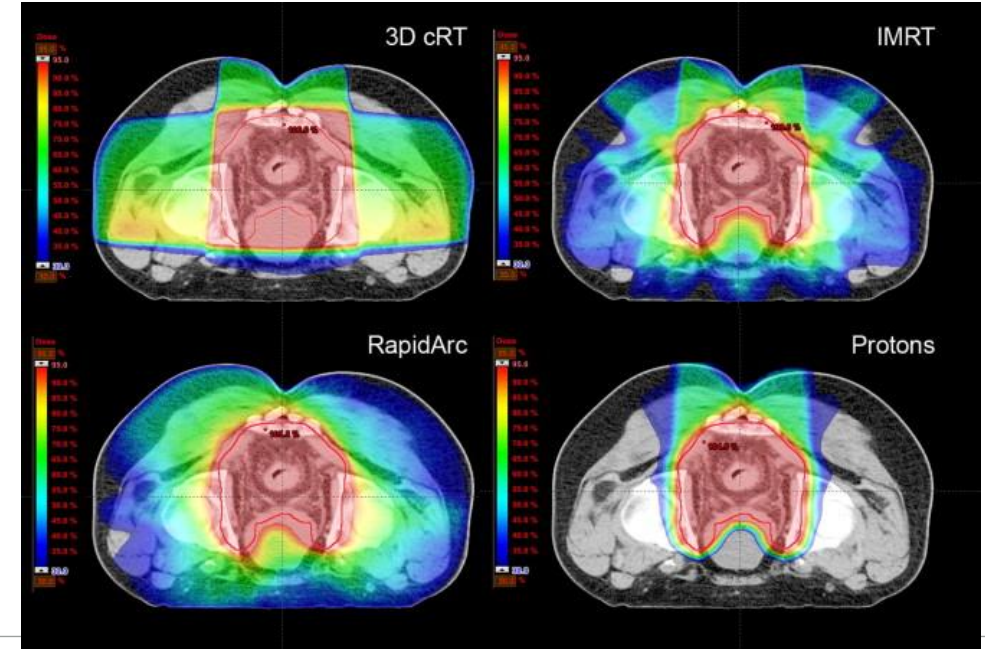
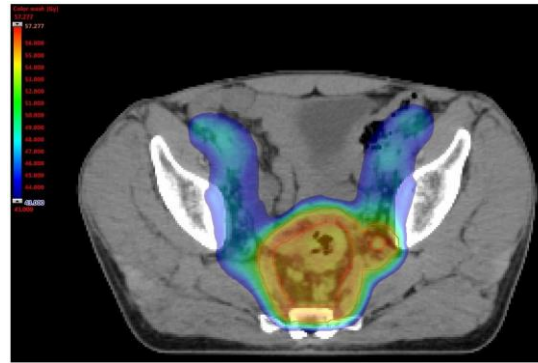
Dimensions of precision radiotherapy

- Spatial precision
- Dose precision
- Temporal precision
- Biologic precision

Spatial precision and functional preservation

Targeting precision: adequately treating both visible and invisible disease by having **precise knowledge** of patterns of local and regional spread of disease, but also reducing complications to adjacent organs-at-risk by using **advanced radiation technologies and techniques**

