Radyoterapisiz tedavi mümkün mü?

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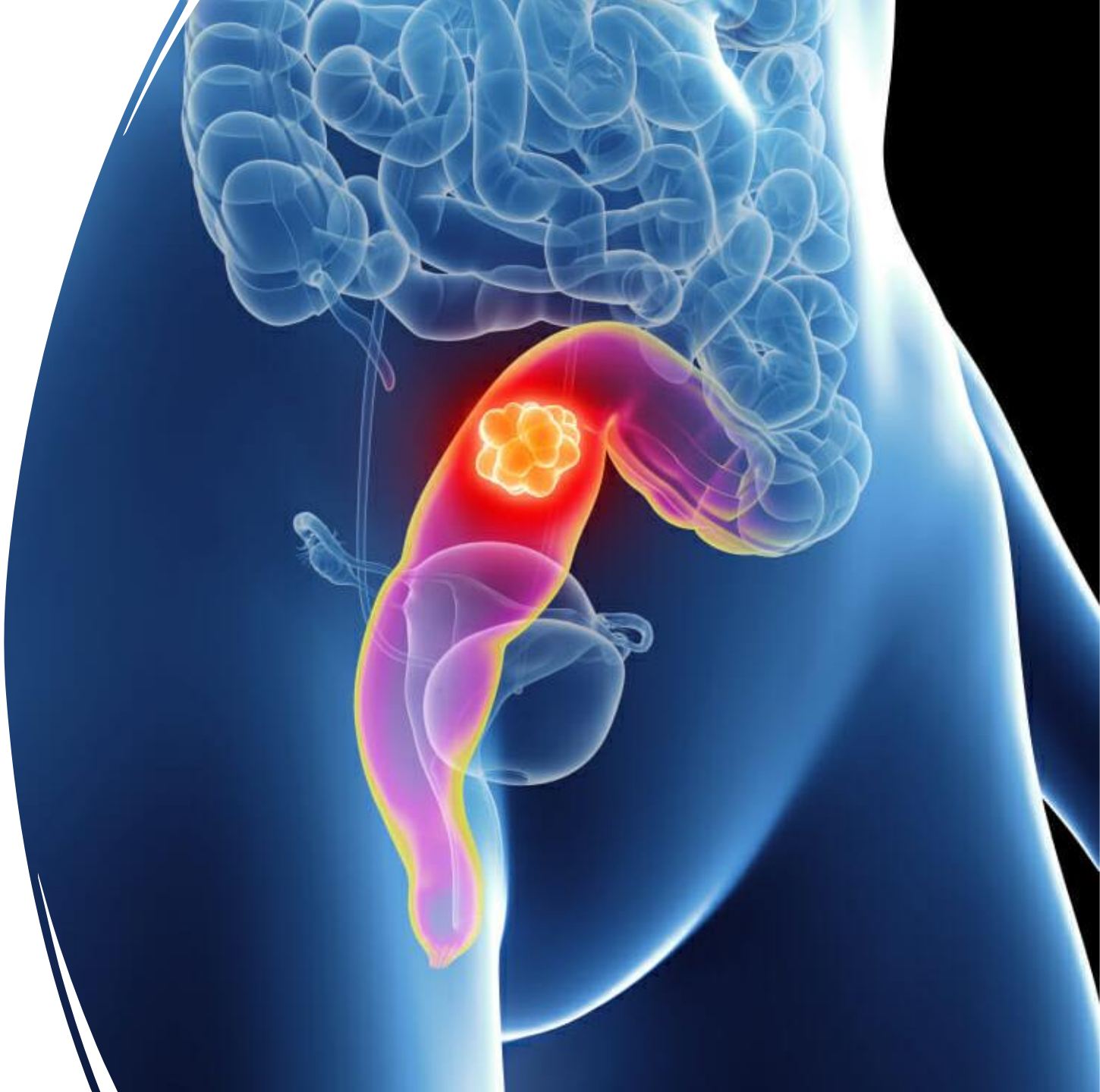


Sunum Akışı

T3abN0

≥T3c; N(+) Çalışmalar

- **FOWARC (Faz 3)**
- **GRECCAR 4 (Faz 2)**
- **CONVERT (Faz 3)**
- **PROSPECT (Faz 3)**
- **Cercek 19-288 (Faz 2)**

Sonuç

NCCN Guidelines Version 2.2024
Rectal Cancer

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy for stage II (T3–4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer usually includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases since this disease is characterized by lower rates of local recurrence.

American Joint Committee on Cancer (AJCC)
TNM Staging System for Rectal Cancer 8th ed., 2017

Table 2. **Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy?

Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC.

Dis Colon Rectum. 1999 Feb;42(2):167-73. doi: 10.1007/BF02237122.

Results: For 25 patients with tumors exhibiting favorable histologic features (well-differentiated or moderately well-differentiated carcinomas invading less than 2 mm into perirectal fat, without lymphatic or venous vessel involvement), the ten-year actuarial rates of local control and recurrence-free survival were 95 and 87 percent, respectively. In contrast, the ten-year actuarial rates of local control and recurrence-free survival were inferior (71 and 55 percent, respectively) for 88 patients with tumors exhibiting moderate to deep perirectal fat invasion, vessel involvement, or poor differentiation.

