ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Organ Preservation for Esophageal Cancer: Are There Options?

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Disclosures

- I do not have any relevant financial relationships.

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

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:

- What are the commonalities and differences among individuals in this population?
- What factors determine the type and level of care that this patient population receives?

Outline

- Building the evidence for organ preservation in esophageal cancers
- Some drawbacks for organ preservation
- Research to enable organ preservation as an option in the future

Why esophagus preservation lags behind rectal cancer

- Surgery as a single modality is the most curative measure compared to any other approaches (CRT alone, RT alone, chemotherapy alnoe)
- Adding neoadjuvant therapy significantly enhances the cure rates for about 50% of patients
- For Unresectable patients, CRT alone is considered inferior therapy overall
- TNT approach has the potential to reduce micrometastatic disease and enhance pathologic response with CRT, but TNT is not widely adopted pre-FLOT
    - Ajani's small phase II RCT shows no disease benefit (Docetaxel/5FU)
    - CALGB 80801 trial is PET directed concurrent chemo based on PET response to induction chemo is niche and not widely adopted

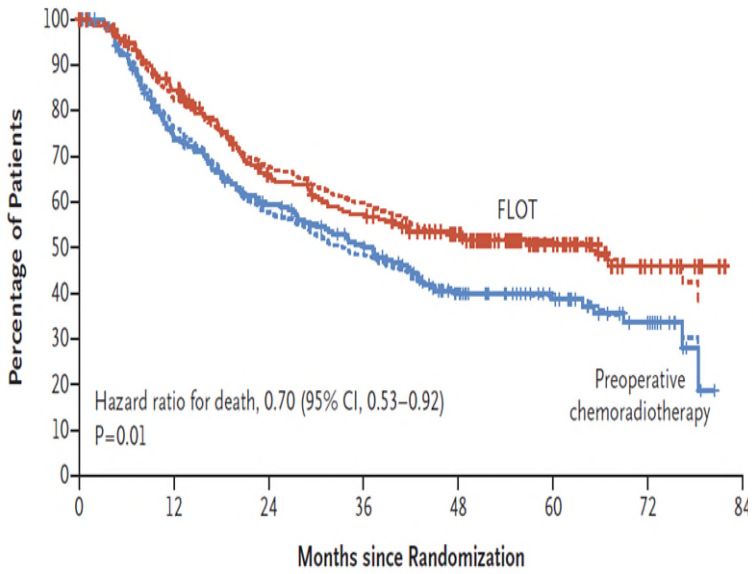
Clinical trials of perioperative chemo vs CRT in esophageal adenocarcinoma in the FLOT era

Trial	N	Key Eligibility Criteria	Treatment	Primary Endpoint
ESOPEC NCT02509286 Germany	438	Adeno of esophagus or GEJ	**CROSS vs FLOT4** PC/**XRT** → Surgery **versus** FLOTx4 → surgery → FLOTx4	OS
NEO-AEGIS NCT01726452 Ireland	540	Adeno of esophagus or GEJ	**CROSS vs. MAGIC** PC/**XRT** → Surgery **versus** ECFx3 or FLOTx4 → surgery → ECFx3 or FLOTx4	OS
TOP GEAR NCT01924819 Australia/New Zealand/Europe/Canada	570	Adeno of stomach or GEJ Siewert type II and III	ECFx2 or FLOT x3 + 5FU/**XRT** → surgery → ECFx3 **versus** ECFx3 or FLOTx4 → surgery → ECFx3 or FLOTx4	OS

Overall survival outcomes of the 3 neoadjuvant studies

ESOPEC

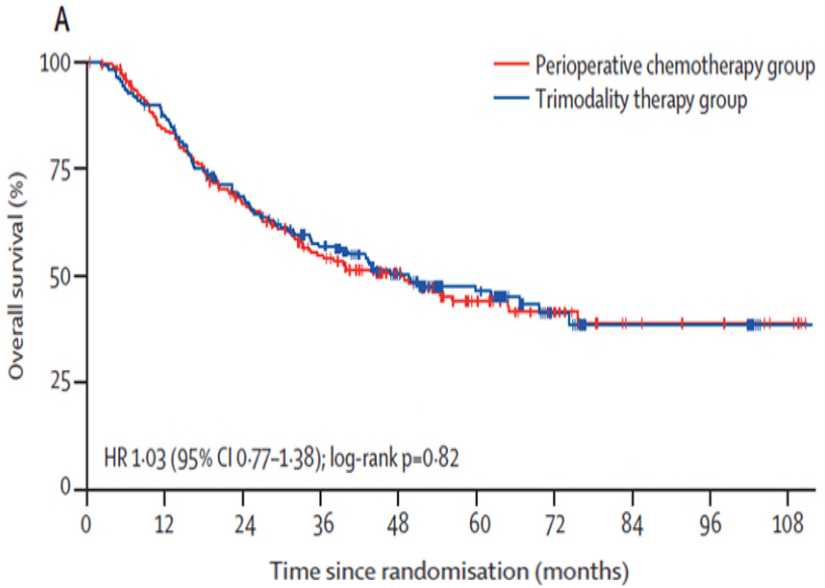
CROSS vs FLOT4
PC/**XRT** → Surgery
versus
FLOTx4 → surgery → FLOTx4



Hoeppner J et al., NEJM 2025

NEO-AEGIS

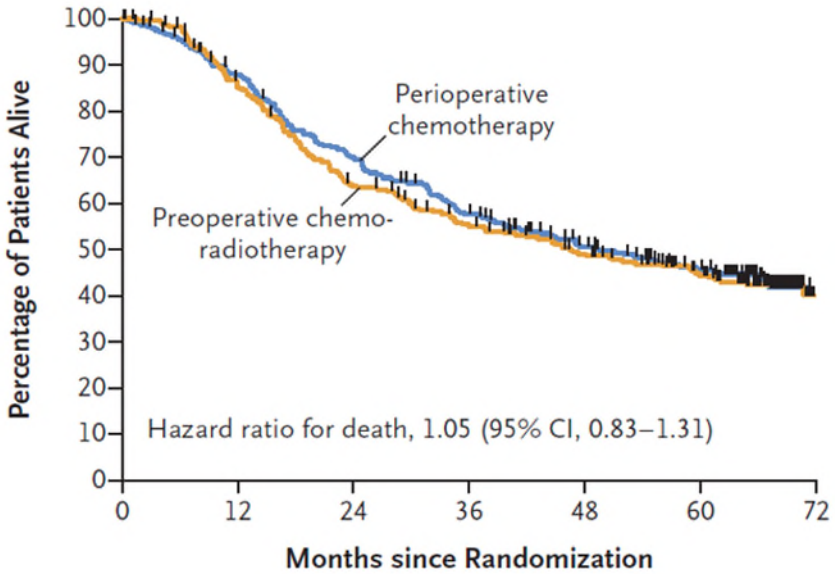
CROSS vs. MAGIC
PC/**XRT** → Surgery
versus
ECFx3 or FLOTx4 → surgery
→ ECFx3 or FLOTx4



Reynolds JV et al., Lancet Gastro Hepato 2023

TOP GEAR

ECFx2 or FLOT x3 + 5FU/**XRT**
→ surgery → ECFx3
versus
ECFx3 or FLOTx4 → surgery
→ ECFx3 or FLOTx4



Leong T et al., NEJM 2024

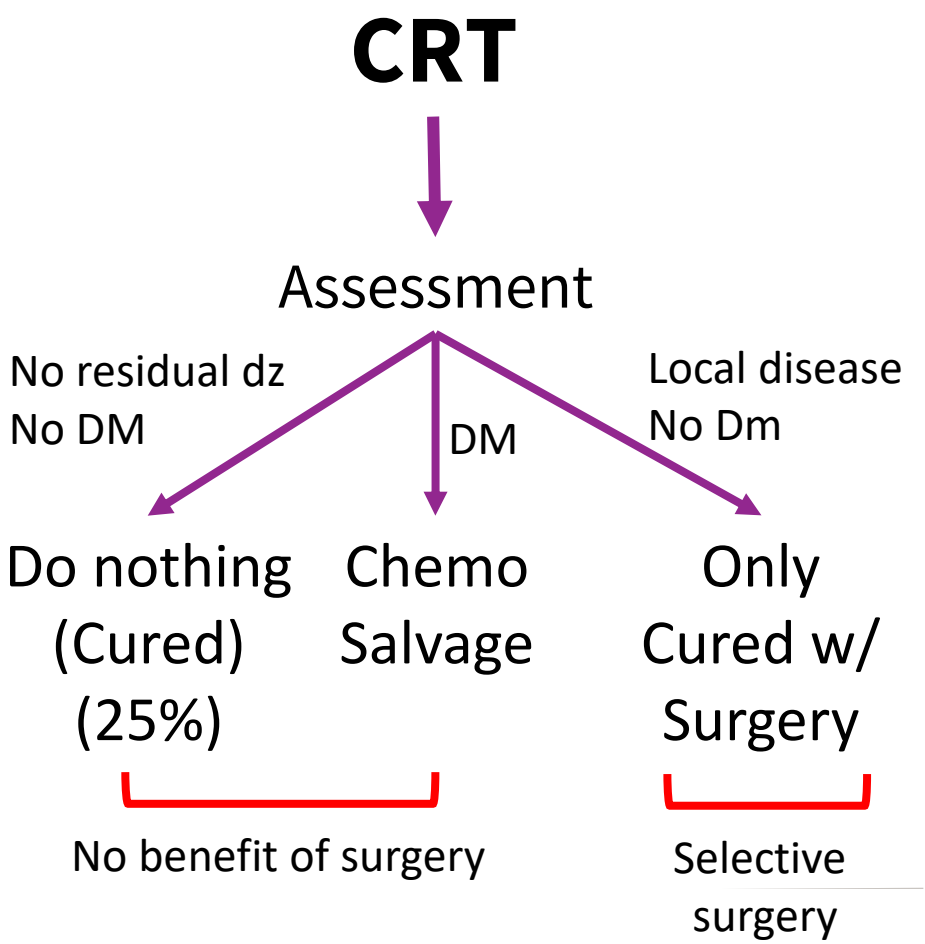
Limitations of the ESOPEC study

- Worse compliance in the nCRT arm (68% vs 87%)
- 11 pts in nCRT vs 1 pt in FLOT had metastatic disease before starting neoadjuvant therapy
- No RT quality assurance, 100% received 3D radiation
- Poorest pCR rate seen compared to contemporary trials and series (10%)
- Non-standard control arm (CROSS vs. CM-577)

Is esophagectomy needed for all?