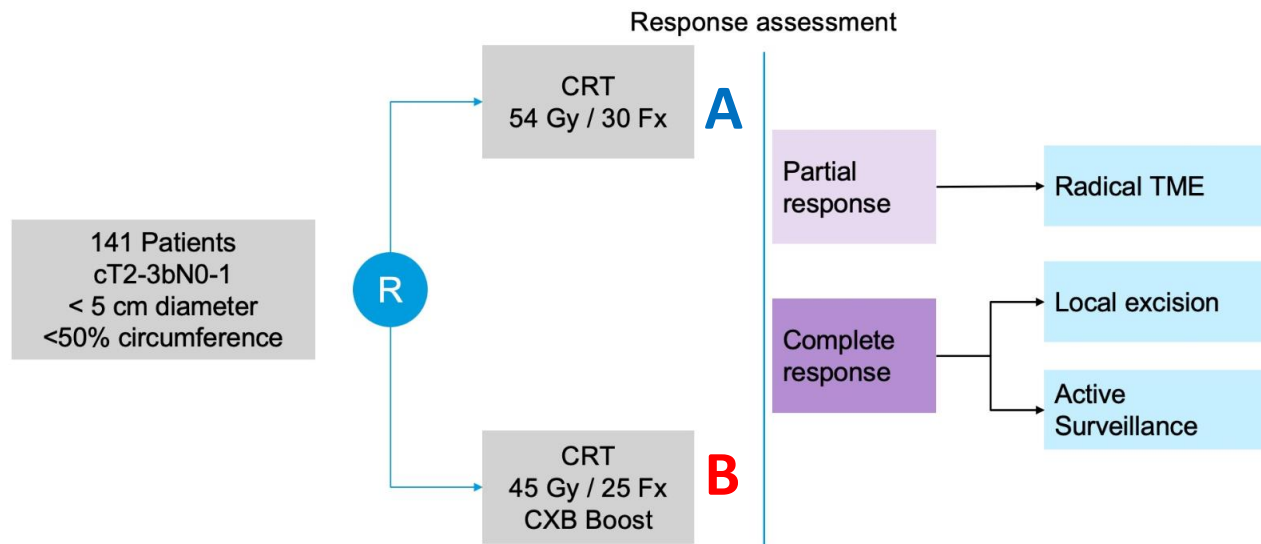
- Gross tumor
- Mesorectum
- Nodal targets
- Small bowel and bladder
- Pelvic bone marrow



Dose precision = enhancing therapeutic index

Delivering enough dose to sterilize gross disease, but at the same time preserve organ function and reduce adjacent normal tissue toxicity

OPERA TRIAL: CRT +/- BRACHYTHERAPY



Redrawn from: Gerard J-P et al. Lancet Gastroenterol Hepatol 2023

- The OPERA Trial: after 45 Gy of pelvic external beam RT (EBRT), boost to **9 Gy with EBRT (A)** vs. **90 Gy using contact x-ray brachytherapy (B)**



OPERA Organ Preservation Trial

- Between weeks 14 and 24, cCR / nCR occurred in 64% of patients in Group A and 92% in Group B ($p < 0.001$). The 3-year OP rate was 59% for Group A compared to 81% for Group B ($p = 0.003$).
- After a median follow-up of 61.1 months (range: 56.8-64.5), the 5-year local regrowth rate was 39% in Group A and 17% in Group B ($p = 0.1$).
- The difference in OP rates remained highly significant, with Group A achieving 56% and Group B 79% ($p = 0.004$).
- This difference was even more striking for tumors smaller than 3 cm, with Group B showing an OP rate of 93% compared to 54% in Group A.

