BARCELONA 2024 ESMO congress

Neoadjuvant chemotherapy in MSS colon cancer: Who, what and for how long?

Jenny Seligmann

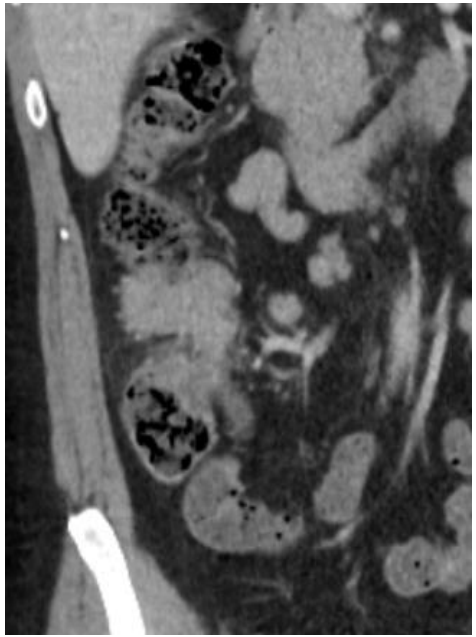
Leeds, United Kingom

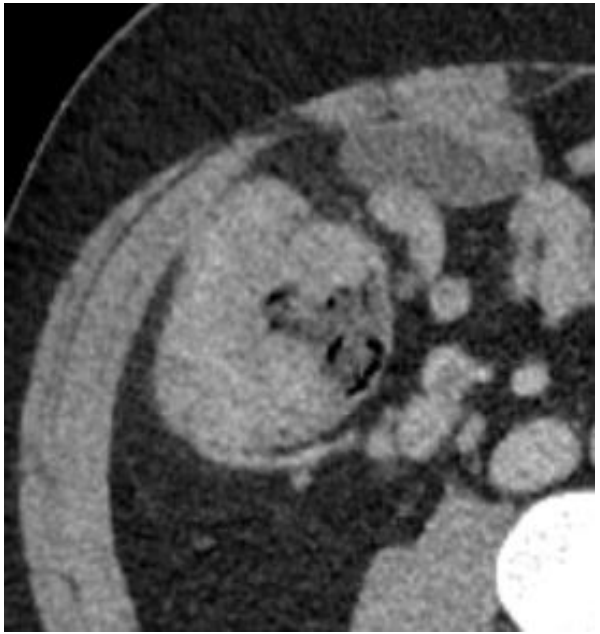
DECLARATION OF INTERESTS

Jenny Seligmann

Consultancy/ Advisory:	Astra-Zeneca, Boehinger-Ellison, BMS, GSK, Pierre Fabre Medicament, Merck Serono, Seagen, Servier, Takeda,
Speaker Fees:	GSK, Merck Serono, Pierre Fabre Medicament, Servier, Takeda
Research Funding:	Amgen, Pierre Fabre Medicament, Merck-Serono, GSK
Travel:	Takeda
CME:	GI Connect, OncLive

How should this patient be treated?



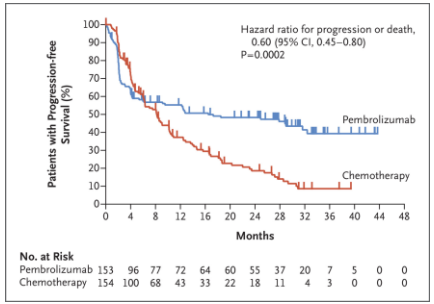


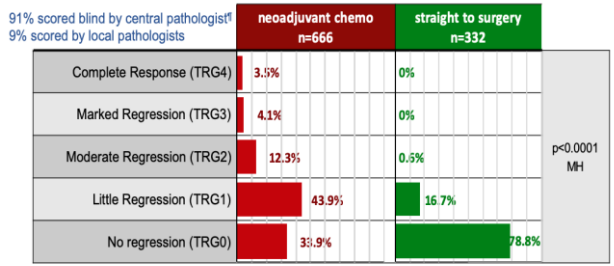
- 1st presentation
- Fit for surgery & systemic therapy
- No metastatic disease

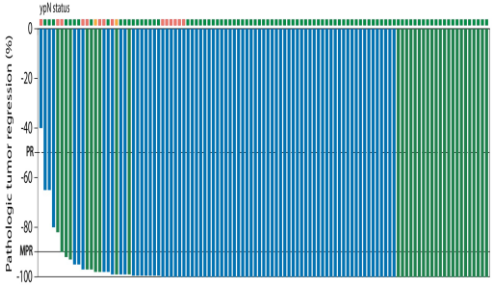
MSI status is critical in LACC

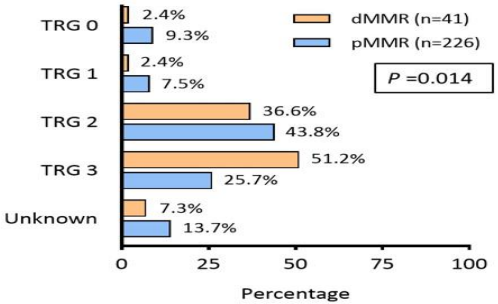
Immunotherapy works for MSI-H!

….Chemotherapy less helpful for MSI-H







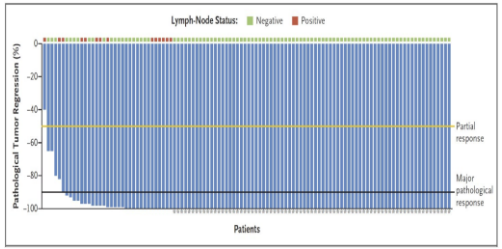


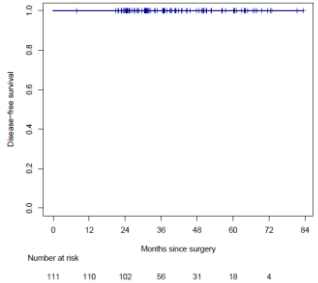
MSS & MSI need to be developed separately….

BARCELONA 2024 ESMO congress

Andre, NEJM, 2021; Chalabi, NEJM, 2024; Morton, JCO, 2022; Deng, JCO, 2024

Neoadjuvant immunotherapy





Neoadjuvant chemotherapy

Neoadjuvant treatment for MSS LACC: from evidence generation to implementation

- Why neoadjuvant chemotherapy can help make gains in the MSS population
- Who should we prioritise?
- What do we give and for how long?
- Implementation

What is wrong with the status quo?

Stage III defined by post-operative TNM stage having Surgery & adjuvant chemo by ESMO Guidance Standard

Problem

Have disease recurrence despite current SOC

Need:

New treatment strategies beyond current SOC

Could neoadjuvant treatment improve outcomes?

Potential advantages & disadvantages of a neoadjuvant therapy in LACC

- Positive experience in other cancers
- Early treatment of micro-metastases
- Downstaging for complete surgical resection
- Prime anti-tumour response when tumour microenvironment intact and tumour antigen heterogeneity may be minimal

- Will patients not proceed to surgical resection?
  - PD in neoadjuvant window
  - Chemotherapy toxicity
- Will NAC lead to an increase in peri-operative complications?
- Can we select appropriate patients for neoadjuvant therapy using radiological staging assessment?