Conclusions: In the design of future trials of rectal cancer, selection of patients with rectal cancer for postoperative adjuvant therapy should be based not only on stage, but also on depth of invasion into the perirectal fat, vessel involvement, tumor grade, and integrity of the radial resection margin. For subsets of patients with Stage T3N0 rectal cancer, there may be little benefit to adjuvant therapy after surgery.

- 1968-1985
- 117 hasta T3N0M0
- 10 yıllık
  - LC %95
  - RFS %87

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Rectal Cancer

pT3, N0, M0 →

- Long-course chemo/RT[r,s]
- Capecitabine[q] or infusional 5-FU[q]
- or
- Chemotherapy
- FOLFOX or CAPEOX
- or
- Consider FOLFOX or CAPEOX alone
- or
- Observation[v]

[v] Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in the upper rectum. Willett CG, et al. Dis Colon Rectum 1999;42:167-173.

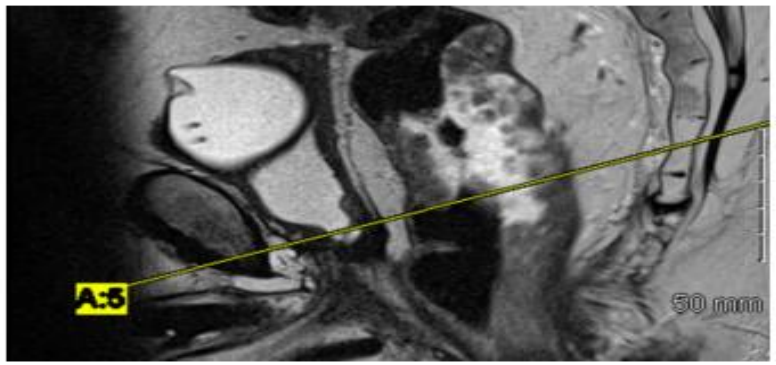
Although radiation therapy (RT) has been associated with decreased rates of local recurrence of rectal cancer, it is alsc associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities) relative to surgery alone.[134,290,291] It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.[134,292,293]

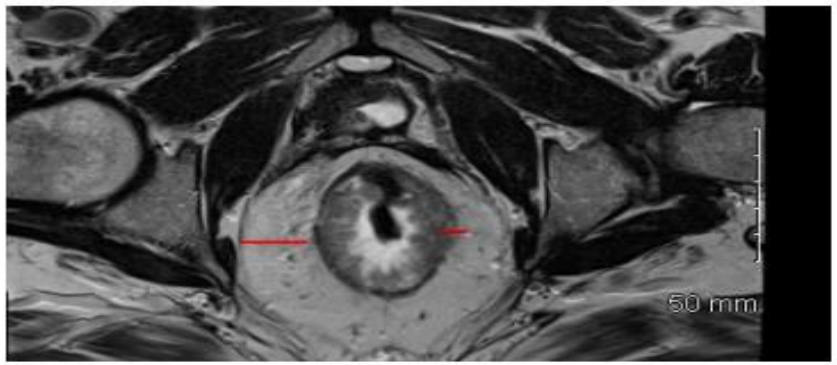
Structured and shared MRI staging lexicon and report of rectal cancer: A consensus proposal by the French Radiology Group (GRERCAR) and Surgical Group (GRECCAR) for rectal cancer

Diagnostic and Interventional Imaging 103 (2022) 127–141

Template	How to assess it on MRI	Clinical relevance at baseline	Representative figure
Primary tumor: Morphology and location			
MRI-T category			
EMS (mm): ☐Tx ☐T1/2 (tumor confined to rectal wall) ☐T3a (tumor penetrates < 1 mm beyond muscularis propria) ☐T3b (tumor penetrates 1- 5 mm beyond muscularis propria) ☐T3c (tumor penetrates >5-15 mm beyond muscularis propria) ☐T3d (tumor penetrates > 15 mm beyond muscularis propria) ☐T4a (tumor penetrates through surface of anterior peritoneal reflection) ☐T4b* (tumor invades or adherent to adjacent organs or structures) * If T4b, structures with possible invasion: []	Depth of invasion of the tumor beyond the rectal wall into the mesorectal fat. On MRI, correspond to the maximum distance from the outer edge of the muscularis propria to the outer edge of the primary tumor. - Evaluation always on axial oblique high-resolution sequences perpendicular to the tumor - Follow the low signal of the muscularis propria and look for disruption with tumor signal: T2 vs. T3. Separation of muscle bundles with gaps is not T3. - The supposed outer edge of the muscularis propria is considered as the starting point. The final point corresponds to the deepest point of tumor extension within the mesorectal fascia. This point is considered as the deepest extension of broad bulging or nodular tumor mass within the mesorectum. It should not include spiculations into the perirectal fat. - Contiguous EMVI should be measured as T3 extension, but only in the oblique axial plane Abutment of the anterior peritoneal reflection does not imply T4a stage. Nodularity and tumor going through the anterior peritoneal reflection must be present for T4a stage	T1 sm1 tumors are treated with local excision. T2 tumors are considered early stage tumor and may be treated with local excision provided the absence of other poor prognosis parameters. T3a and b without other poor prognosis parameters may be treated either by surgery or referred to neoadjuvant treatment. T3c, T3d, T4a and T4b tumor are referred to neoadjuvant therapy	Figure 5

*MRI Assessment of T3 Extent and Distance to Mesorectal Fascia





- **T3a:** tumor extends <1 mm beyond muscularis propria
- **T3b:** tumor extends 1-5 mm beyond muscularis propria
- **T3c:** tumor extends 5-15 mm beyond muscularis propria
- **T3d:** tumor extends 15 mm beyond muscularis propria