- Yes, for those receiving **neoadjuvant chemotherapy alone**
- **The benefit of surgery after CRT is still controversial given two old negative phase 3 trials** (*Stahl (German) JCO 2005; Bedenne (French) JCO 2007*)
    - Significant morbidity/mortality of surgery from those trials
- Patients **who are cured by chemoradiation** (25% of adeno and >40% SCCA), **surgery only adds toxicity without any benefit to patients**
- **Surgery has significant impact on the QoL for many patients, and could be reserved as salvage for those with locally persistent disease and without DM after CRT**

Personalized organ preservation approach



Impact of esophagectomy and patient perspective

- In a HRQoL study from two high volume centers in the US and UK, with the exception of dysphagia, which improved over time, esophagectomy was associated with decreased HRQOL and lasting gastrointestinal symptoms up to 20 years after surgery (*Boshier et al., Ann Surg 2022*).
- A survey to determine patient preference after CRT found that patients were willing to accept a 5-year survival reduction by 16% if the chance of an esophagectomy could be reduced to 35% (*Noodman et al., Br J Surg 2018*)

The Holy Grail: Proper patient selection for the right Rx

Localized EC treated with CRT

Cured with CRT alone

5 year **25%**
(RTOG 8501)

Organ Preservation!!

Cured with Sx alone

5 year **30%**
(CROSS)

Cured with Multimodality

5 year **45-50%**
(CROSS or ESOPEC)

Will NOT be Cured with local therapy

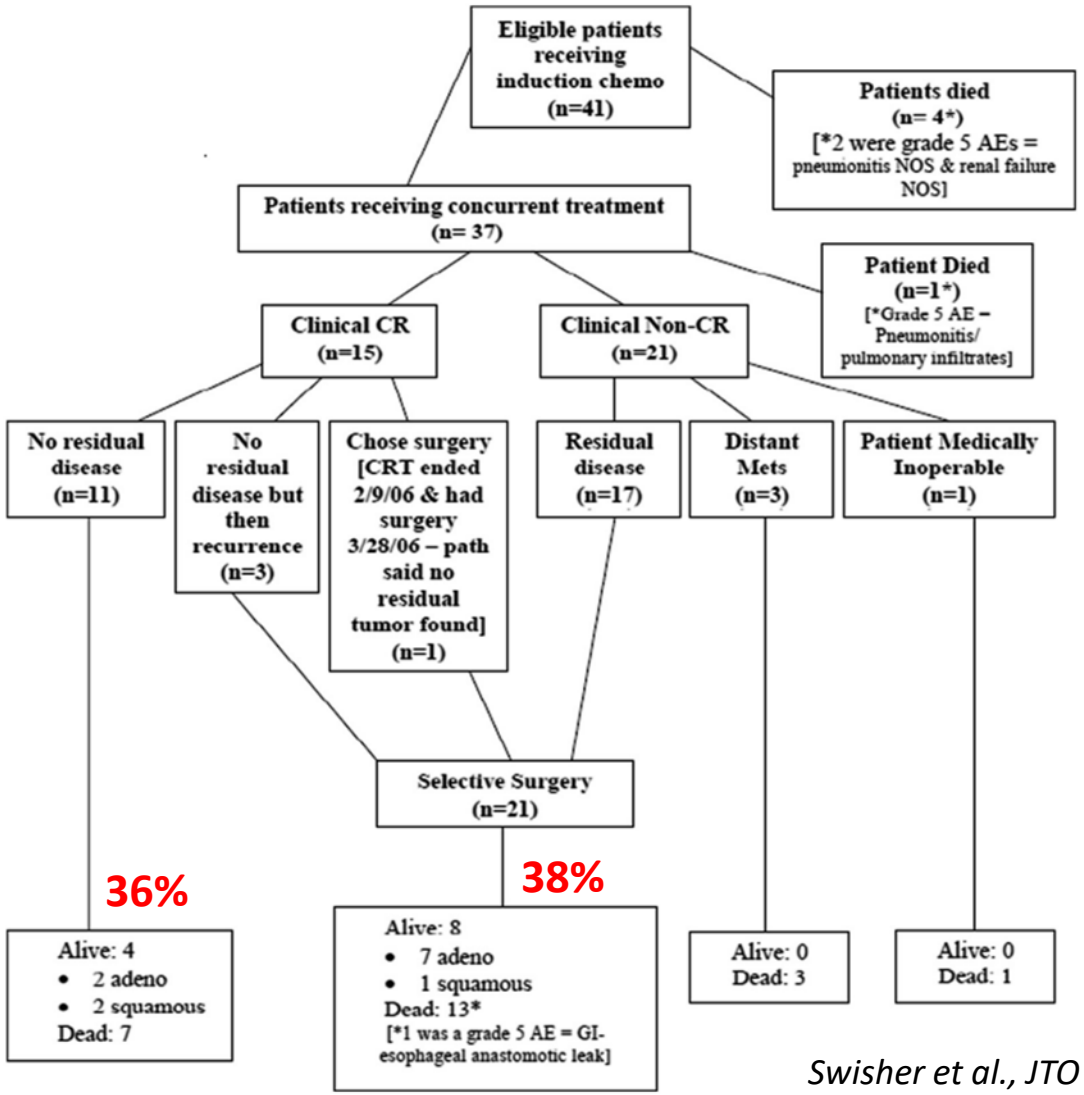
40%
(**90%**-50%=40%)

Needs Tx intensification

Background 5 yr survival in the non-cancer population

5 yr survival of the ESOPEC or CROSS cohort

Is organ preservation possible after CRT? RTOG 0246



Swisher et al., JTO 2016

ORIGINAL ARTICLE

Final Results of NRG Oncology RTOG 0246: An Organ-Preserving Selective Resection Strategy in Esophageal Cancer Patients Treated with Definitive Chemoradiation

Stephen G. Swisher, MD,[a,*] Jennifer Moughan, MS,[b] Ritsuko U. Komaki, MD,[a] Jaffer A. Ajani, MD,[a] Tsung T. Wu, MD,[c] Wayne L. Hofstetter, MD,[a] Andre A. Konski, MD,[d] Christopher G. Willett, MD[e]

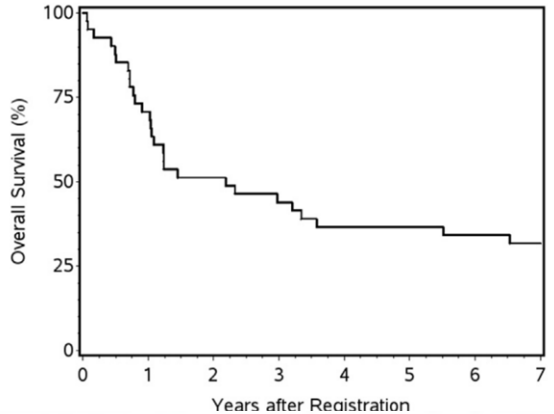


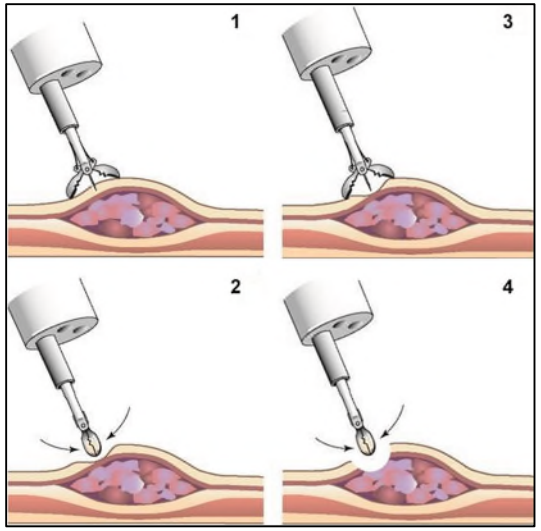
Table 3. Esophageal Multimodality Trials

Trial	3-Year OS	5-Year OS	7-Year OS
RTOG 0246 (Def CRT → Selective S)[4]	44%	37%	32%
RTOG 8501 (Def CRT)[1]	28%	20%	14%
PRODIGE5/ACCORD17 (Def CRT)[7]	27%	—	—
SCOPE1 (Def CRT)[8]	26%	—	—
CROSS (CRT → S)[17]	60%	47%	—
CALGB 9781 (CRT → S)[15]	63%	39%	—
Urba et al. (CRT → S)[16]	30%	20%	20%

OS, overall survival; Def, definitive; CRT, chemoradiation; S, surgery.

Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study

*Bo Jan Noordman, Manon C W Spaander, Roelf Valkema, Bas P L Wijnhoven, Mark I van Berge Henegouwen, Joël Shapiro, Katharina Biermann, Ate van der Gaast, Richard van Hillegersberg, Maarten C C M Hulshof, Kausilia K Krishnadath, Sjoerd M Lagarde, Grard A P Nieuwenhuijzen, Liekele E Oostenbrug, Peter D Siersema, Erik J Schoon, Meindert N Sosef, Ewout W Steyerberg, J Jan B van Lanschot, for the SANO study group**



	False-negative cases (95% CI)*	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)
Endoscopy with regular biopsies and fine-needle aspiration	31% (13–49)	54% (38–70)	69% (44–94)	35% (16–53)	83% (68–98)
Endoscopy with bite-on-bite biopsies and fine-needle aspiration	11% (1–21)	74% (64–83)	77% (59–95)	45% (29–62)	92% (85–99)
Endoscopic ultrasonography with maximum tumour thickness (second clinical response evaluation)	29% (15–43)	59% (48–70)	58% (40–75)	38% (25–52)	76% (64–87)
PET–CT (second clinical response evaluation)	14% (3–24)	82% (73–90)	38% (21–55)	44% (26–63)	77% (68–87)