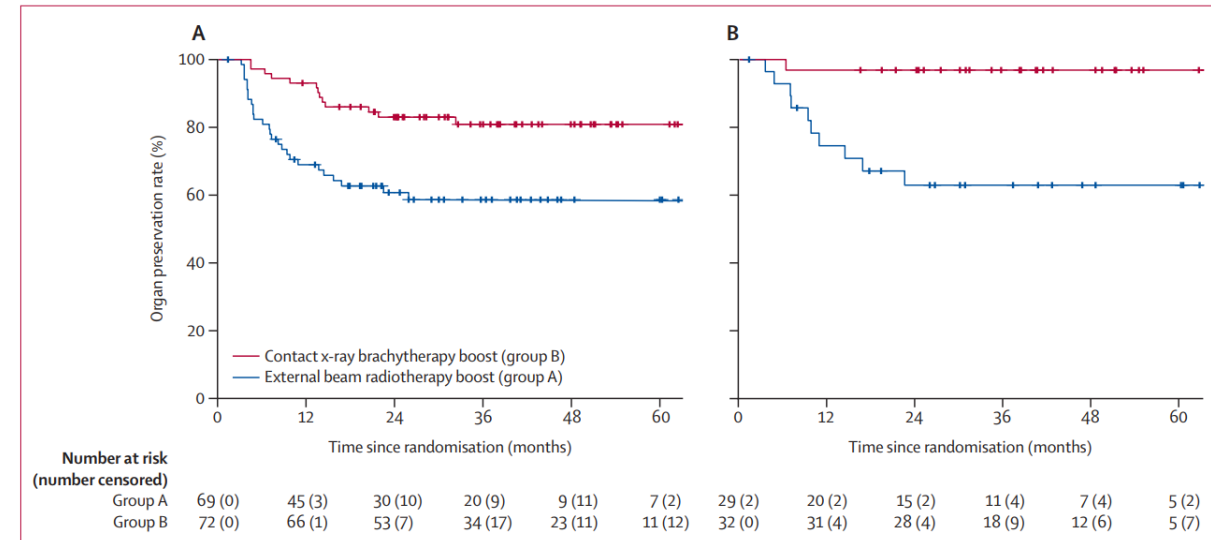


Figure 3: 3-year organ preservation rate
(A) All patients (n=141). (B) Patients with tumours smaller than 3 cm (n=61).

Gerard JP et al., Lancet Gastro & Hepatology 2023

Biologic strategies to increase complete response

Biologic setting

- dMMR/MSI-high
- pMMR/MSS
- Resistant subvolumes
- High residual-risk signatures