T3 with > 5mm extension associated with worse OS

Siddiqui et al Eur J Cancer 2018

MERCURY Study Group : Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006; 333: pp. 779

MRI Radyolojik Evrelemesi

cT-stage	cT1 or cT2: confined to rectal wall cT3: extending beyond rectal wall into mesorectal fat cT3ab ≤ 5 mm (cT3a < 1 mm; cT3b 1-5 mm) cT3cd > 5 mm (cT3c 5-15 mm; cT3d >15 mm) cT4a: invading the peritoneum or peritoneal reflection cT4b: invading adjacent organs or structures
MRF	Involved: ≤ 1mm distance between tumor and MRF (mention location of involvement) Free: > 1 mm distance between tumor and MRF (mention shortest distance)
EMVI	EMVI+ : tumor signal extending within vessel EMVI- : no involved vessels in vicinity of tumor

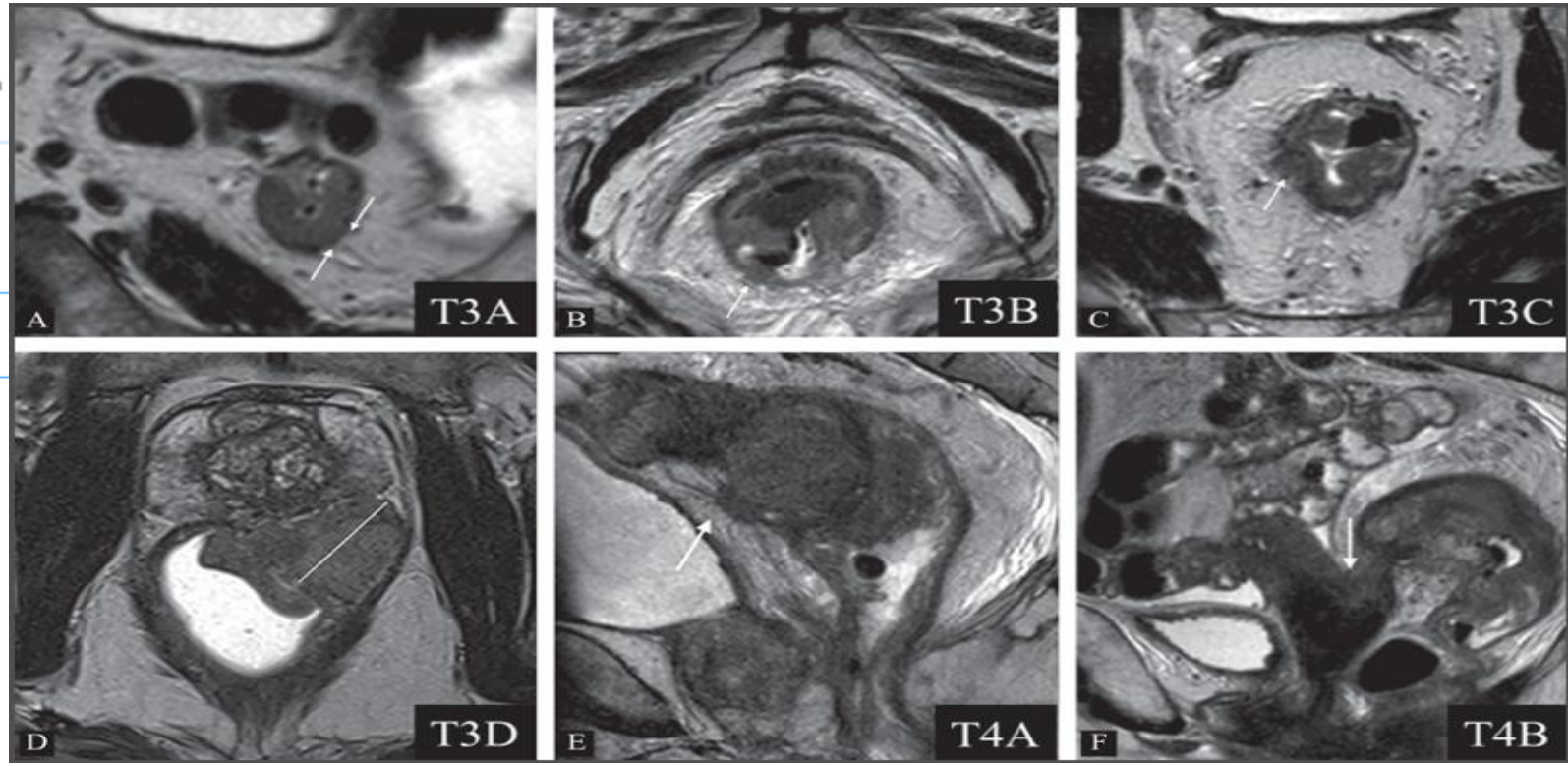
Subclassification of T3 stage according to invasion depth:

Low-risk T3-tumors:

- T3a: tumor extends <1 mm beyond muscularis propria
- T3b: tumor extends 1-5 mm beyond muscularis propria

High-risk T3-tumors:

- T3c: tumor extends 5-15 mm beyond muscularis propria
- T3d: tumor extends > 15 mm beyond muscularis propria
- T3 MRF+ tumor ≤ 1mm of the MRF



Recommendations/*Gastrointestinal imaging*

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Diagnostic and Interventional Imaging 103 (2022) 127–141

CONCLUSION of the report

For Baseline staging: Identification of factors either for direct surgery or for CRT

ITEMS	Good prognosis tumor	Poor Prognosis Tumor
T	< T3C	T3C/T3D/T4
Anal Canal	Not involved	Involved
N1c	No	Yes
MRF	Not involved	Involved
EMVI	Not present	Present

The presence of one out of 5 of this poor prognosis parameter imply CRT.