Battaglin F,Clin Adv Hematol Oncol, 2018

Neoadjuvant Chemotherapy in LACC

original reports

Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial

Dion Morton, MD[1]; Matthew Seymour, MD[2]; Laura Magill, PhD[3]; Kelly Handley, PhD[3]; James Glasbey, MD[1]; Bengt Glimelius, MD[4]; Andy Palmer[3]; Jenny Seligmann, MD[2]; Søren Laurberg, MD[5]; Keigo Murakami, MD[6]; Nick West, MD[6]; Philip Quirke, FMedSci[6]; and Richard Gray, MSc[7]; on behalf of the FOxTROT Collaborative Group

RANDOMIZED CONTROLLED TRIAL

Perioperative FOLFOX 4 Versus FOLFOX 4 Plus Cetuximab Versus Immediate Surgery for High-Risk Stage II and III Colon Cancers

A Phase II Multicenter Randomized Controlled Trial (PRODIGE 22)

M. Karoui, MD, PhD,[*]✉ *A. Rullier, MD,*[†] *G. Piessen, MD, PhD,*[‡] *J. L. Legoux, MD,*[§] *E. Barbier, MD,*[¶] *C. De Chaisemartin, MD,*[‖] *C. Lecaille, MD,*[**] *O. Bouche, MD, PhD,*[††] *H. Ammarguellat, MD,*[‡‡] *F. Brunetti, MD,*[§§] *M. Prudhomme, MD, PhD,*[¶¶] *J. M. Regimbeau, MD, PhD,*[‖‖] *O. Glehen, MD, PhD,*[***] *A. Lievre, MD, PhD,*[†††] *G. Portier, MD, PhD,*[‡‡‡] *J. Hartwig, MD,*[§§§] *G. Goujon, MD,*[¶¶¶] *B. Romain, MD, PhD,*[‖‖‖] *C. Lepage, MD, PhD,*[****] *and J. Taieb, MD, PhD*[††††],

2022 ASCO ANNUAL MEETING

Perioperative Chemotherapy With mFOLFOX6 or CAPOX for Patients With Locally Advanced Colon Cancer (OPTICAL): A Multicenter, Randomized, Phase III Trial

Huabin Hu, Meijin Huang, Yunfeng Li, Ziqiang Wang, Xiaozhong Wang, Ping Liu, Ruyi Zhang, Hao Zhang, Zhongcheng Huang, Haiping Pei, Yongming Zeng, Jiajun Lai, Wenbin Chen, Jiansi Chen, Zhijie Ding, Hongbo Wei, Qingwen Xu, Jigui Chen, Jianping Wang, Yanhong Deng✉

2023 ASCO ANNUAL MEETING

Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer

The Scandinavian **NeoCol** trial

BARCELONA 2024 ESMO congress

Morton et al, JCO 2023; Karoui et al, Ann Surg 2020; Hu et al, JCO, 2024, Jensen, ASCO Annual Meeting 2023

Delivery of NAC

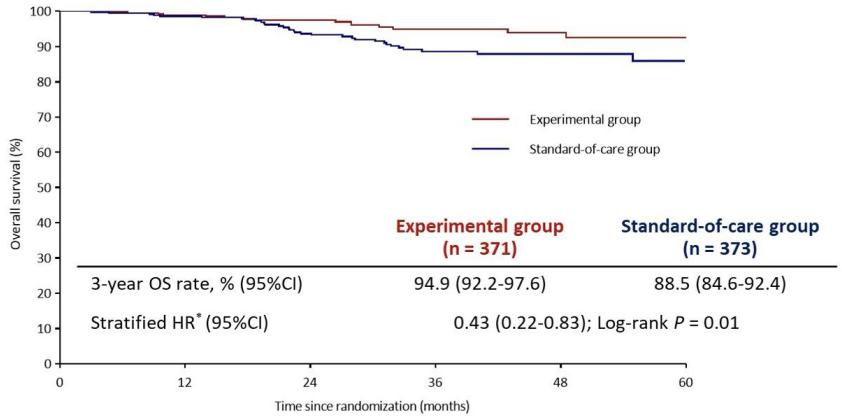
Study	No of patients	Median age	% pts with rT4	% pts with rN +ve	Completed NAC	Peri-op safety
FOxTROT	1052	65	25.5%	75.3%	90%	✓
PRODIGE -22	104	63.5	11.5%	76.9%	96%	✓
OPTICAL	738	56	75.4%	77.2%	62%	✓
NEOCOL	250	66	26%	-	-	✓

Morton et al, JCO 2023; Karoui et al, Ann Surg 2020; Hu et al, JCO, 2024, Jensen, ASCO Annual Meeting 2023

Randomized trials of neoadjuvant chemo in LACC

Study	Downstaging	R0 resection (NAC vs	3 year DFS (NAC vs STS)	MSI/MMR data available
FOxTROT (n=1052)				
PRODIGE-2 (n=104)				
OPTICAL (n=744)				
NEOCOL (n=250)	✓	✓	93% vs 90%	*P=0.98*

Overall Survival (OS) in mITT Population



	Experimental group (n = 371)	Standard-of-care group (n = 373)
3-year OS rate, % (95%CI)	94.9 (92.2-97.6)	88.5 (84.6-92.4)
Stratified HR* (95%CI)	0.43 (0.22-0.83); Log-rank *P* = 0.01	

Number at risk (number censored)						
Experimental group	371 (0)	319 (49)	233 (130)	132 (227)	71 (287)	16 (340)
Standard-of-care group	373 (0)	321 (50)	251 (103)	155 (189)	80 (262)	15 (327)

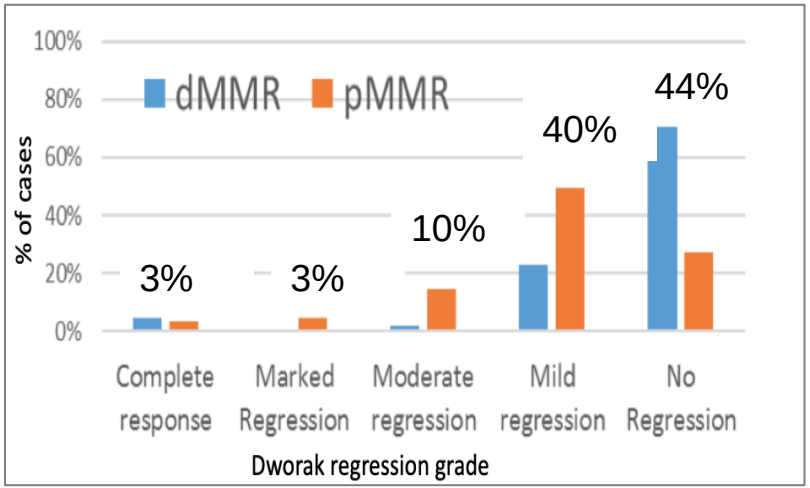
** Stratified factors included center, clinical T stage (cT3 vs cT4), clinical N stage (cN0 vs cN1-2*