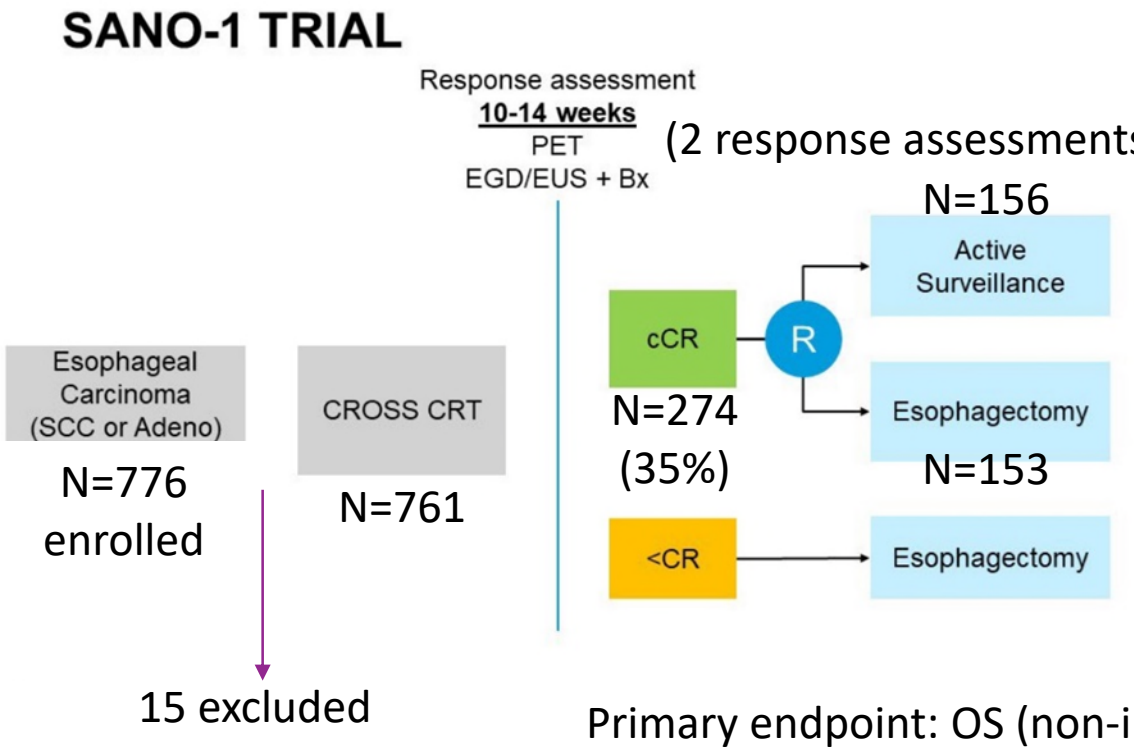
Accuracy estimates were calculated as TRG1 vs TRG2–4 after multiple imputation (for age, sex, histology, tumour grading, clinical T stage, clinical tumour stage, clinical lymph-node stage, WHO performance score, number of cycles of chemotherapy, total radiation dose, and results from endoscopic biopsies, fine-needle aspiration, maximum tumour thickness measurement, and PET–CT) per diagnostic modality for patients who had active surveillance instead of surgery after clinical response evaluations. Totals per group cannot be calculated, since this is a multiple imputation analysis. TRG=tumour regression grade. *Calculated as the proportion of TRG3 and TRG4 residual tumours missed during clinical response evaluations per diagnostic modality.

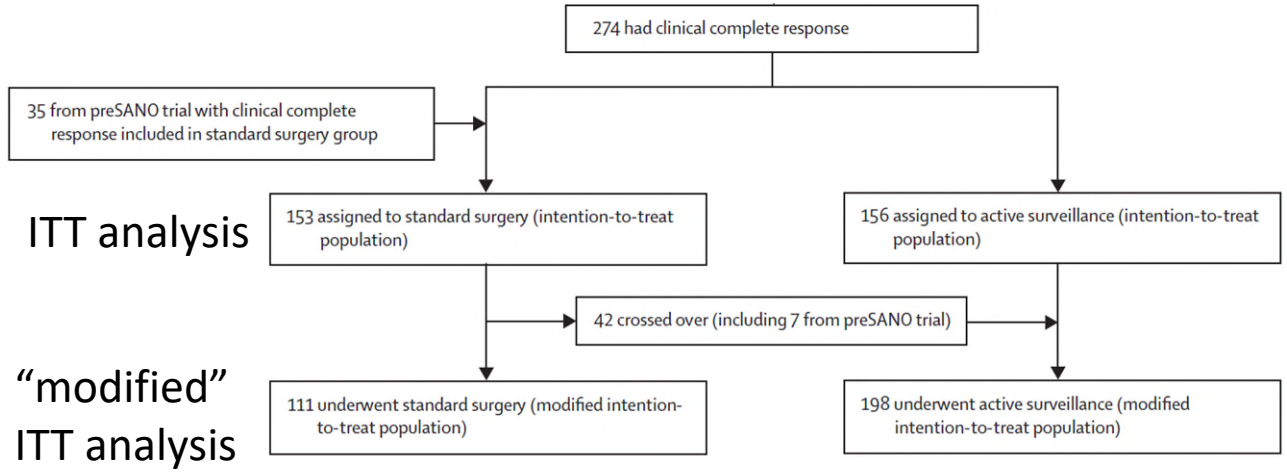
Table 3: **Sensitivity analysis for accuracy of residual tumour detection in clinical response evaluations and predictive value of the tumour regression grades**

NPV 45% means 55% false negative

Noordman BJ et al., Lancet Oncol 2018

Is post-CRT surveillance possible? SANO-1



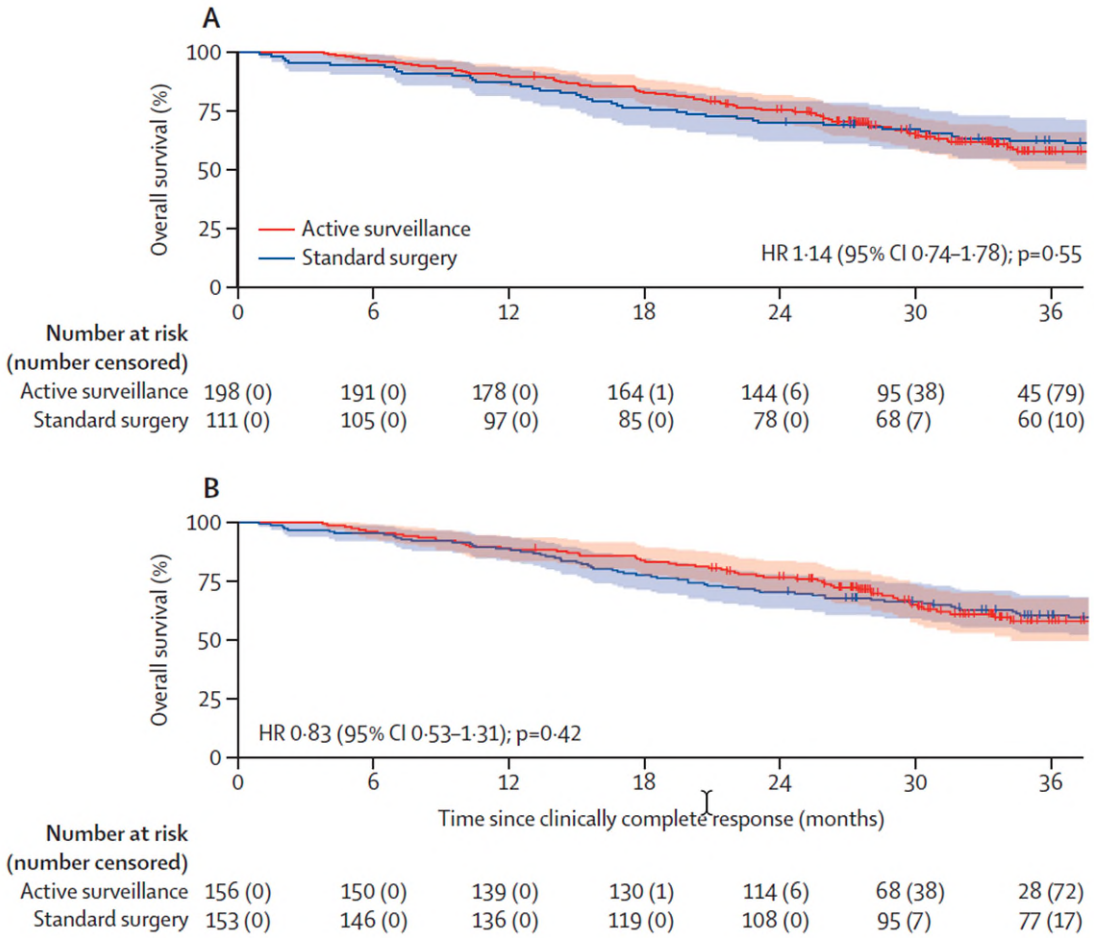


76% Adeno
21% SCCA
3% other

74% Adeno
24% SCCA
2% other

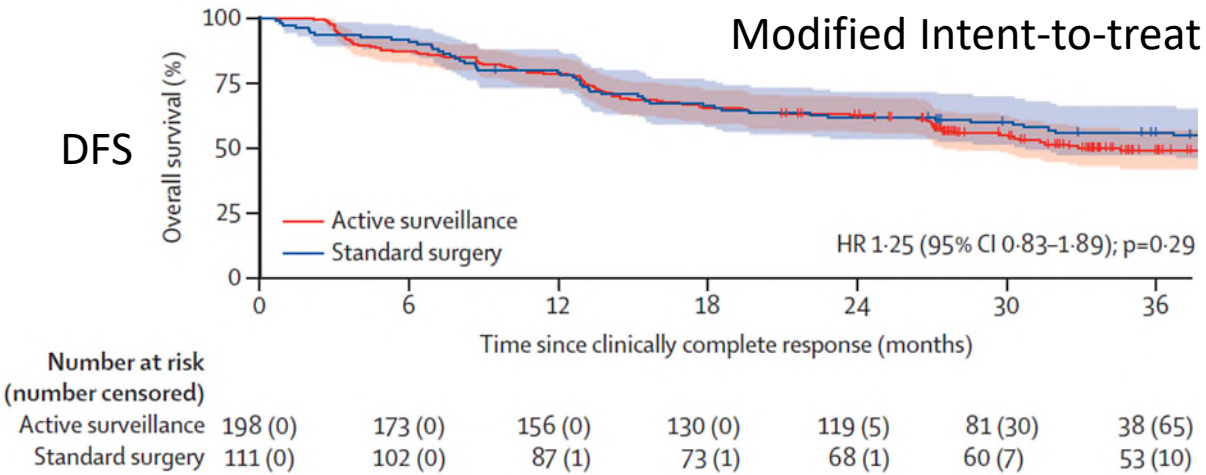
van der Wilk et al., Lancet Oncol 2025

Primary endpoint of SANO-1: AS is non-inferior to US



DFS

Modified Intent-to-treat



- Median DFS: 35 mos AS vs 49 mos US (HR 1.25, p=0.29)
- Distant mets (second PET after CRT): 43% AS vs 34% US (OR 1.45, p=0.18)

van der Wilk et al., Lancet Oncol 2025

POCs and HRQoL in the SANO-1 trial

	Active surveillance (n=83)	Standard surgery (n=101)
Any complication	68 (82%)	85 (84%)
Anastomotic leakage	18 (22%)	27 (27%)
Severity of anastomotic leakage		
Subclinical, spontaneous recovery	2 (2%)	3 (3%)
Subclinical, requiring surgery	1 (1%)	0
Clinical, spontaneous recovery	10 (12%)	15 (15%)
Clinical, requiring surgery	5 (6%)	9 (9%)
Pulmonary complications		
Any	39 (47%)	64 (63%)
Pneumonia	20 (24%)	29 (29%)
Respiratory failure requiring reintubation	2 (2%)	5 (5%)
Cardiac complications		
Any	28 (34%)	44 (44%)
Dysrhythmia requiring intervention	11 (13%)	20 (20%)
Vocal cord outcome		
Normal vocal cord	71 (86%)	94 (93%)
Vocal cord dysfunction, unilateral	3 (4%)	3 (3%)
Vocal cord dysfunction, bilateral	2 (2%)	1 (1%)
Unknown vocal cord dysfunction	7 (8%)	3 (3%)
Thromboembolic complications		
Pulmonary embolus	0	2 (2%)
Adverse events from clinical response evaluations		
PET-CT	0	0
Endosonography with fine-needle aspiration	1 (1%)	0
Endoscopy with biopsies	0	0
Chylothorax, requiring TPN	3 (4%)	10 (10%)
Chylothorax, requiring surgery	0	1 (1%)
Multi-organ failure	1 (1%)	1 (1%)
Length of ICU stay, days	2 (1–2)	2 (1–3)
Length of hospital stay, days	10 (8–17)	11 (8–17)
30-day mortality	1 (1%)	3 (3%)
90-day mortality	3 (4%)	5 (5%)