Positive mesorectal N (excluding N1C/tumor deposit) is controversial as they are not associated with worse prognosis.

CRM: circumferential margin; EMVI: extramural venous invasion; MRF: mesorectal fascia; EMS: extramural spread

T3N0 rectal cancer: radiation for all?

Wo JY, Mamon HJ, Ryan DP, Hong TS.

Semin Radiat Oncol. 2011 Jul;21(3):212-9. doi:

Summary of Retrospective Series of T3N0 Patients Treated with Surgery Alone

Series	Number of Patients	High-Risk Features Identified	Patient Subgroup	Local Recurrence
MGH [19]	117	Tumor differentiation *, LVI *, extent of perirectal tumor invasion †	Overall	10 year: 24
	25		No high-risk features	10 year: 5
	88		≥1 high-risk features	10 year: 29
MSKCC [18]	108	None	Overall	5 year: 8
MSKCC [20]	95	LVI *	Overall	5 year: 12
MSKCC [26] ‡	49	LVI *, age >70 *, abnormal pretreatment CEA †	Overall	Crude: 4.1
Norwegian Rectal Cancer Group [27] ‡	679	Circumferential margin status	CRM >3 mm	5 year: 11.1
	41		2.1-3	5 year: 9.7
	69		1.1-2	5 year: 16.8
	101		CRM ≤1 mm	5 year: 19.4

† Significant on multivariate analysis.

* Significant on univariate analysis.

‡ Only T3N0 patients included in the summary table.

Which Patients Can Safely Omit Radiation Therapy?

- Approaches
  - Baseline MRI Imaging criteria to identify favorable patients
    - Mercury, Quicksilver, OCUM
  - Response based omission of RT after neoadjuvant chemotherapy
    - Alliance Prospect Trial

Trials Omitting RT Based on MRI Features

Trial	Eligibility	Stage I/II	Result
Mercury (Europe multicenter) N=122	T2/T3(<5mm Extramural Depth) >1 mm mesorectal fascia distance Low tumors if stage I/II	82%	5 yr LR 3.3%
OCUM (Switzerland/Germany) N=254	-cT2-T3,any N with >1 mm mesorectal fascia distance Upper 2/3 rectum	45%	5 yr LR 2.7%
Quicksilver (Canada) N=82	-T2, T2/early T3, or definite T3 with less than 5 mm >1 mm mesorectal fascia distance	71%	5% circumferential margin LR not reported yet

Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results

Hagen F. Kennecke, MD, MHA[1]; Chris J. O'Callaghan, PhD, DVM, MSc[2]; Jonathan M. Loree, MD, MS[3]; Hussein Moloo, MD, MPH[4];

J Clin Oncol 41:233-242.