BARCELONA 2024 ESMO congress

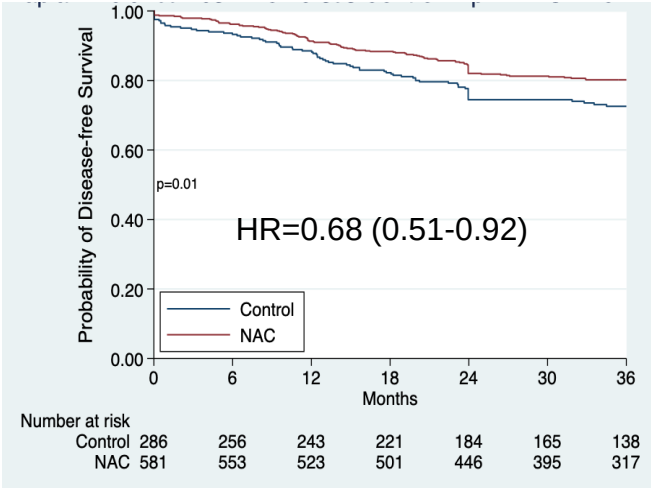
Morton et al, JCO 2023; Karoui et al, Ann Surg 2020; Hu et al, JCO, 2024, Jensen, ASCO Annual Meeting 2023

FOxTROT Trial: Outcomes for pMMR patients

- MMR status available for 914/1052 (86.8%) of patients
- 20.2% dMMR; 79.8% pMMR or unknown



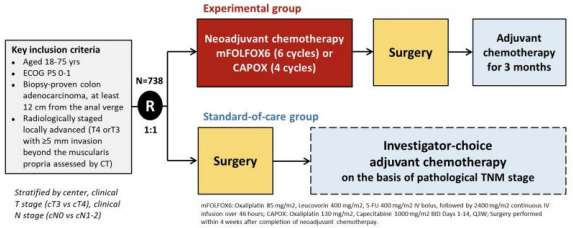
3 year DFS: NAC vs Upfront surgery MSS pts (80.7% vs 75.8%)



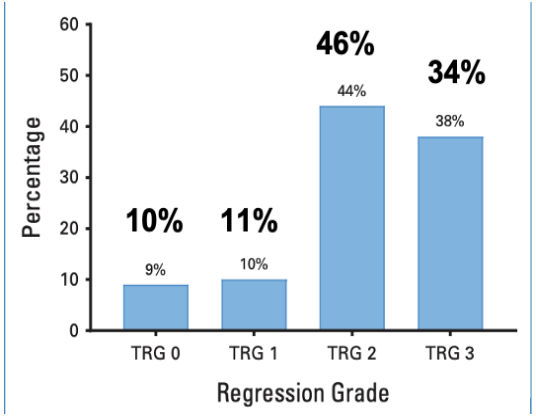
Morton et al, JCO, 2023

OPTICAL Trial: Outcomes for pMMR patients

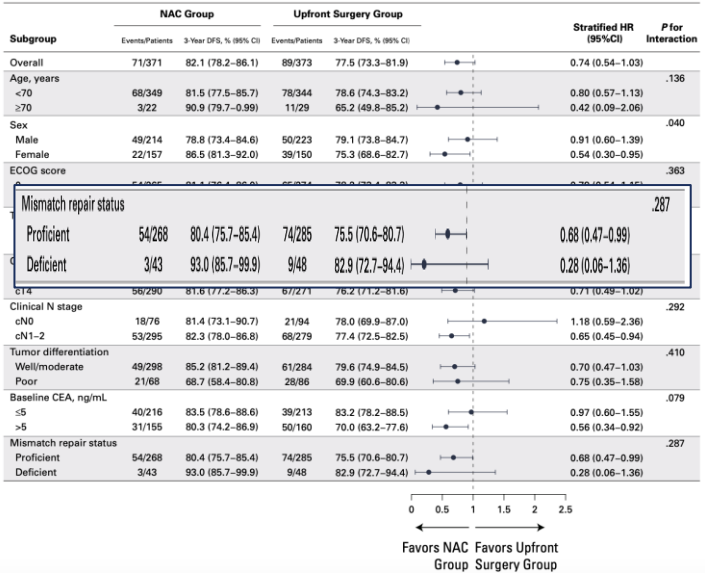
- MMR status available for 87% of patients



Pathological response rates in pMMR patients treated with NAC



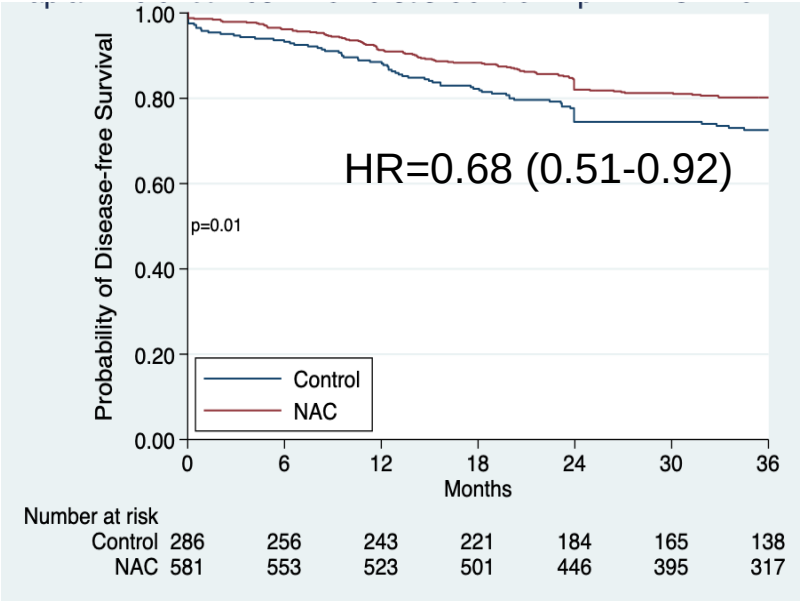
3 year DFS for NAC vs upfront surgery in MSS pts = 79.9% vs 74.0% (HR = 0.68 [0.61-0.99])



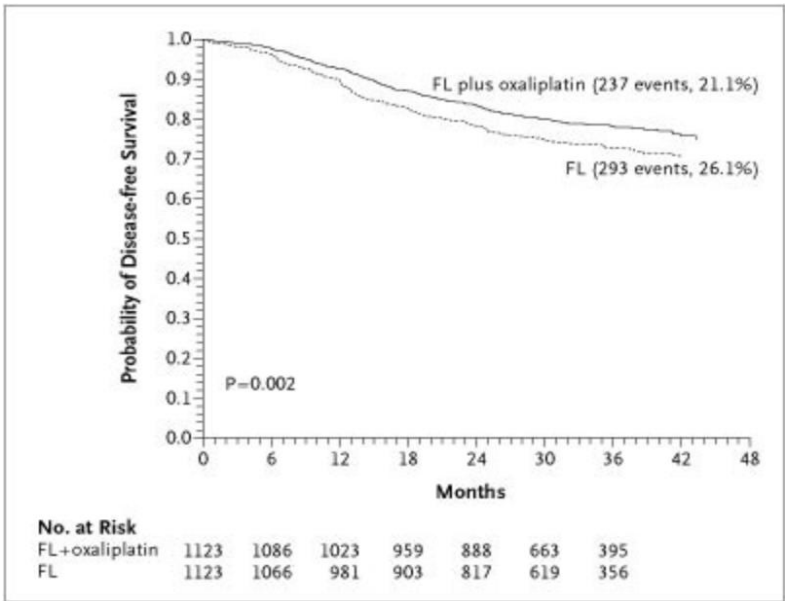
Hu et al, JCO, 2024

What effect is needed to change practice – 3 yr DFS?