Data are n (%) or median (IQR). Percentages represent the occurrence of complications, as part of the total. TPN=total parenteral nutrition. ICU=intensive care unit.

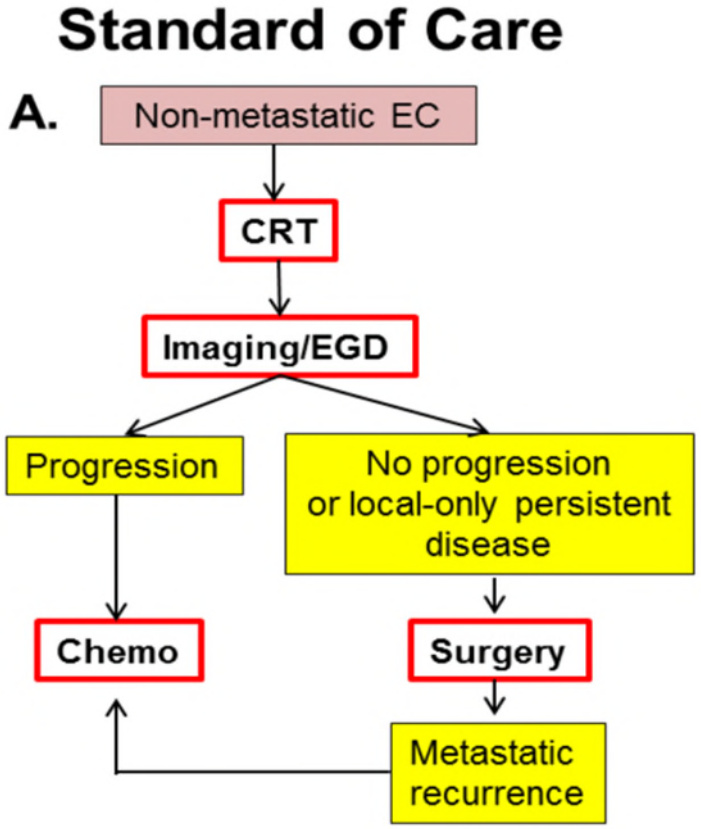
Table 2: **Postoperative complications and serious adverse events from clinical response evaluations of patients undergoing oesophagectomy**

- No difference in POCs comparing patients who underwent salvage surgery in the AS group at time of locoregional recurrence vs. those with US
- No differences in leak rates, length of hospitalization, postoperative mortality
- HRQoL better for AS in the first **6 mos after CRT** (increase of 10•4 [95% CI 4•1–16.5], p=0•0010, Cohen's *d*=0•58) and **9 months** (increase of 8•5 [2•0–15.0], p=0•0099, Cohen's *d*=0•47), but not SS at 12 mos, vs US.

van der Wilk et al., Lancet Oncol 2025

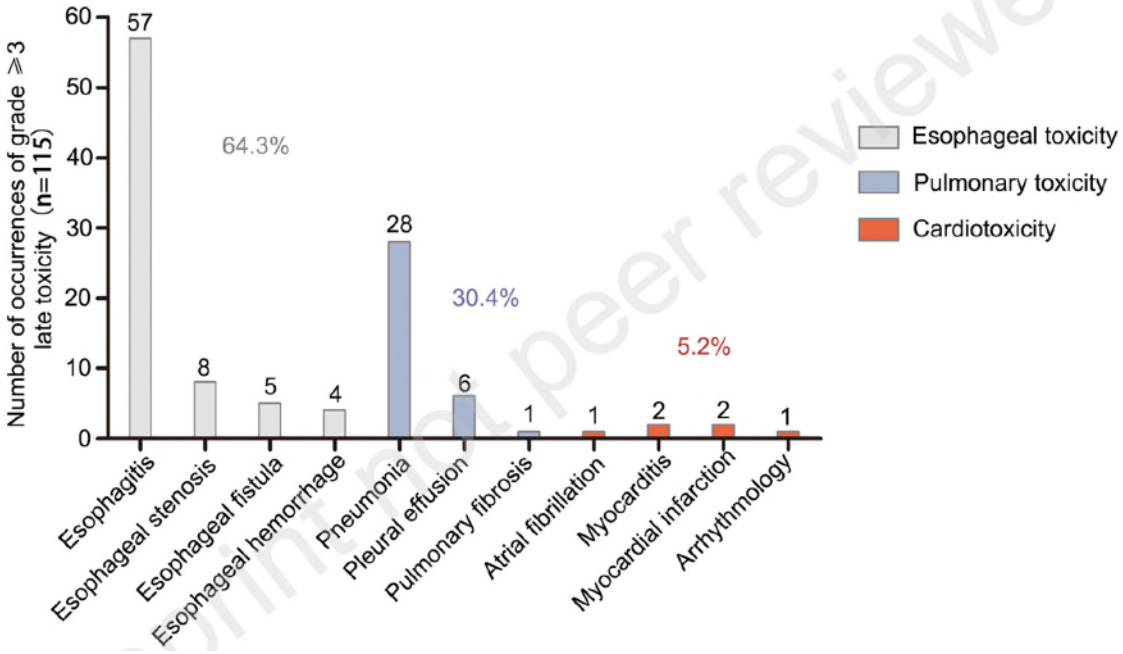
Drawbacks of organ preservation

- Current standards after CRT is a guess work using imperfect and imprecise measures of residual disease
    - **Even SANO-1 approach is just marginally better**
- Frequent surveillance using imaging and EGD increases inconvenience, patient anxieties, and cost
- Surveillance of patients with residual inapparent disease may theoretically lead to greater risk of distant dissemination
    - SANO trial: numerically higher DM in the surveillance arm
    - Rectal cancer using TNT and surveillance can increase DM risk (Fernandez et al. *Dis Colon Rectum* 2023)



Is dCRT adequate for functional organ preservation?

- In a HRQoL survey of 102 pts with CRT vs Surgery, dCRT had a lower impact than surgery, particularly in the domains of physical function, emotional function and general health situation (*LV et al., Mol Clin Onc 2014*)
    - Both decline in the first 6 months, but was restored after 6 months, but dCRT had superior HRQoL than Surgery
- Cross sectional survey across 1140 pts in 25 centers in China for ESCCA after CRT (*Dong et al., ASTRO 2024, preprint)*
    - Long term QoL assessment for those cured of dCRT without surgery were generally good (Global QoL of 80, functional score of >85, with appetite loss and dysphagia that persists years after CRT



Salvage surgery for locoregional recurrence after CRT

- If can be done, yields the best curative outcomes
- Salvage esophagectomy has long been viewed to be more toxic than upfront esophagectomy
- At high volume centers, salvage esophagectomy is done with long morbidity and mortality
- Should certainly be done with the most experienced surgeons

Salvage endoscopic therapy after local-only recurrence

- Luminal recurrence occurs in 14% of pts, or new lesions in 7% of pts with ESCCA
- Indicated for cT1a and cT1-2 residual or recurrent tumors (salvage EMR, ESD or strip biopsy)
- The en bloc resection rates ranged from 46%-100%, with strictures or perforations being the most severe complications
- 5-year survival after salvage local excision could be 30-50%.

Salvage reirradiation of local only recurrence after dCRT

- Last resort, mainly for those who refuses or are inoperable
- Series of using definitive CRT to 50 Gy, esophago-tracheal, esophago-bronchial fistula and esophageal perforation were identified as severe lethal comorbidities of re-CRT/RT occurring as high as 20-30% of the time
- The 5-year survival rates were 0%-3.1%
- Nowadays, NGS testing and systemic therapy is preferred over any consideration of reirradiation (MSI, claudin, HER-2)

Identifying the right patients for organ preservation

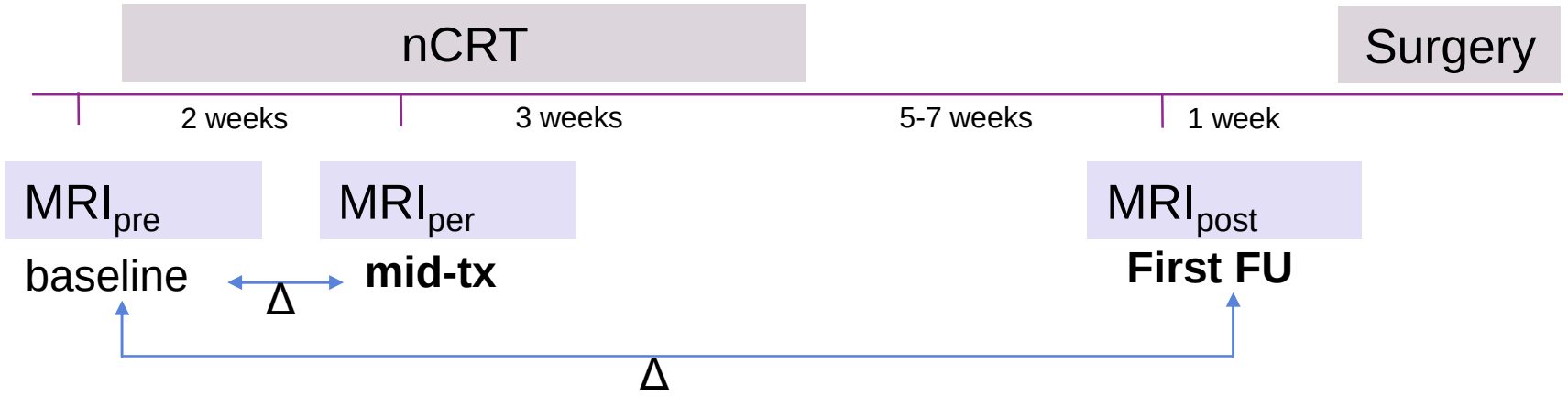
- **Improved Local response assessment**
  - o Accurate enough to predict complete treatment response early in the course of treatment in order to guide therapy
  - o Completeness of local response may determine the need for surgery after CRT
- **Better distant metastatic disease detection at the beginning of treatment**