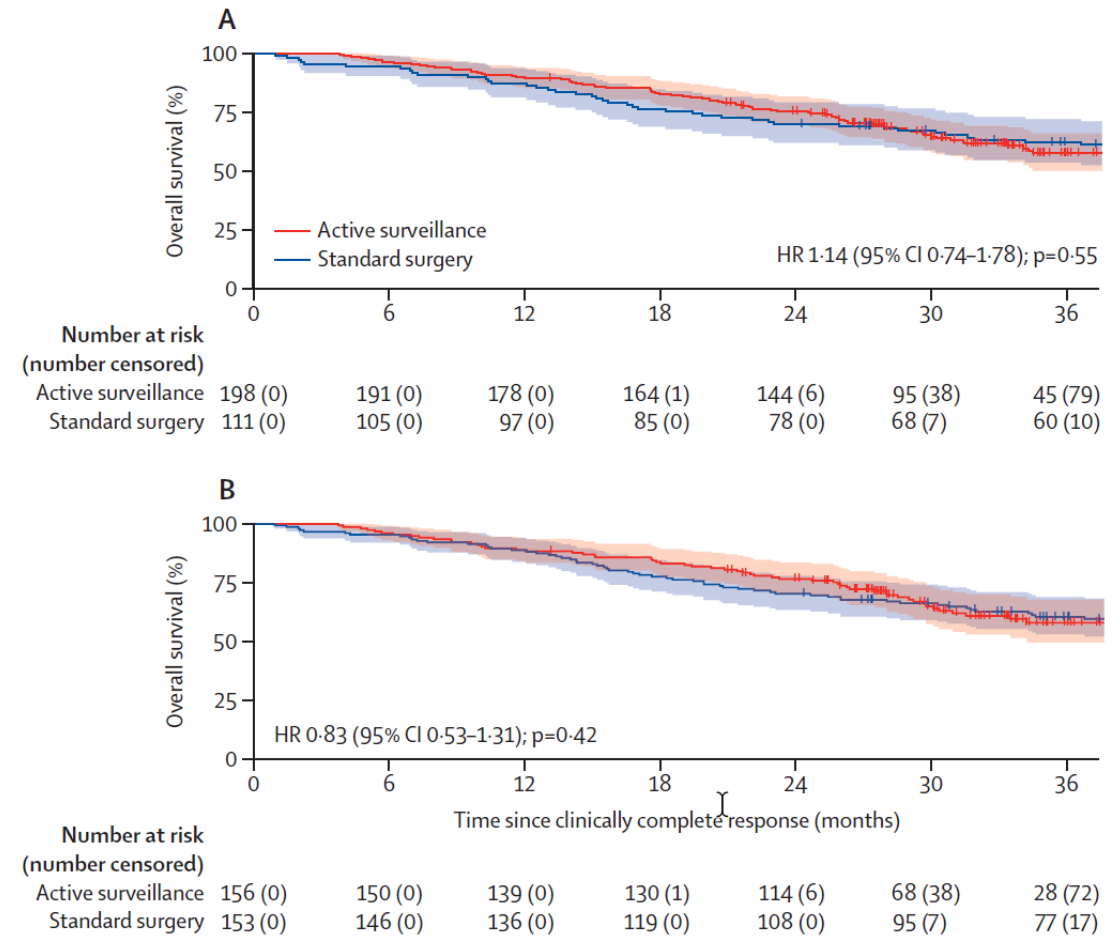
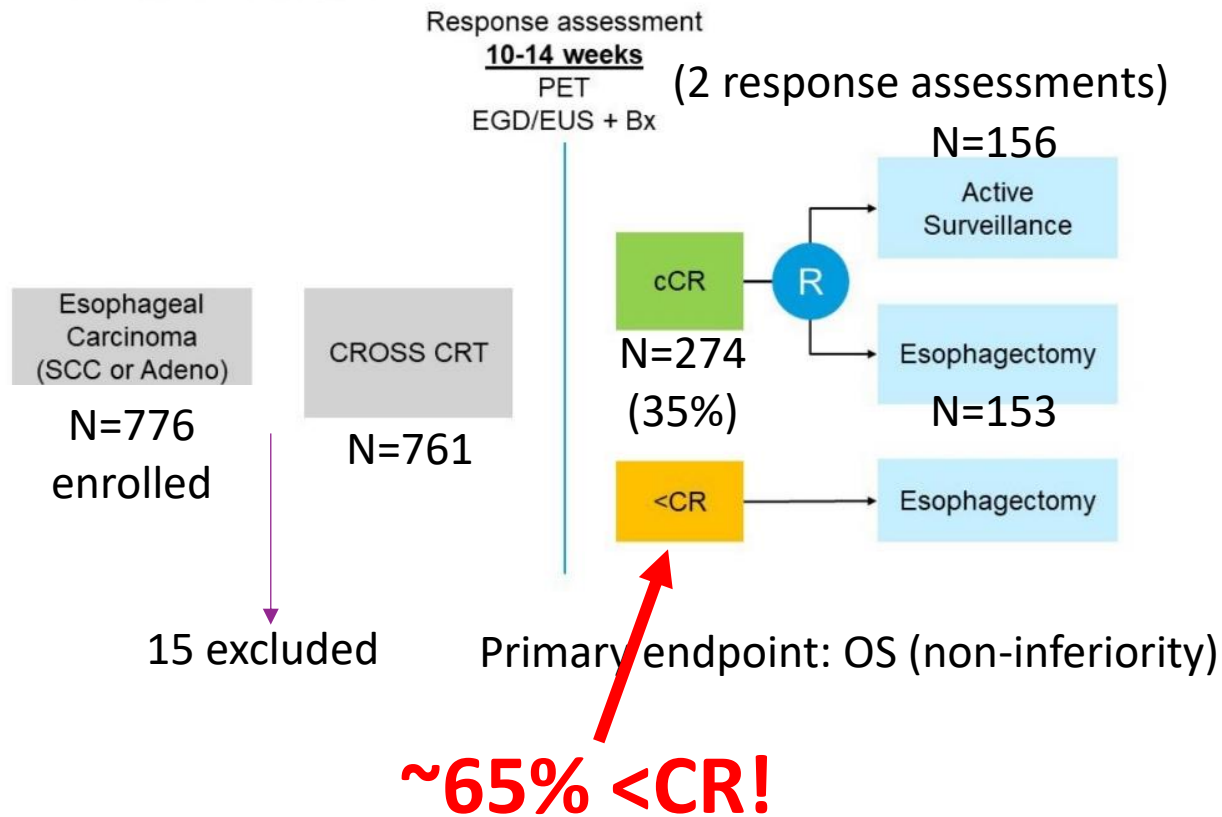
Organ-preserving strategy