NAC vs Upfront surgery MSS pts (5.3%)



Addition of oxaliplatin to 5FU (5.3%)

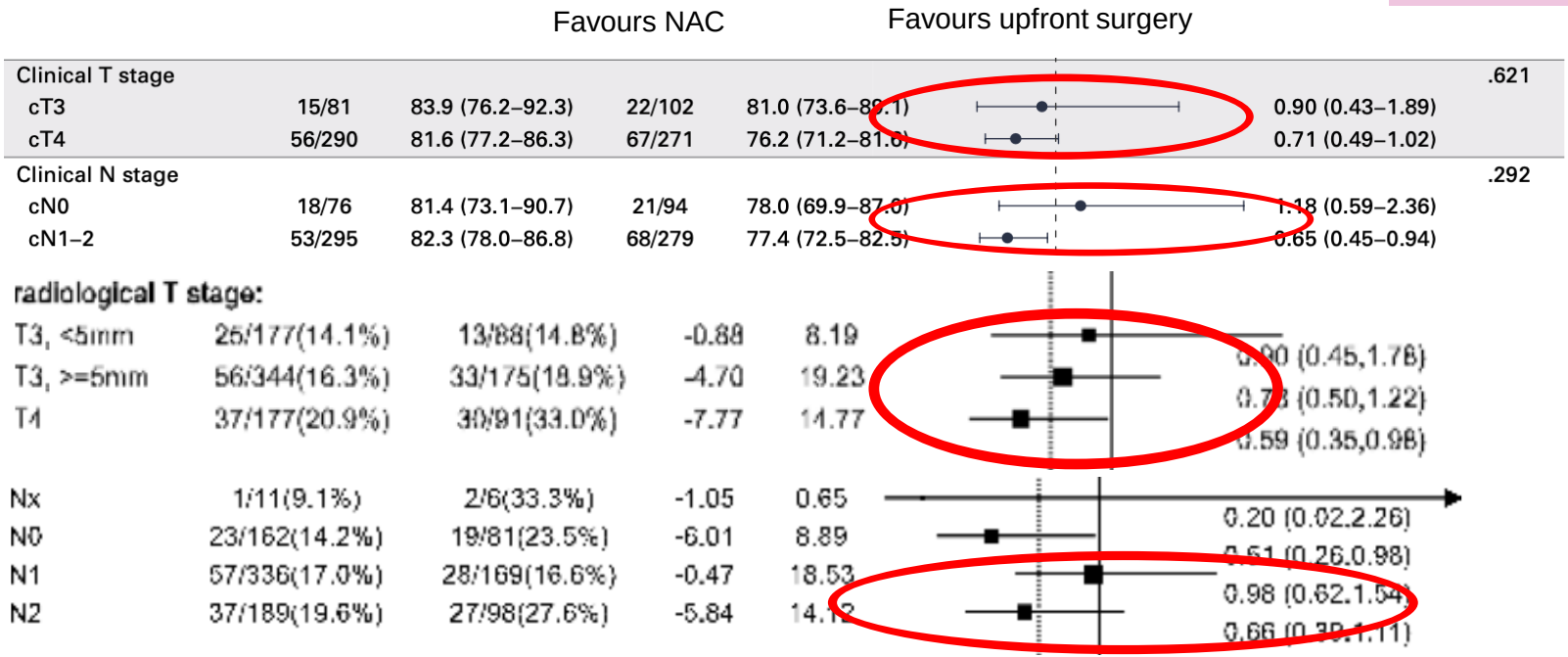


Morton et al, JCO 2023, Andre, NEJM, 2004

Do some patients benefit more from NAC?

Subgroup analysis from OPTICAL and FOxTROT

Highest risk clinically staged tumors appear to benefit MOST from NAC

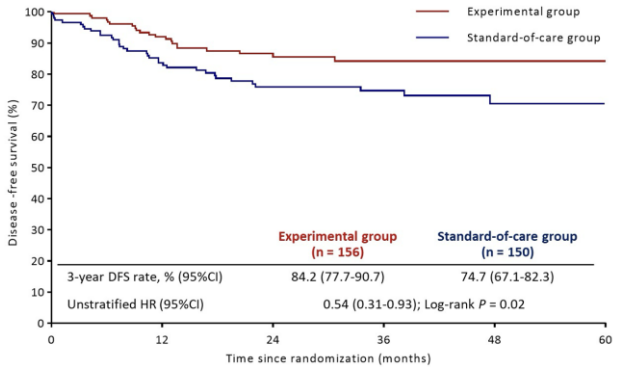


Do some patients benefit more from NAC?

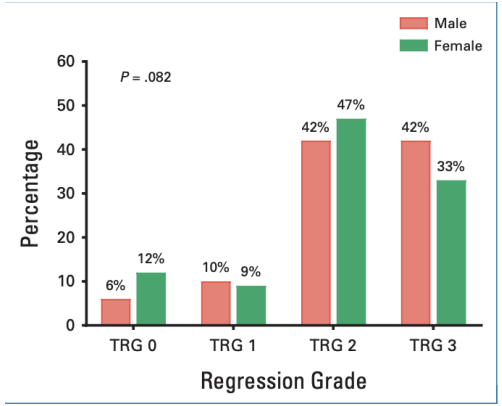
Subgroups Analysis on DFS

	Experimental group		Standard-of-care group		Hazard ratio (95% CI)	*P* for interaction
	Events / patients	3-year DFS (95% CI)	Events / patients	3-year DFS (95% CI)		
Age, years						0.069
≤50	22/121	78.1 (69.7-86.5)	35/123	68.1 (58.5-77.7)	0.56 (0.33-0.96)	
>50	46/250	78.6 (72.7-84.5)	44/250	80.5 (75.2-85.8)	1.04 (0.69-1.58)	
Sex						0.049
Male	47/215	74.5 (67.6-81.4)	44/223	77.8 (71.7-83.9)	1.09 (0.72-1.64)	
Female	21/156	84.2 (77.7-90.7)	35/150	74.7 (67.1-82.3)	0.54 (0.31-0.93)	
ECOG performance status						0.369
0	51/265	77.1 (71.2-83.0)	57/274	77.0 (71.5-82.5)	0.91 (0.63-1.33)	
1	17/106	81.7 (73.3-90.1)	22/99	75.0 (65.0-85.0)	0.65 (0.35-1.23)	