(i.e. occult metastasis) **or after treatment (i.e. minimal residual disease)**

  - o Determine the need for or the effectiveness of systemic treatment for these patients before or after local therapy

PA13-0380: Prospective Trial at MDACC Evaluating DWI-MR for Pathologic Response in EC (50 ADC, 10 SCCA)

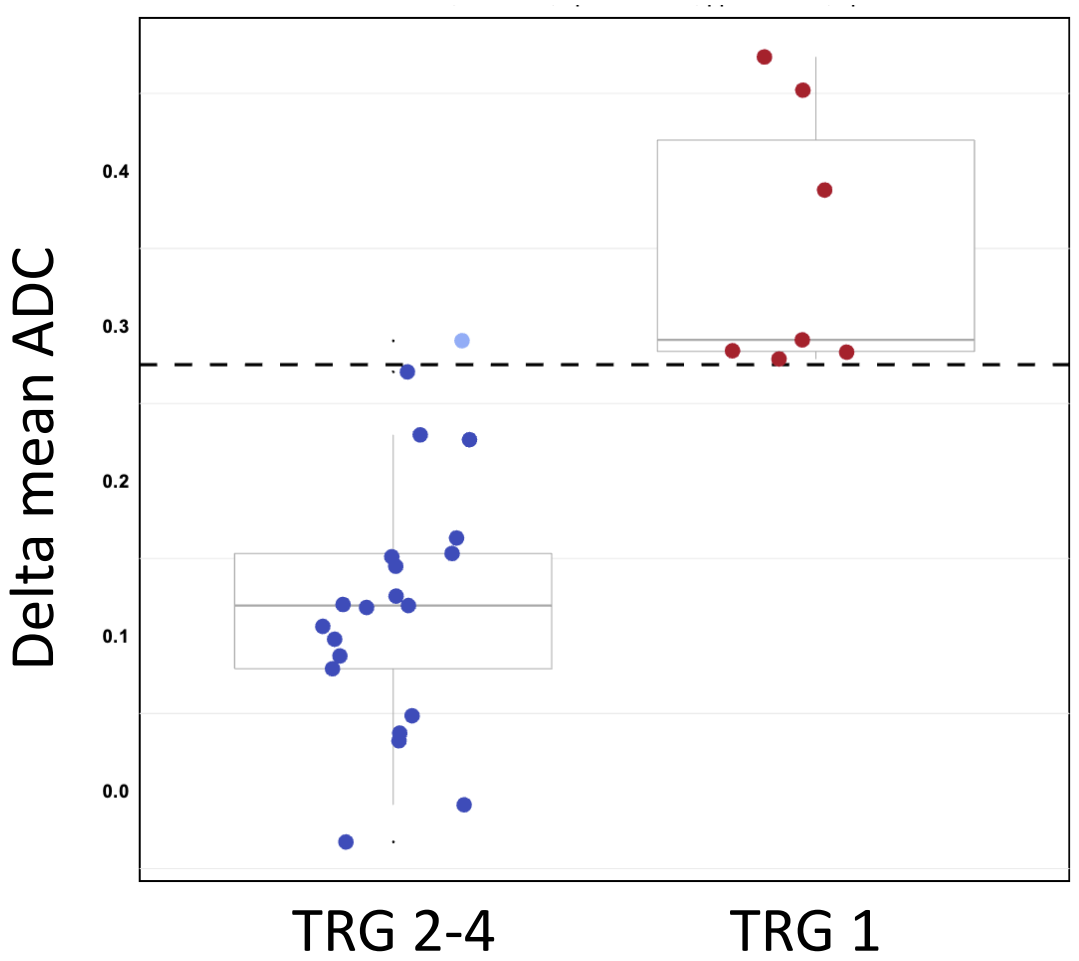
Schema

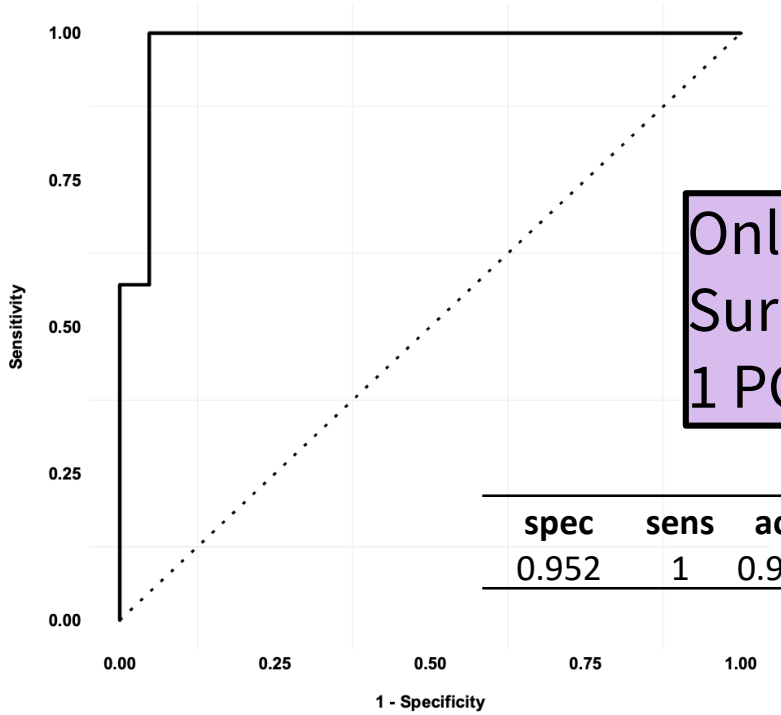


- Completed Accrual: 60 patients: 27 of 60 had surgery after CRT (Median F/U: 48 mos)
- MRI before, during, and after CRT
- **Scanner: GE MR750 3.0T scanner with 32-channel torso phase array coil**
- b-values: 0, 200, 800 s/mm^2 ; FOV 32 x 32 cm; TR/TE: 8000 / 100 ms ; 4 mm slices

Funded by R. Lee Clark Fellowship

27 patients had surgery after CRT, 7 patients had pCR
Δmean ADC-midtx associates strongly with pCR





Only 3 SCCA had Surgery;
1 PCR=37% ΔADC

spec	sens	acc	npv	ppv	fdr	auc
0.952	1	0.964	1	0.875	0.125	**0.98**

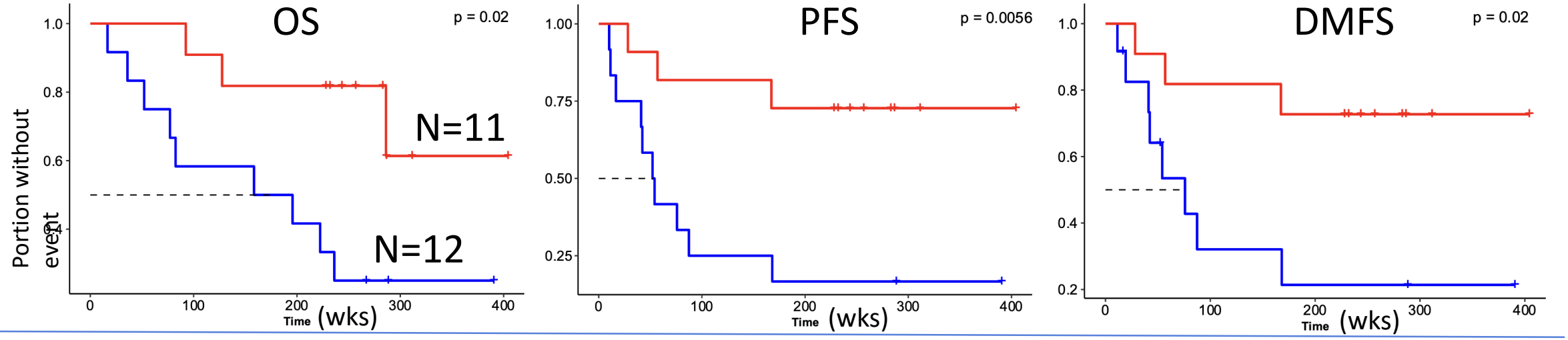
Lin et al: at ≥ 27.7% Δmean ADC, the AUC = 0.98

von Rossum et al:
At > 28% Δmean ADC, the AUC = 0.90

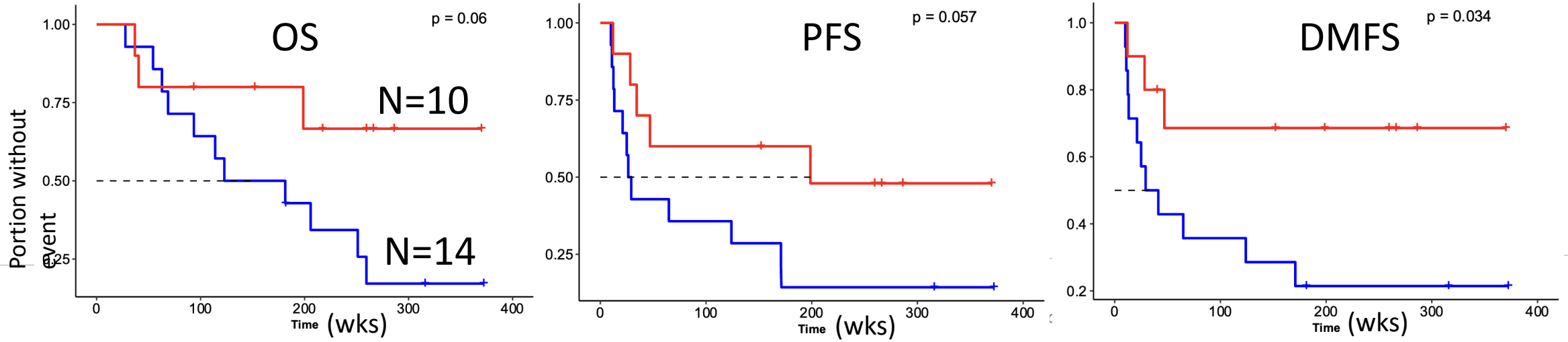
Under review

ΔADCmax > 0.116 strongly associated with outcomes stratified by surgical and non-surgical cohorts