- PD-1 blockade
- Improved radiosensitization needed
- Image-guided intensification
- Targeted combination therapy

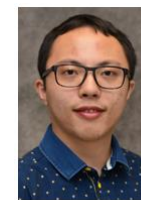
Ultimately, pretreatment biomarkers and early response measurements may allow us to separate tumors that need intensification from those already likely to respond to standard therapy.

Beyond the rectum: Esophagus preservation after CRT: SANO-1 Trial

SANO-1 TRIAL



MT1E/X upregulation are associated with radiation resistance in esophageal tumors and in radiation resistant tumor models



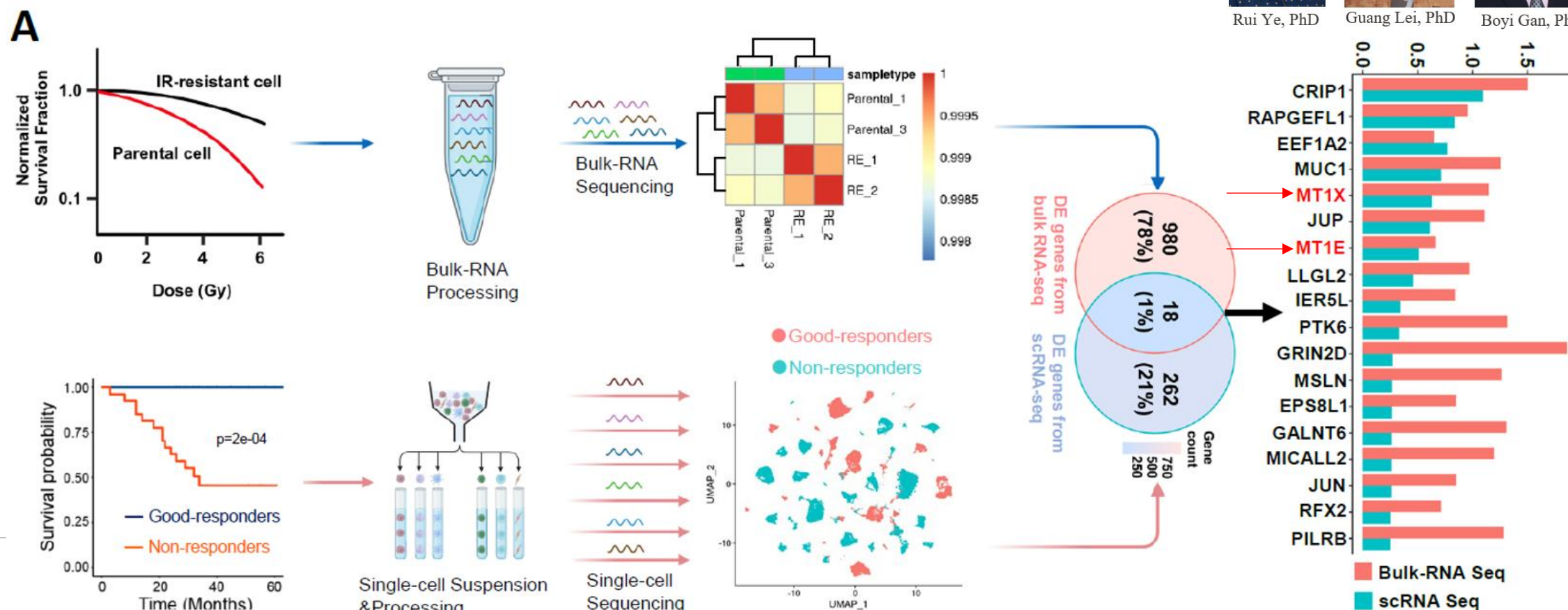
Rui Ye, PhD



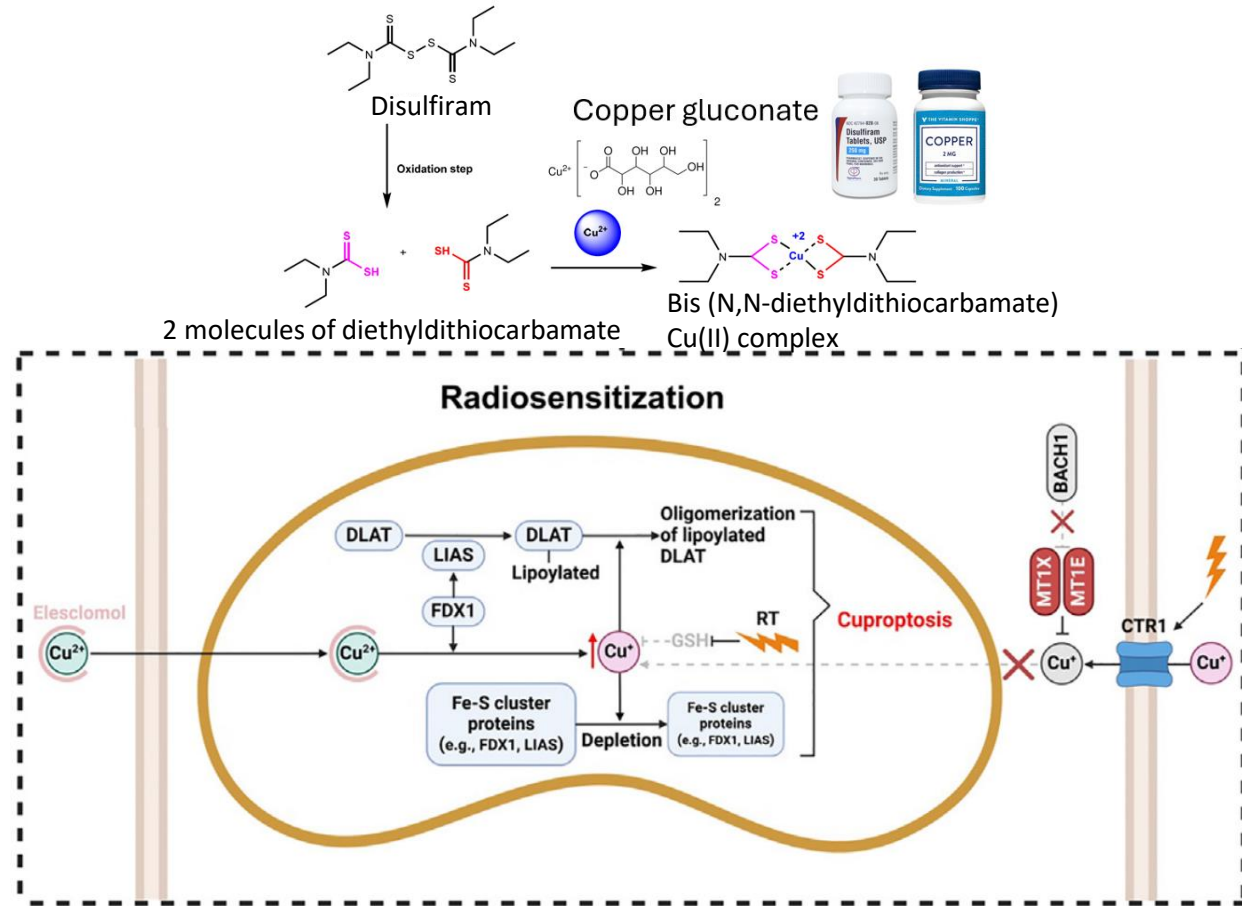