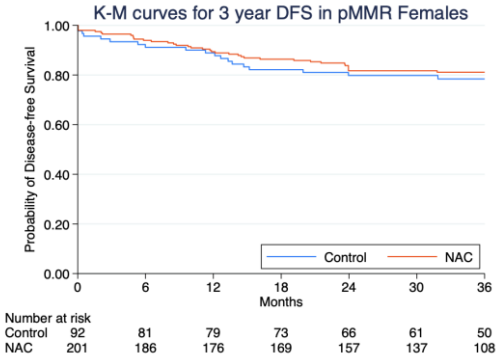
DFS in Subgroup of Female Patients



Pathological response post NAC by sex



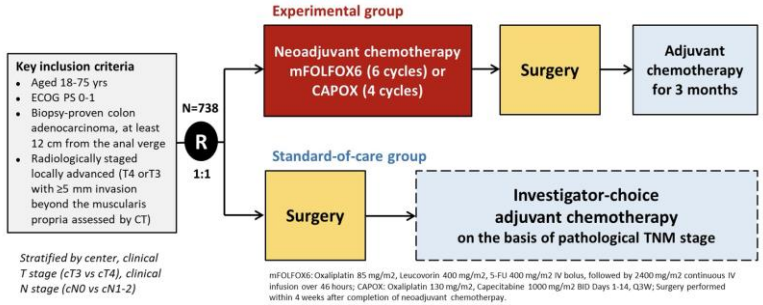
Same effect not seen in FOxTROT



BARCELONA 2024 ESMO congress

Hu et al, JCO, 2024;

What NAC to give?



- 70% received FOLFOX
- 30% received CAPOX

	mFOLFOX6 (n = 238)			CAPOX (n = 102)		
Adverse Events	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any adverse event	223 (94)	63 (26)	16 (7)	86 (84)	17 (17)	2 (2)
Serious adverse events	0	12 (5)	4 (2)	0	2 (2)	2 (2)

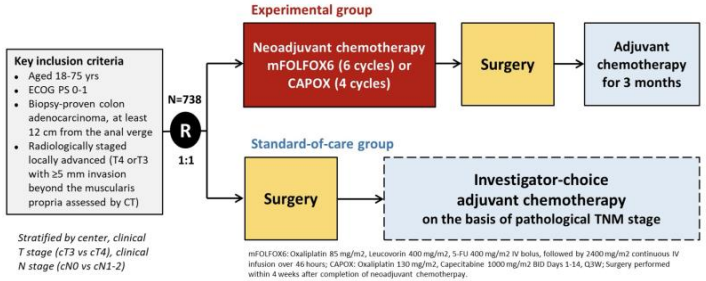
Most common grade 3/4 were neutropenia (16%) & anemia (11%)

Most common grade 3/4 were anemia (5%) & hand-foot (5%)

BARCELONA 2024 ESMO congress

Hu et al, JCO, 2024

What NAC to give?



- No results on differential efficacy
  No data on diarrhea rates
- All patients were planned to have 6 months duration of treatment

Delivering either drug reasonable, but:

- Consider baseline characteristics of patients as per adjuvant chemo choices
- Less confidence in applicability to older patients/ co-morbidities
- Consider duration of planned treatment as per IDEA recommendations

Hu et al, JCO, 2024

How much pre-operative treatment to give?

6 weeks (FOxTROT)

- pCR rate of 2.3%
- 44% no response
- 90% completed planned chemotherapy
- 3 year DFS = 81%

👍 Well tolerated

👎 Lower rates of pathological response

Stop/ start impact

12 weeks (OPTICAL)

- pCR rate of 10%
- 34% no response
- 62% completed planned chemotherapy
- 3 year DFS = 79.9%%

👍 Higher pCR rate for those who completed

Deliver total neoadjuvant treatment

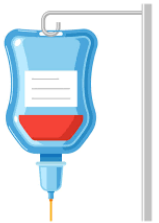
👎 Poorer compliance

Higher rate of symptomatic progression

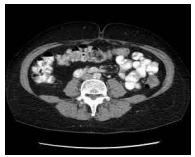
Duration of pre-operative treatment: speculation

MDT review of diagnosis & staging

6 weeks



Clinical assessment of treatment strategy



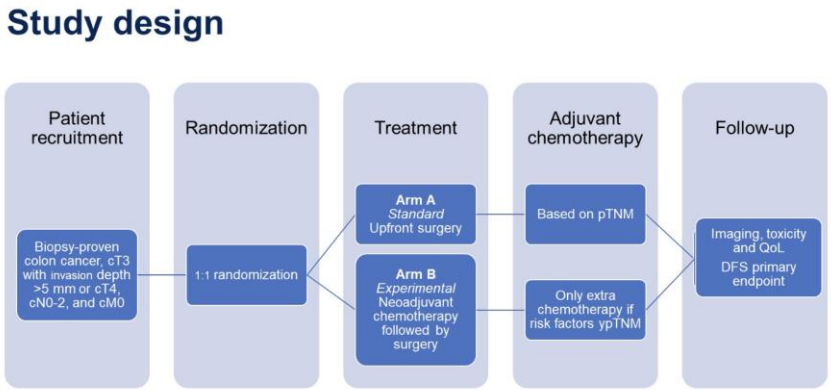
Well tolerated AND signs of response

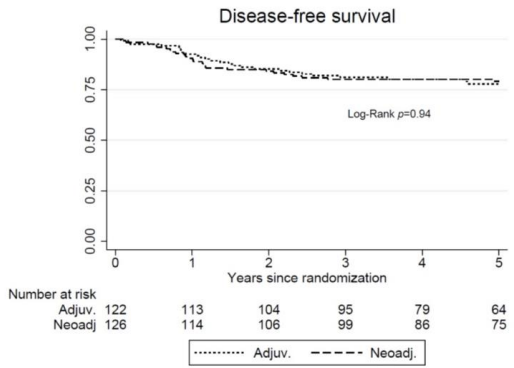
Poorly tolerated OR no signs of response

Adjuvant chemotherapy following NAC

- Can you de-escalate AC if good pathological response post NAC
- 41% of patients did not receive AC following NAC
- Elements of design limit interpretation
  - Aim 10% improvement with NAC
  - N = 250
- ctDNA may help this decision