Trimodality

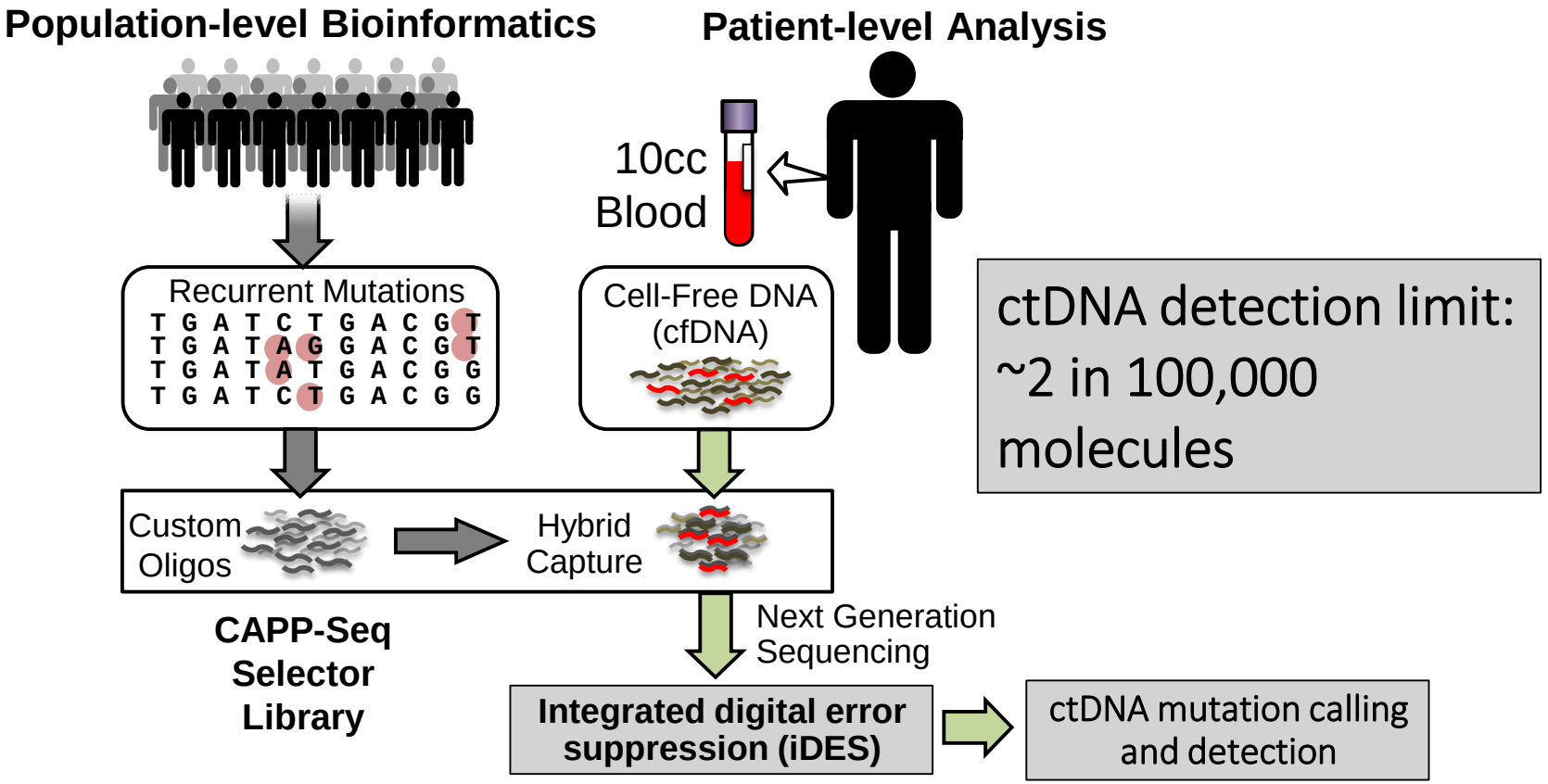


Bimodality



Under review

CAPP-Seq for ctDNA quantitation of MRD in EC



ctDNA detection limit: ~2 in 100,000 molecules

Customized CAPP-seq Esophagus Cancer selector: 607 genes, 757 mutated regions

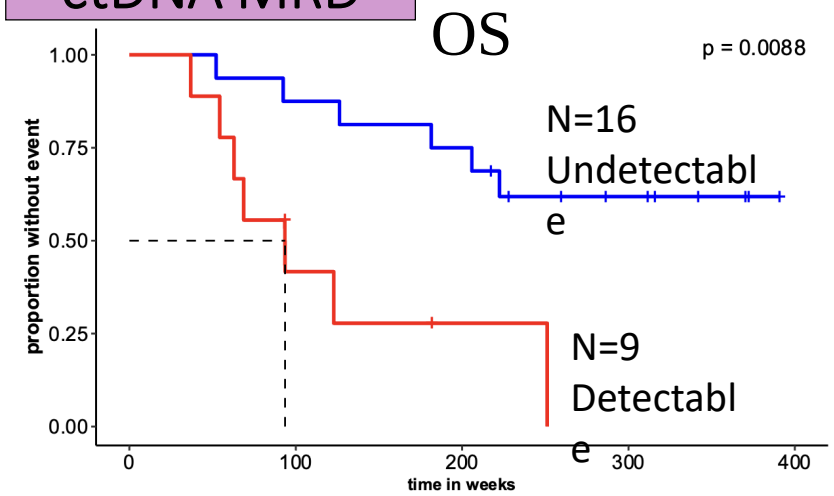
Azad, Lin, and Diehn et al. Gastroenterology 2020

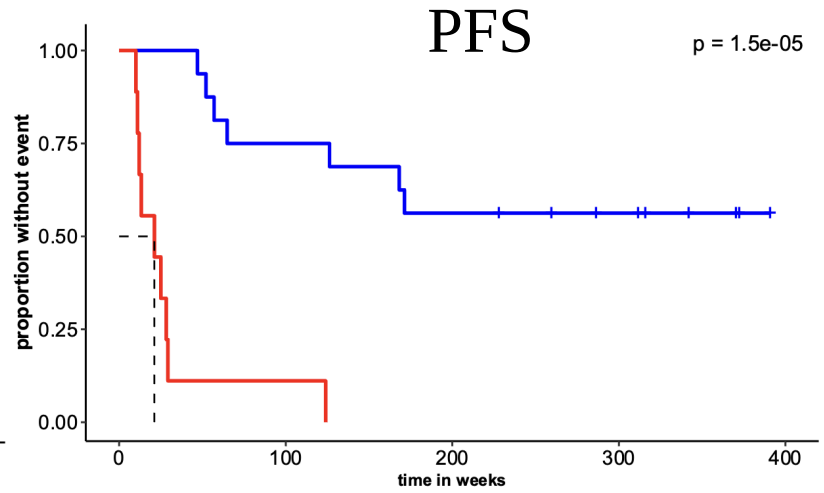
CAPP-Seq generates a <u>personalized</u> biomarker for every patient without the need for optimization

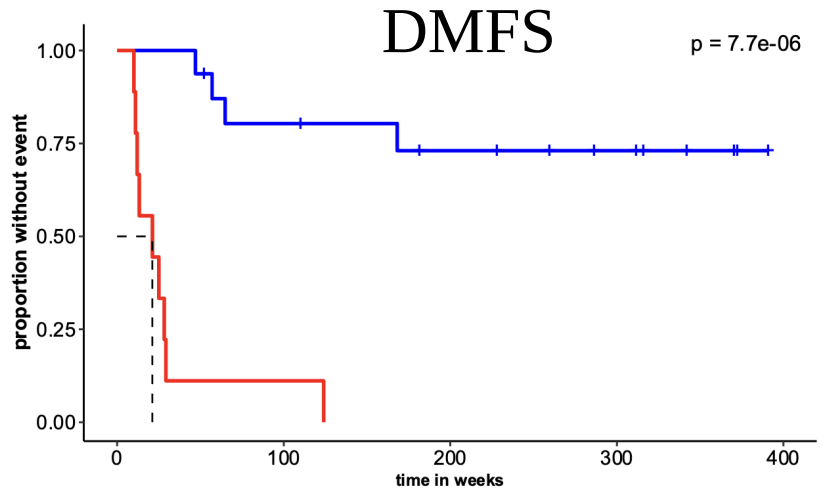
Newman & Bratman et al, Nat Med, 2014
Newman, Lovejoy & Klass et al, Nat Biotech, 2016