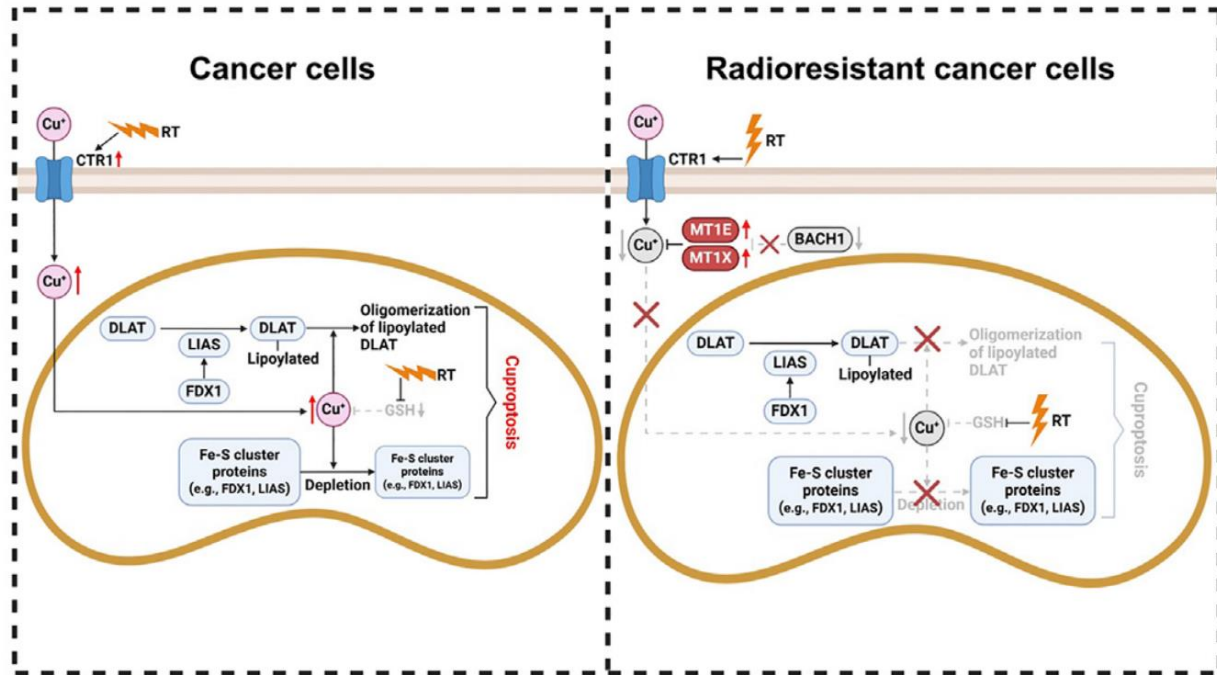
Guang Lei, PhD



Boyi Gan, PhD



Radiotherapy promotes cuproptosis and synergizes with cuproptosis inducers to overcome esophageal cancer radioresistance



Lei G et al., Cancer Cell 2025

Esophageal organ preservation as the next frontier

- Rectal cancer has established the framework
- Organ preservation in esophageal cancers could be even more important due to differences in surgical complexity, morbidity (esp with age), and impacts on QoL
 - TNT approaches for esophageal cancer are currently ongoing
 - Sequencing question could also be important
- Greater challenges → greater opportunities
 - Submucosal residual disease → limited accuracy of current response assessment
 - Occult regional and distant metastatic disease require better systemic disease assessments
 - Radiation resistance in a large proportion of adenocarcinomas → could this be better targeted?

Conclusions

Precision radiotherapy for organ preservation

- TNT enables rectal preservation in selected patients
- Treatment sequence and focal intensification affect response
- Surveillance and salvage protect oncologic safety
- Biology can support de-intensification or selective radiosensitization

Thank you!



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