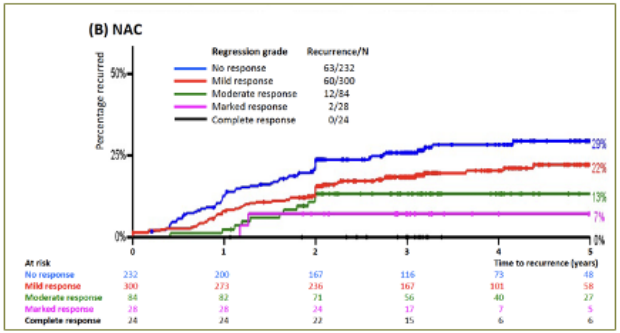
My recommendation is to complete planned chemotherapy duration based upon IDEA recommendations

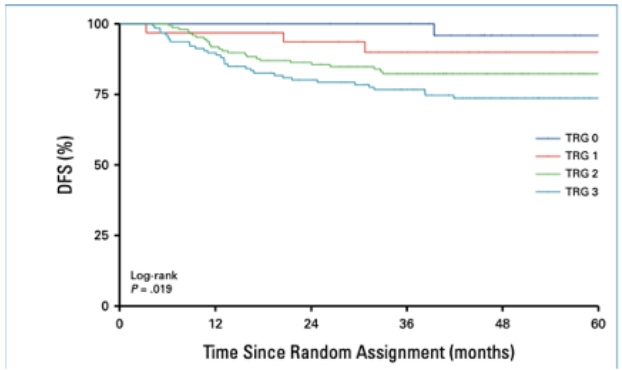


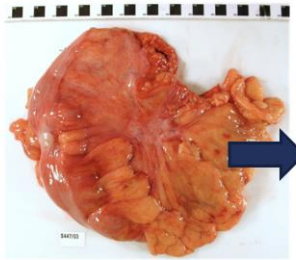


Larsson, ASCO Annual Meeting, 2023

…Can we do better?







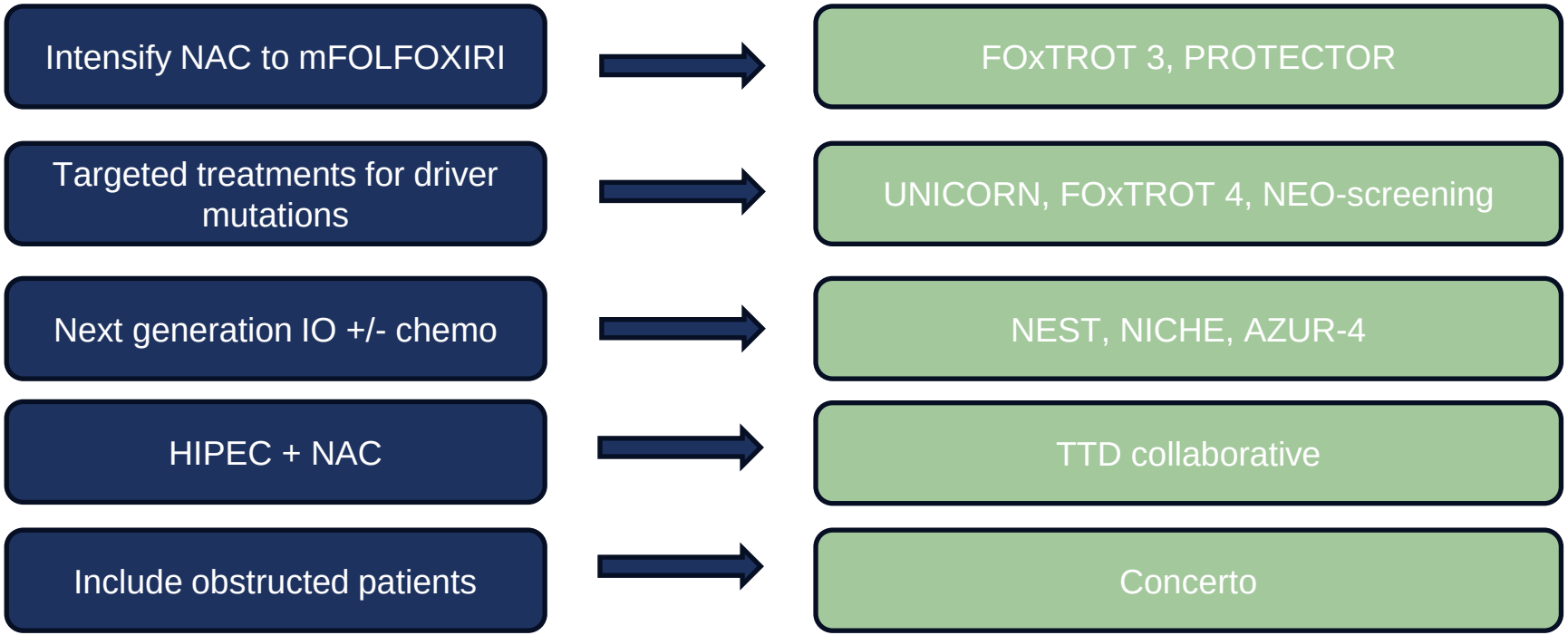
OxFp

Target treatment not approved in EU
Target treatment approved

Alterations	Prevalence, %	Targetability Evidence	Enrichment
Non-G12C *RAS* mutations[1,2]	~50	NO	-
*KRAS*G12C mutation[3]	3-4	YES	-
*BRAF*V600E mutation[4]	~10	YES	(> if right colon, *RAS*WT, MSI)
PIK mutations[5,7]	10-20	Probably YES	-
Microsatellite instability[1,4]	3-5	YES	(> if right colon, *BRAF*Mut)
BRAF non-V600E mutations[5,6]	~2	NO	(> if left/rectum colon, *RAS*Mut, MSS)
HER2 amplification[1,7,8]	2-3	YES	(> if left/rectum colon, *RAS*/*BRAF*WT)
MET amplification[7]	~2	Case report	-
POLE mutations[1,9]	1-2	YES	(> if right colon, MSS)
TRK1-3, *ALK*, *ROS1* translocations[1,7,9]	0.2-2.4	YES	(> if right colon, *RAS*/*BRAF*WT, MSI)
RET translocations[7]	0.2-1.6	YES	(> if right colon, *RAS*/*BRAF*WT, MSI)

Morton et al, JCO, 2023; Hu et al, JCO, 2024

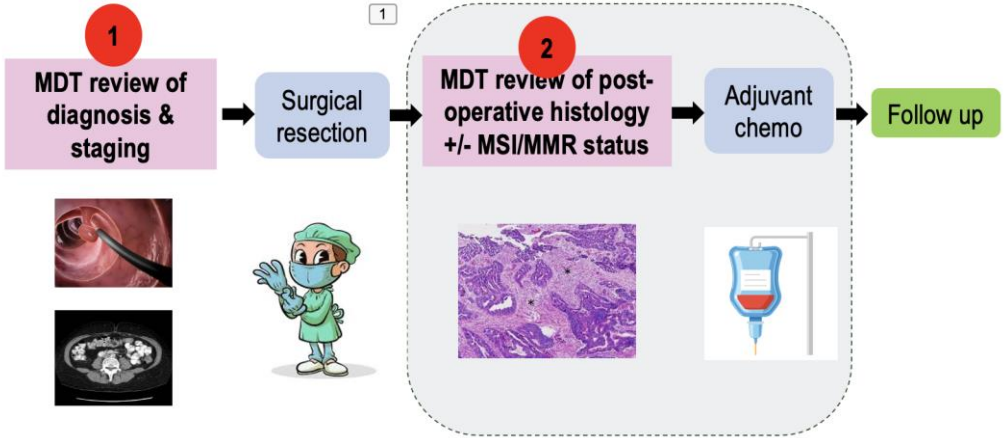
Strategies to improve neoadjuvant outcomes in MSS LACC