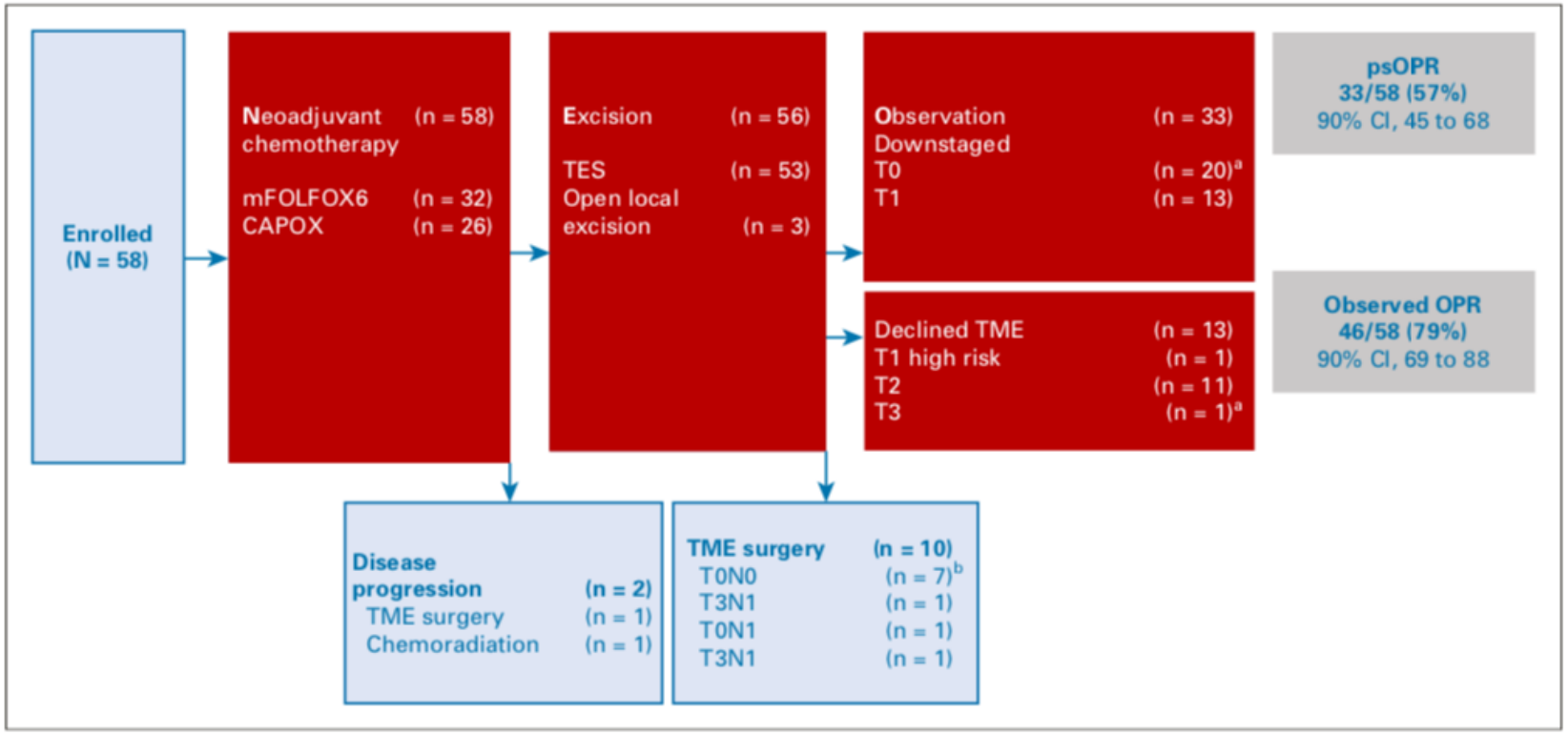

FIG 1. Flow diagram of 58 patients enrolled in the study. [a]Represents ypT, cN0 stage. [b]Represents yp stage. c, clinical; CAPOX, capecitabine-oxaliplatin; mFOLFOX, modified folinic acid–flurouracil-oxaliplatin 6; N, node; oOPR, observed organ preservation rate; psOPR, protocol-specified organ preservation rate; T, tumor; TES, transanal excision surgery; TME, total mesorectal excision; yp, pathologic stage following systemic or radiation therapy prior to surgery.

- T1-3bN0
- Neoadjuvan KT+TES
- Hastalık progresyonu yoksa RT (-)
- TME yerine Transanal eksizyon cerrahi (TES) yeterli mi?
- TES sonrası organ preservasyon oranı %57

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J Clin Oncol 41:233-242.

ASCO Journal of Clinical Oncology

CONTEXT

Key Objective

Can 3 months of modified folinic acid–fluorouracil-oxaliplatin 6 (mFOLFOX6)/capecitabine-oxaliplatin (CAPOX) followed by transanal excision surgery be used to treat magnetic resonance imaging-stage cT1-3bN0 rectal cancer?

Knowledge Generated

Induction mFOLFOX6/CAPOX followed by transanal excision surgery was well tolerated and resulted in downstaging to ypT0/T1 cN0 tumors in 57% of 58 enrolled patients with well to moderately differentiated adenocarcinoma and preserved mismatch repair. Overall, 79% of patients pursued an organ-sparing strategy, with two patients experiencing a locoregional relapse during the 15.4-month follow-up period. Quality of life and rectal function scores demonstrated almost no change compared with baseline.

Relevance

Early results suggest that this novel treatment strategy leads to downstaging to ypT0/T1 cN0 in the majority of selected patients with early rectal cancer. The approach offers a much-desired organ-sparing option and warrants further investigation.

- 2 hastada lokal relaps (median takip 15.4 ay)
- Toplam organ koruyucu yaklaşım oranı %79

Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results

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J Clin Oncol 41:233-242. © 2022 by American Society of Clinical Oncology

Çalışmada hedeflendiği gibi lokal eksizyon %57; (lokal +TME)OP oranı %79

- KRT+lokal eksizyon çalışmalarında bu oran:
  - CARTS'da %74 ve
  - ACOSOG Z6041'da %91