Both ctDNA MRD and dADCmax are <u>independent</u> predictors

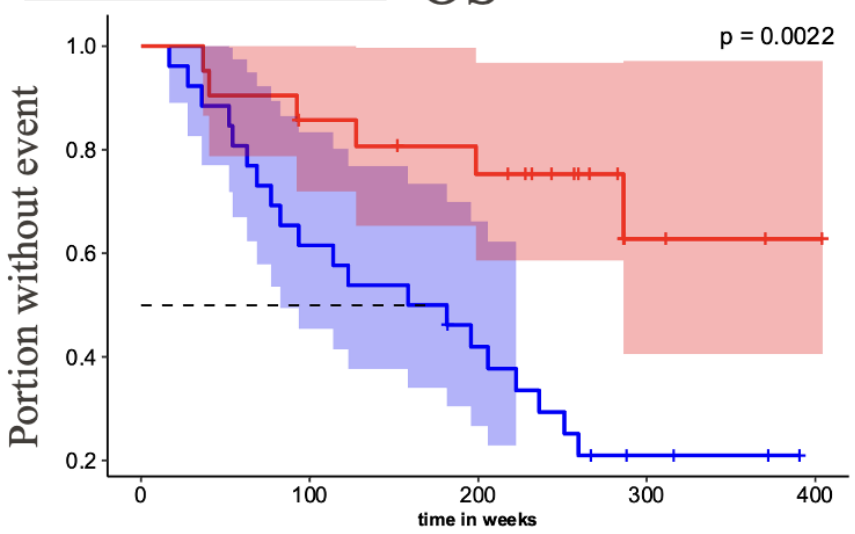
ctDNA MRD

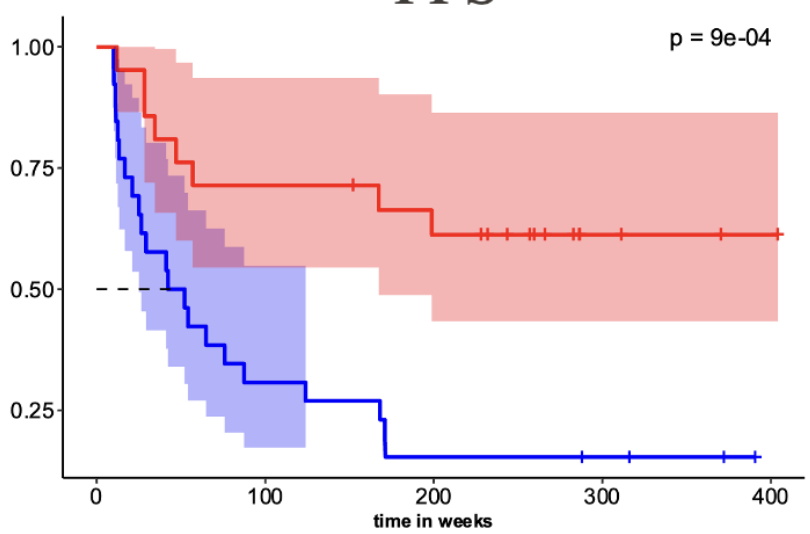


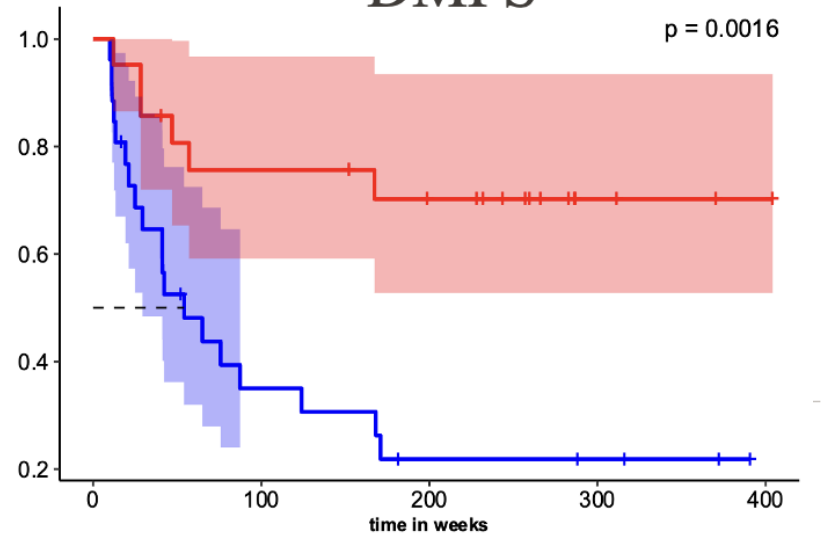




dADCmax



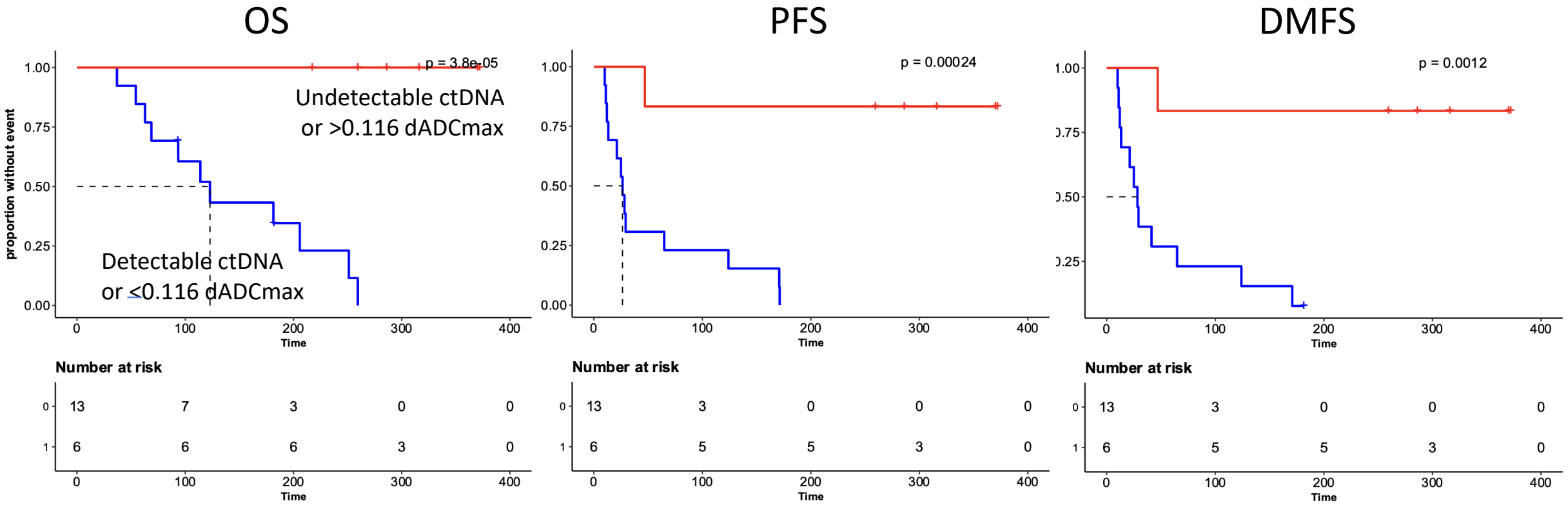




Under review

Combining ctDNA MRD with dADCmax improves detection of MRD after CRT: non-surgical cohort

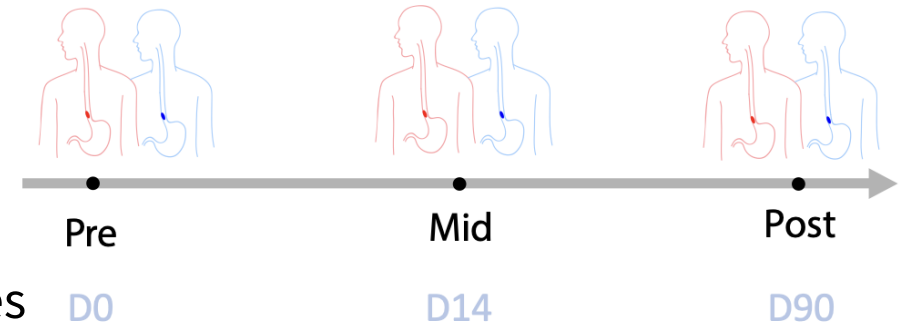
Non-surgical cohort

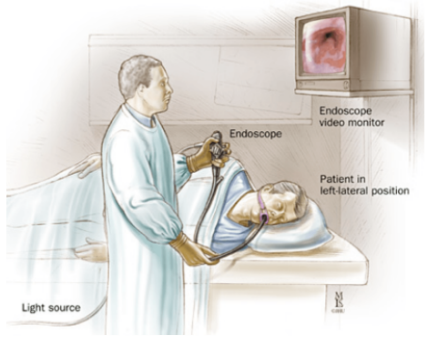


Combining ctDNA MRD and dADCmax > 0.116 improves prediction of outcomes after CRT

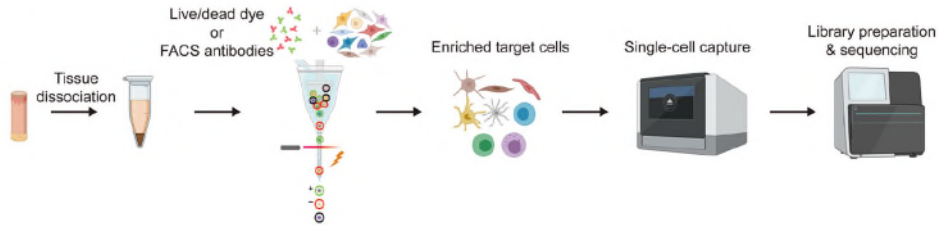
Under review

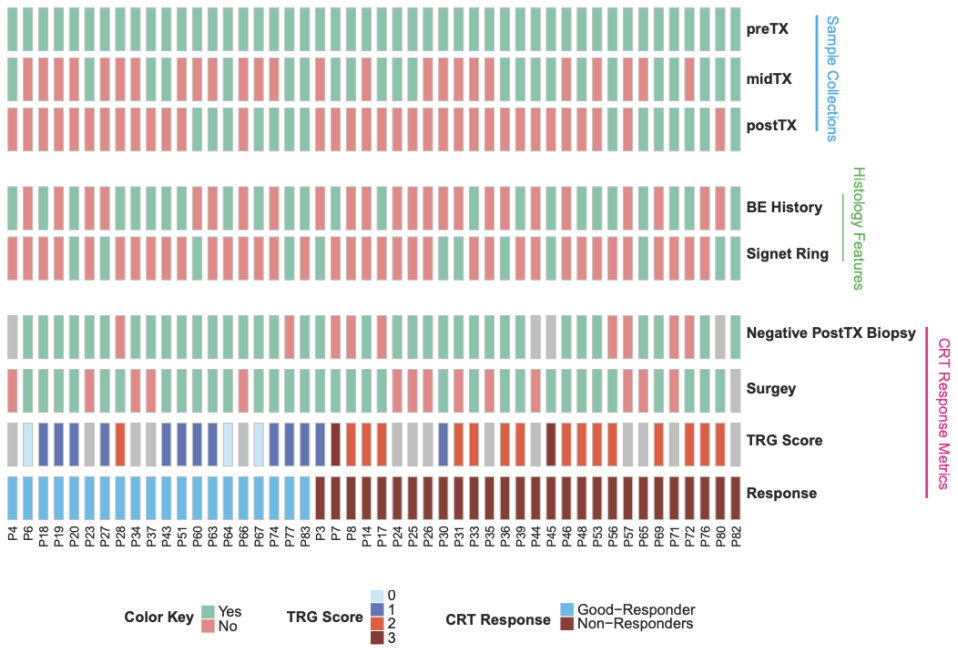
Understanding the biology of responders (pCR and/or no recurrence) vs non-responders after CRT (**all adenoca**)