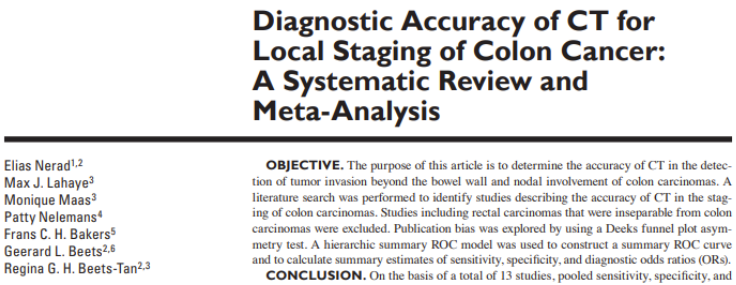
Implementation of neoadjuvant treatments

How do we select patients for neoadjuvant treatment?

How do we integrate this into our existing patient pathways?



The Accuracy of Radiological Staging in Colon Cancer has been Well Studied

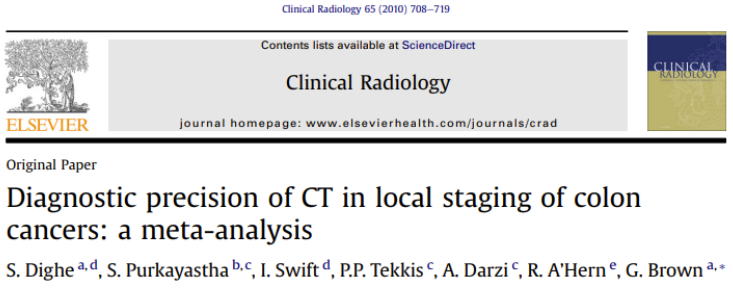


Diagnostic Accuracy of CT for Local Staging of Colon Cancer: A Systematic Review and Meta-Analysis

Elias Nerad[1,2]
Max J. Lahaye[3]
Monique Maas[3]
Patty Nelemans[4]
Frans C. H. Bakers[5]
Geerard L. Beets[2,6]
Regina G. H. Beets-Tan[2,3]

OBJECTIVE. The purpose of this article is to determine the accuracy of CT in the detection of tumor invasion beyond the bowel wall and nodal involvement of colon carcinomas. A literature search was performed to identify studies describing the accuracy of CT in the staging of colon carcinomas. Studies including rectal carcinomas that were inseparable from colon carcinomas were excluded. Publication bias was explored by using a Deeks funnel plot asymmetry test. A hierarchic summary ROC model was used to construct a summary ROC curve and to calculate summary estimates of sensitivity, specificity, and diagnostic odds ratios (ORs).
CONCLUSION. On the basis of a total of 13 studies, pooled sensitivity, specificity, and

Hewish et al., *AJR Am J Roentgenol.* 2016 Nov;207(5):984-995



Clinical Radiology 65 (2010) 708–719

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.elsevierhealth.com/journals/crad

Original Paper

Diagnostic precision of CT in local staging of colon cancers: a meta-analysis

S. Dighe [a,d], S. Purkayastha [b,c], I. Swift [d], P.P. Tekkis [c], A. Darzi [c], R. A'Hern [e], G. Brown [a,*]

Dighe et al., *Clin Radiol.* 2010 Sep;65(9):708-19

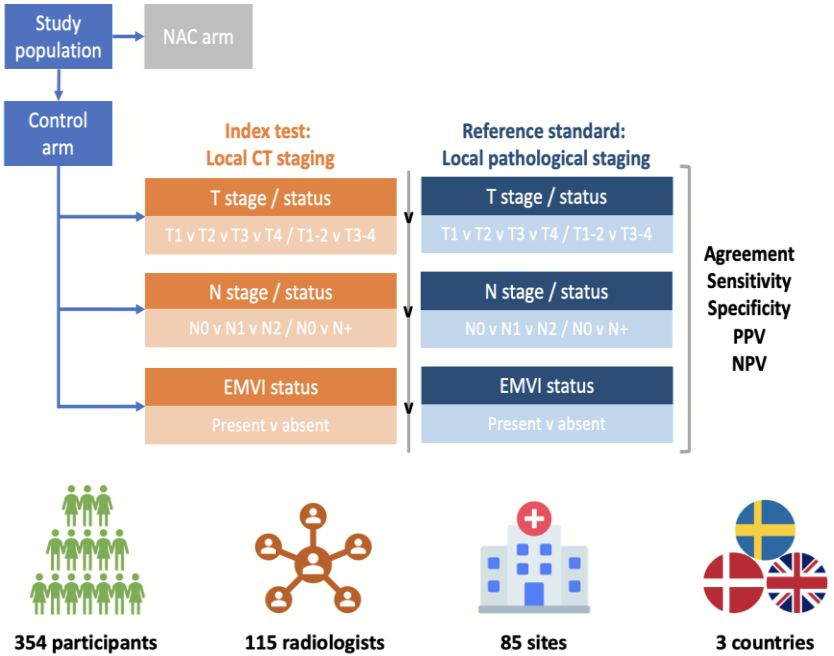
In summary:

T stage accuracy = GOOD

N stage accuracy = POOR

Slide courtesy of James Platt

Comparison of radiological & pathological staging



- T stage
  - Overall agreement = 60.0%
  - T1/2 vs T 3/4 PPV = 94.5%
- N stage
  - Overall agreement = 54.1%
  - PPV for N0 vs N+ = 57.1%
- EMVI status
  - PPV for EMVI +/- = 50.7%

Platt et al, ESGAR Congress, 2023

Do other factors influence performance?