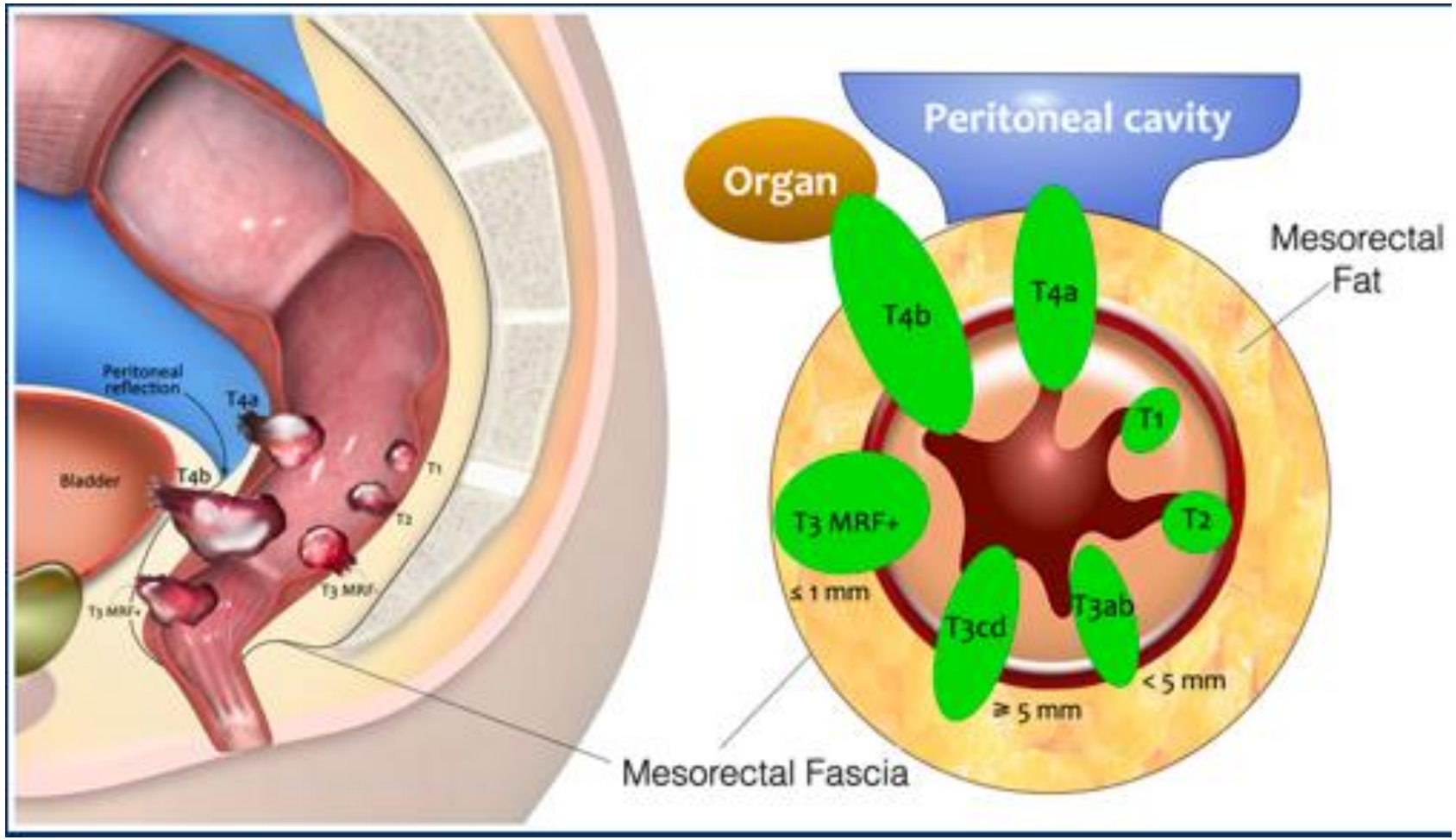
Toksisite

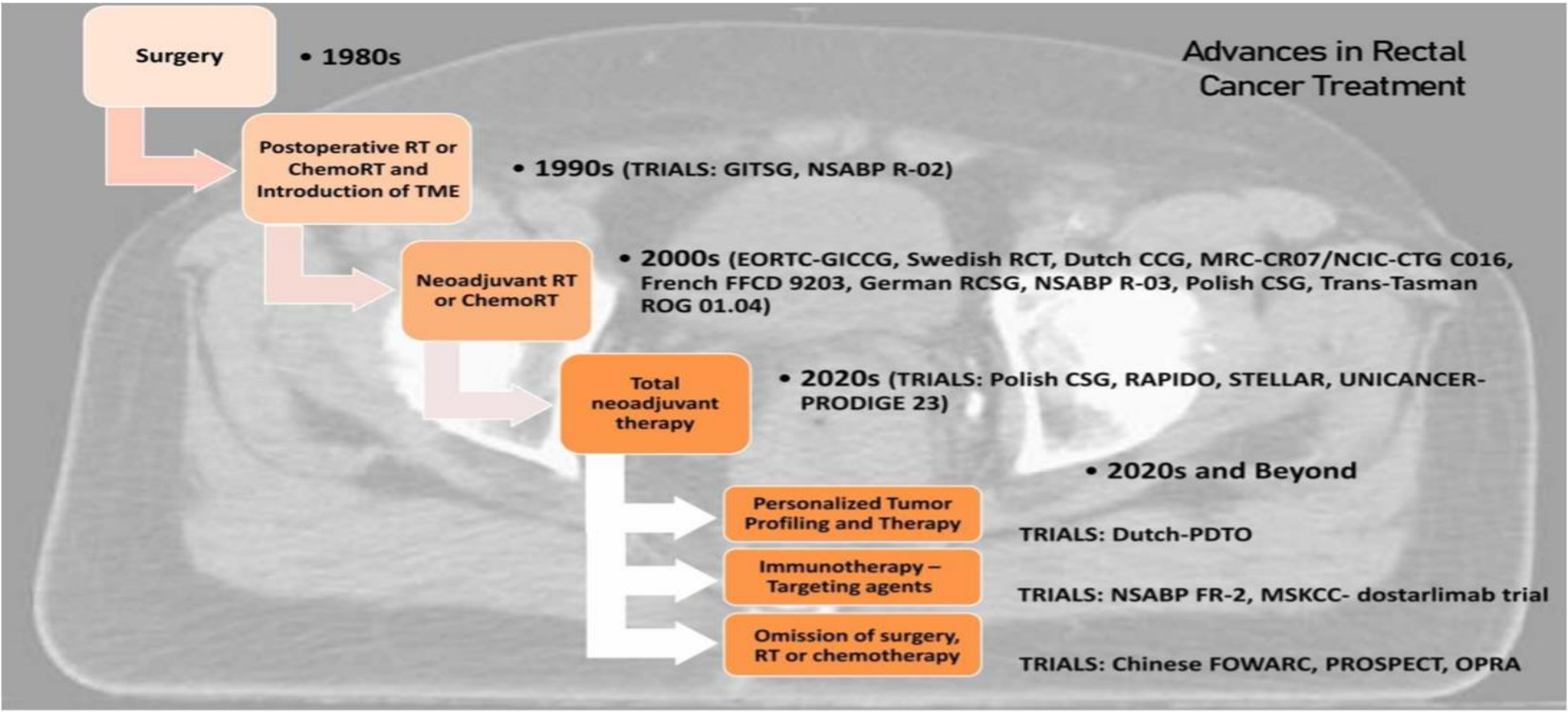
- Major LARS (low anterior rezeksiyon sendromu) oranı eksizyondan
  - 6 ay sonra %22 ve 12 ayda %14 idi (ortalama tm boyutu ?)
  - CARTS'da bu oran %50 (ortalama tm boyutu 3.4cm)
  - ACOSOG Z6041'da grade 3 toksiste %22
- Çok ajanlı oksaliplatin kemoterapisi ile nöropati oranlarını bildirmemektedir. Median takip kısa !