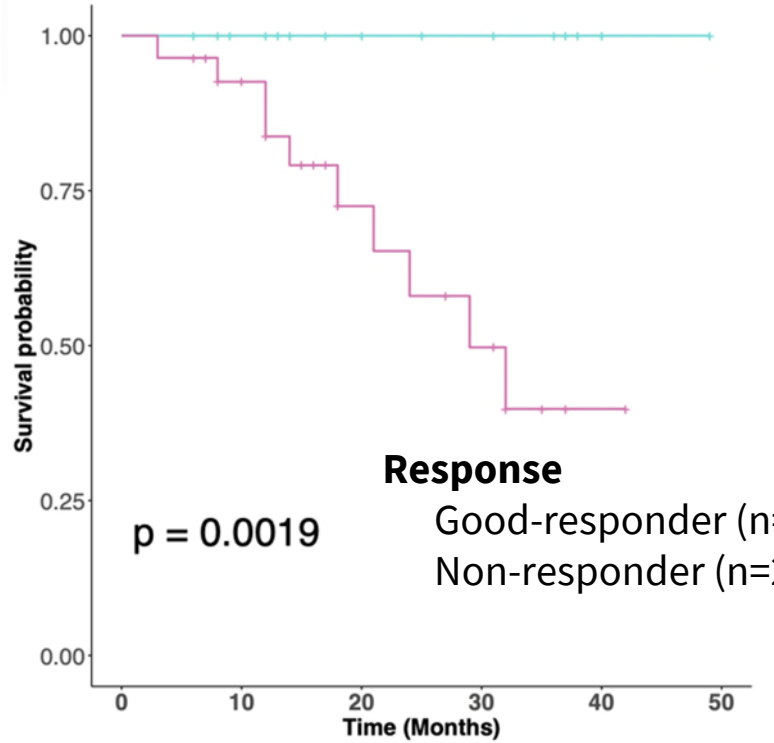




Single cell RNA seq from biopsies





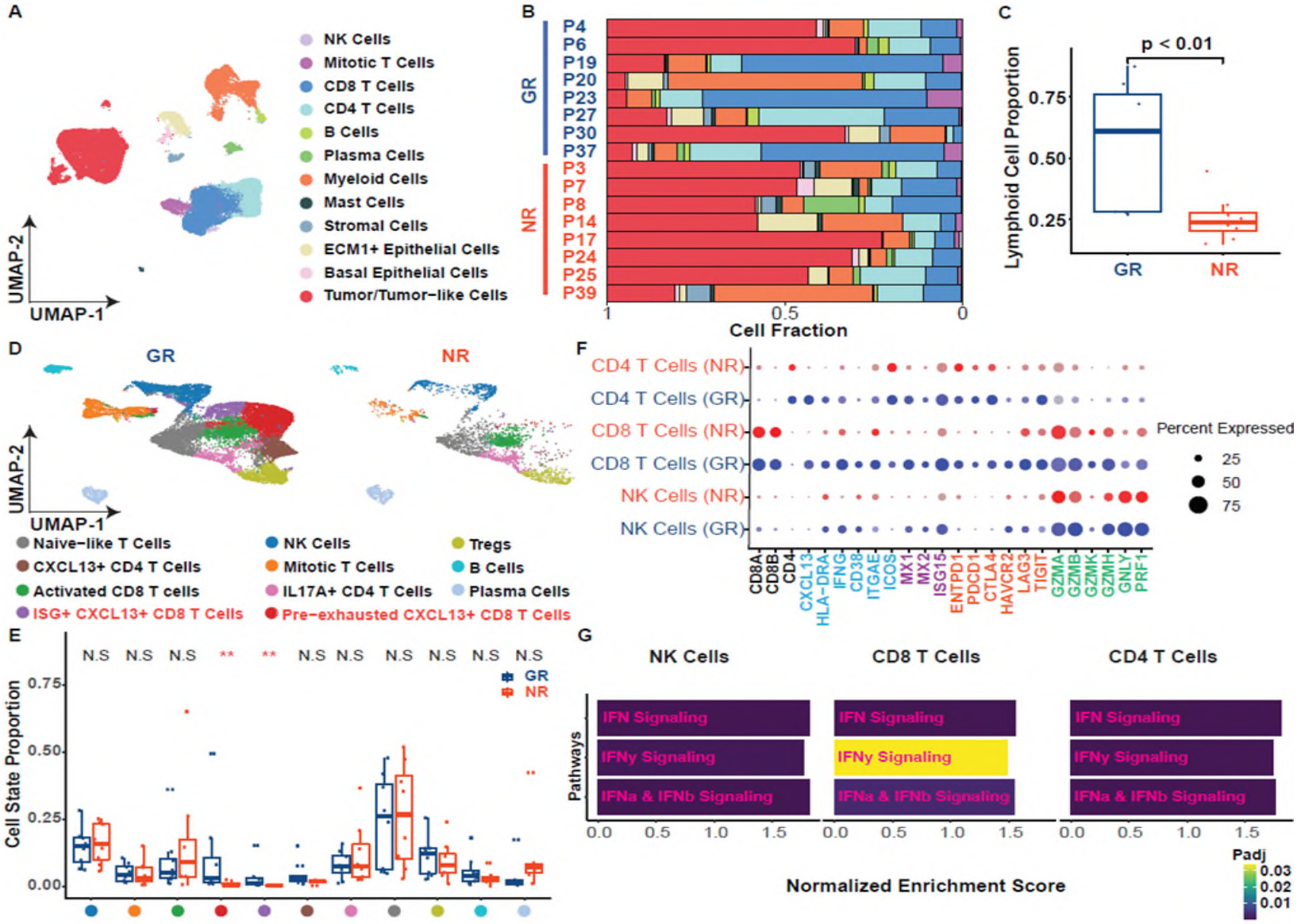


Response

Good-responder (n=20)

Non-responder (n=28)

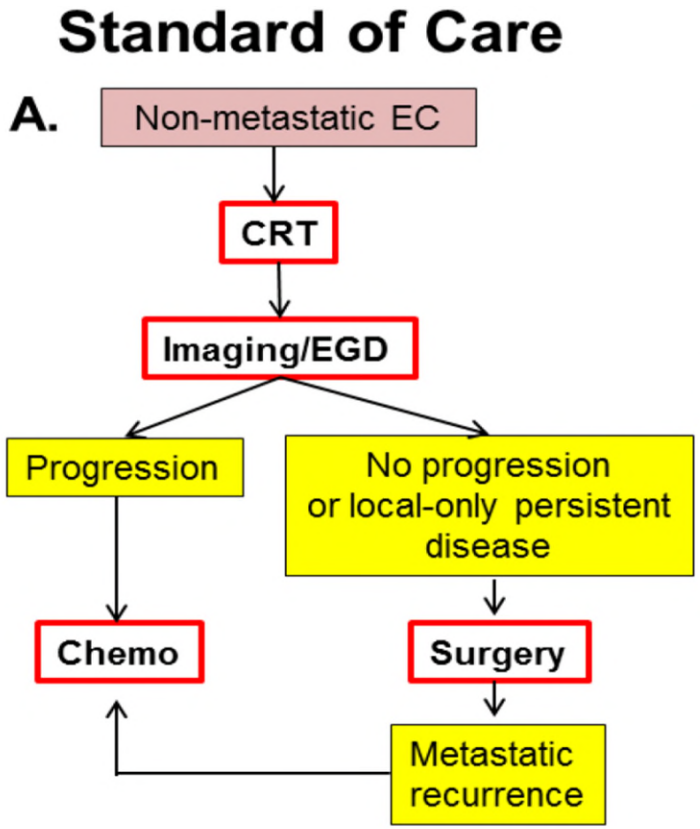
Pre-treatment TME shows activated lymphocytes enriched in the responders to CRT



Under review

DO NOT POST

Risk Stratified Selection of Therapy based on BOTH local tumor response and distant disease burden



Major RCTs of surveillance vs surgery after CRT without induction chemo (>1300 pts)

	Country (N)	Inclusion	Randomization Timepoint	Arms	Primary Endpoint	Status
SANO	Netherlands (300)	SCC or Adeno Esophagus/ GEJ	After chemoRT (only patients with CR)	A: ChemoRT* → surgery B: ChemoRT* → surveillance *41.4 Gy + carbo/taxol	OS (non-inferiority)	Accrual completed (2017-2023)
ESOSTRATE	France (188)	SCC or Adeno Esophagus/ GEJ	After chemoRT (only patients with CR)	A: ChemoRT* → surgery B: ChemoRT* → surveillance *regimen not specified	OS, DFS	Accrual completed (2016-2023)
CELAEC	China (176)	SCC Mid or lower esophagus	At diagnosis	A: ChemoRT* (42Gy) → surgery B: ChemoRT* (50Gy) → surveillance *CAPOX or Cis/5-FU or cape)	2-year DFS	Accruing (2016-
ESORES	Germany (670)	SCC or Adeno Esophagus	After chemo(RT) (all patients)	A: Chemo(RT)* → surgery B: Chemo(RT)* → response assessment → surveillance if CR, esophagectomy if < CR *regimen not specified	OS (non-inferiority), QOL	Accruing (2024-

Courtesy of Nina Sanford, ASCO GI 2025

1. *van der Wilk et al., Lancet Oncol 2025*
2. *https://clinicaltrials.gov/study/NCT02551458*
3. *Https://clinicaltrials.gov/study/NCT02972372*
4. *Hipp J et al., ASCO 2024*

Setting up for organ preservation: Trials to intensify systemic therapy prior to surgery or after CRT (if cCR)

Clinicaltrials.gov	Design	Eligibility	Regimen	Accrual goal	Attempt for organ preservation
NCT05713838 (**PRESTO**)	Single arm phase II	cT1, T2N0 adeno	FLOT+durva x 2 → CRT + durva → if cCR → durva maintenance	32	Yes
NCT05491616 (**SANO-3**)	Single arm phase II	cT2-4aN0-2M0 adeno or SCCA	CROSS → if cCR → nivolumab	77	Yes
NCT06161818 (**TNT-OES-2)**	Randomized phase II	cT2-4aN+ M0 adeno	FLOT x4 → CROSS → surgery vs. CROSS → surgery → FLOT x4	216	No
NCT04028167 (**Colorado, IIT**)	Single arm phase II	cT3-T4N0-N+ adeno	FLOT x4 → CROSS → surgery	40	No

Take Home Message

- Esophagectomy is life altering for many patients as part of “curative therapy”, so selective use for those who really need it will be the best use of this local modality
- CRT +/- systemic therapy is the only organ sparing curative therapy (for a subset of adenocarcinoma pts and for most squamous cell carcinoma pts)
- Organ preservation for esophageal cancer is behind rectal cancer, but we now have some evidence as well as ongoing trials that CRT with proper surveillance after cCR should be discussed as an option for patients
- Salvage local therapy can be well integrated into the AS paradigm
- Advanced imaging, tumor and circulating biomarkers has the potential to further risk stratify patients for personalized therapy that will improve QoL and disease outcomes

Thank you!