MMR Proficient vs. MMR Deficient

		MMR proficient	MMR deficient
N status	Sensitivity	79.7 ([illegible] – 86.2)	89.5 ([illegible] – 97.7)
	NPV	52.6 (39.0 – 66.0)	78.6 (49.2 – 95.3)
	PPV	56.4 (49.0 – 63.6)	46.3 (32.6 – 60.4)

Higher neutrophil count associated with N1/2 'status' (*P* = 0.0077)[2]

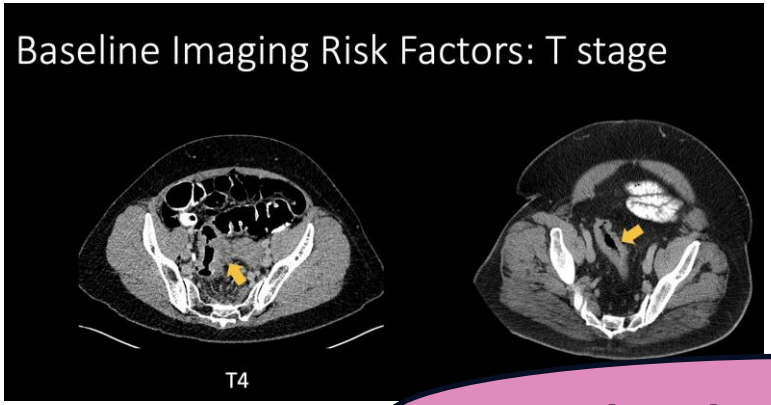
Platt et al, ESGAR Congress, 2023

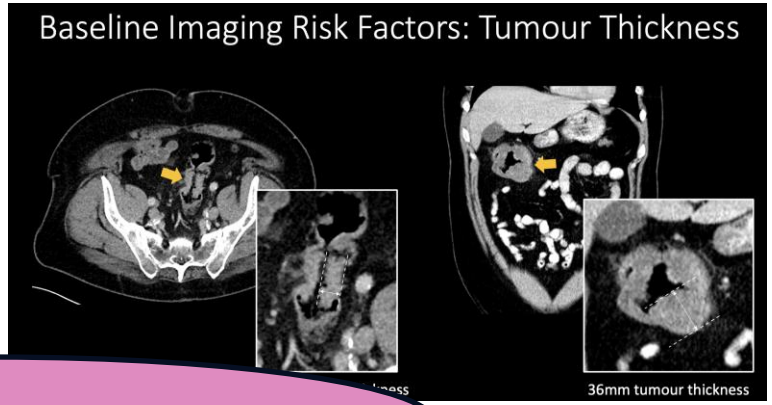
Can we identify the high risk patient on CT?

Radiological Feature		Hazard ratio (95% CI) For any recurrence	P value [c]
T stage [b]	T3	1.0	
	T4	1.57 (1.19-2.07)	0.001
Depth of extramural extension	Continuous	1.03 (1.02-1.04)	0.00001
	≤7	1.0	
	>7	1.67 (1.29-2.18)	0.0001
Maximum tumour thickness	Continuous	1.16 (1.06-1.27)	0.001
	≤25	1.0	
	>25	1.59 (1.21-2.09)	0.001
Node ≥10mm	No	1.0	
	Yes	1.40 (1.07-1.83)	0.01
EMVI	Absent	1.0	
	Present	1.41 (1.07-1.86)	0.02

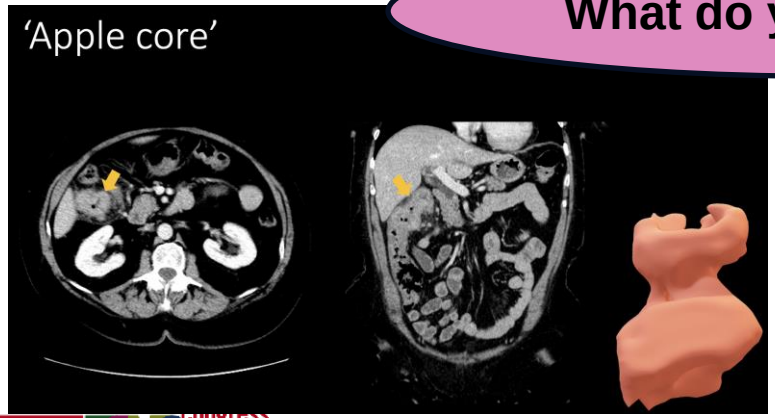
Platt et al, ESMO Congress, 2024

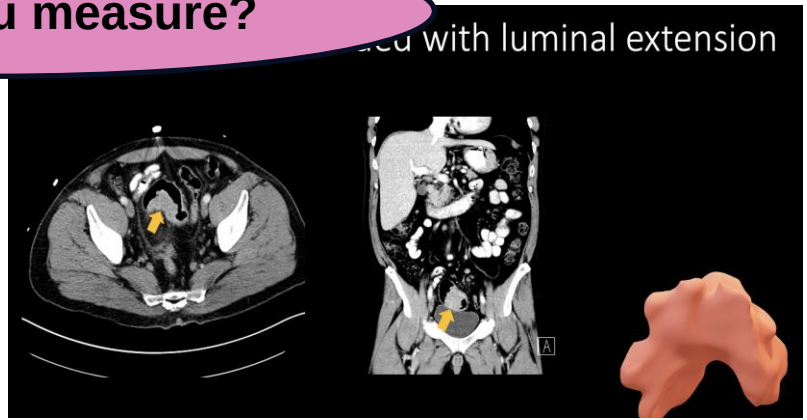
Beyond T stage





What do you measure?





Slide courtesy of Dr James Platt

Patient selection – how to move forward

- Engagement with radiology
- Prioritise training in planned studies
- Transition toward radiological phenotyping – don’t limit to information collected by TNM
- Future likely to involve artificial intelligence algorithms & multi-modal risk stratification

Decision points in the Treatment pathway

Pathway coordination

1

MDT review of diagnosis, staging

PATIENT CHOICE

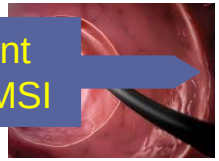
2

MDT review of post-operative histology, MSI/MMR status

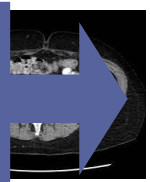
Assessment of post-rx response

Follow up

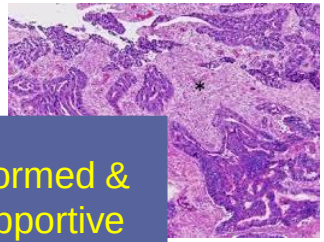
Upfront MMR/MSI

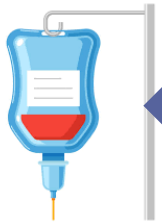


Radiology call on T & N stage



Informed & supportive surgical colleague





Ability to review & treat rapidly

Summary

- Clinical need to **improve** outcomes in MSS localized colon cancer
- Consistent moderate efficacy demonstrated with neoadjuvant chemotherapy
    - **5% with just change in sequence!**
- Most benefit likely with most advanced tumors
- 6 or 12 weeks NAC reasonable depending upon clinical situation
- Need for improvements in patient selection
    - Ongoing development need rather than Stop/Go
- Implementation requires buy-in from multidisciplinary team

Acknowledgements

FOxTROT
Personalising neo-adjuvant chemotherapy in locally advanced but operable colon cancer

- To all the multidisciplinary FOxTROT collaborators from contributing international centres
- To Yorkshire Cancer Research for FOxTROT Platform Core Funding
- Cancer Research UK and Yorkshire Cancer Research for core funding of the FOxTROT Trial and associated laboratory research
- All of the patients and carers who participate in this research
- Pernille for administrative support

UNIVERSITY OF LEEDS

Yorkshire Cancer Research

BARCELONA 2024 ESMO congress

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org