Takip süresinin artmasıyla KRT tedavisinin ihmal edilmesi durumunda mezorektal veya pelvik lenf nodu nüksü riskinin ve onkolojik sonuç üzerindeki etkisinin daha iyi anlaşılacaktır

- Stijns RCH, Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: The CARTS study. JAMA Surg 2019;154:47-54.
- Garcia-Aguilar J, Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): Results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 2015;16: 1537-1546.

≥T3c; N(+)


Peritoneal reflection
T4a
Bladder
T4b
T1
T2
T3 MRF+
T3 MRF+
Peritoneal cavity
Organ
Mesorectal Fat
T4b
T4a
T1
T3 MRF+
T2
≤ 1 mm
T3cd
T3ab
< 5 mm
≥ 5 mm
Mesorectal Fascia


Advances in Rectal Cancer Treatment
Surgery
• 1980s
Postoperative RT or ChemoRT and Introduction of TME
• 1990s (TRIALS: GITSG, NSABP R-02)
Neoadjuvant RT or ChemoRT
• 2000s (EORTC-GICCG, Swedish RCT, Dutch CCG, MRC-CR07/NCIC-CTG C016, French FFCD 9203, German RCSG, NSABP R-03, Polish CSG, Trans-Tasman ROG 01.04)
Total neoadjuvant therapy
• 2020s (TRIALS: Polish CSG, RAPIDO, STELLAR, UNICANCER-PRODIGE 23)
• 2020s and Beyond
Personalized Tumor Profiling and Therapy
TRIALS: Dutch-PDTO
Immunotherapy – Targeting agents
TRIALS: NSABP FR-2, MSKCC- dostarlimab trial
Omission of surgery, RT or chemotherapy
TRIALS: Chinese FOWARC, PROSPECT, OPRA

FUTURE ONCOLOGY, VOL. 10, NO. 14 | REVIEW

Neoadjuvant chemotherapy without radiotherapy for locally advanced rectal cancer

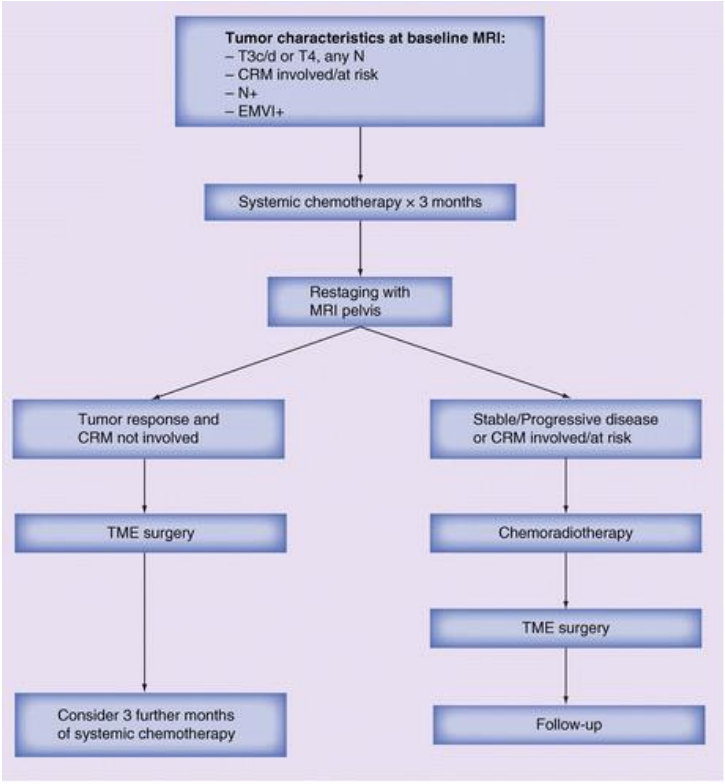
Francesco Sclafani & David Cunningham

2014

Table 1. Studies of neoadjuvant chemotherapy without radiotherapy in locally advanced rectal cancer.

Study (year)	Patients (n)	Patient population	Patients with 'ugly' features†	Treatment	Follow-up (months)	R0 resection rate (%)	pCR (%)	Local relapse (%)	Distant relapse (%)	Relapse-free survival (%)	Overall survival (%)	Ref.
Ishii *et al.* (2010)	26	T3–4, any N, within 12 cm of the anal verge	T4: 3/26 (12%) CRM+: NR	IFL	75	100	3.8	11.5	7.7	74‡	84‡	[86]
Cercek *et al.* (2010)	6	T2–3, N1	T4: 0% CRM+: NR	FOLFOX	NA	100	33.3	0	16.7	NA	NA	[87]
Fernandez-Martos *et al.* (2012)	28	T3 middle third tumors ≥2 mm from the mesorectal fascia	T4: 0% CRM+: 0%	CAPOX – bevacizumab	NA	96.4	14.3	NA	NA	NA	NA	[88]
Uehara *et al.* (2013)	32	T3 >5 mm, T4, N2, CRM involved/at risk	T4a: 9/32 (28%) T4b: 10/32 (31%) CRM+: NR	CAPOX – bevacizumab	NA	84.3	12.5	NA	NA	NA	NA	[89]
Schrag *et al.* (2014)	32	T2N1, T3 any N (except N2 bulky), within 5 and 12 cm of the anal verge	T4: 0% CRM+: 0%	FOLFOX – bevacizumab	54	100	25.0	0	12.5	92§	91.6§	[90]

†'Ugly' features are T4 tumors and CRM involvement [60].
‡Survival rates at 5 years.
§Survival rates at 4 years.
CAPOX: Capecitabine and oxaliplatin; CRM: Circumferential resection margin; FOLFOX: Bolus 5-fluorouracil, infusional 5-fluorouracil, folinic acid and oxaliplatin; IFL: Bolus 5-fluorouracil, folinic acid and irinotecan; NA: Not available; NR: Not reported; pCR: Pathologic complete response.



EXECUTIVE SUMMARY

Background

- • Neoadjuvant long-course chemoradiotherapy or short-course radiotherapy followed by total mesorectal excision is a standard of care for patients with locally advanced rectal cancer.
- • Alternative therapeutic options are under investigation to reduce the risk of treatment-related toxicities and improve the outcome.

Relative & absolute local recurrence risk reduction with radiotherapy

- • Before the standardization of total mesorectal excision, delivery of preoperative radiotherapy was associated with a reduction in local recurrence and an improvement in survival.
- • If high-quality rectal surgery and optimal pathological assessment are performed, the impact of preoperative radiotherapy on local tumor control is marginal and does not translate into a survival benefit.

Radiotherapy-related toxicities

- • Preoperative pelvic radiotherapy is associated with acute, mid- and long-term side effects including bowel and urogenital disfunction and risk of second cancers.

A selective approach to rectal cancer is feasible

- • A tailored approach to rectal cancer is feasible and does not compromise the overall oncological outcome.
- • Following the improvements in diagnostic imaging, it is possible to identify those patients who may not benefit from the use of preoperative radiotherapy.

Why & when neoadjuvant chemotherapy without radiotherapy may be an option

- • Upfront combination chemotherapy without radiotherapy yields several theoretical advantages including delivery of chemotherapy at full systemic doses, early treatment of micrometastases and reduction of the risk of distant failure.
- • Neoadjuvant chemotherapy without radiotherapy may be an option for patients who need tumor downstaging/downsizing to achieve a safe circumferential resection margin or patients who are likely to receive adjuvant combination chemotherapy.

EXECUTIVE SUMMARY

Available data on neoadjuvant chemotherapy without radiotherapy

- • Very few studies of neoadjuvant chemotherapy without radiotherapy have been conducted.
- • Overall, the available data suggest that this treatment strategy is associated with promising short- and mid-term outcomes.

Ongoing trials of neoadjuvant chemotherapy without radiotherapy

- • Prospective clinical trials are currently investigating the role of neoadjuvant chemotherapy without radiotherapy in locally advanced rectal cancer.

Conclusion

- • Systemic chemotherapy without radiotherapy is a promising treatment strategy for patients with locally advanced rectal cancer. More data are needed before this approach may become a new standard of care.

Future perspective

- • Characterization of the individual patient risk profile and prediction of treatment response by means of reliable and reproducible tumor biomarkers are crucial to identify those patients who are most likely to benefit from the use of neoadjuvant chemotherapy without radiotherapy.

Financial & competing interests disclosure

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Neoadjuvant chemotherapy without radiation as a potential alternative treatment for locally advanced rectal cancer: A meta-analysis

Pei Wu, Hui-Mian Xu, Zhi Zhu *World J Gastrointest Oncol* 2021 September 15; 13(9): 1196-1209

RESULTS

A total of 19 studies of 60870 patients were included in the meta-analysis. There was no significant difference in overall survival [hazard ratio = 1.09, 95% confidence interval (CI) = 0.93–1.24; *P* = 0.19] or the pathological complete response (RR = 0.79, 95%CI = 0.61–1.03; *P* = 0.086) between the Neo-CT and Neo-CRT groups. As compared to the Neo-CRT group, the incidences of anastomotic fistula (RR = 0.49, 95%CI = 0.35–0.68; *P* = 0.000) and temporary colostomy (RR = 0.69, 95%CI = 0.58–0.83; *P* = 0.000) were significantly lower in the Neo-CT group, with a simultaneous increase in the sphincter preservation rate (RR = 1.07, 95%CI = 1.01–1.13; *P* = 0.029). However, there was no significant difference in the tumor downstaging rate, overall complications, and urinary complications.

Data on the rate of sphincter preservation, incidences of temporary colostomy, and anastomotic fistula were available from nine, three, and six trials, respectively. As compared to Neo-CRT, Neo-CT without radiotherapy was associated with a significant decrease in the incidences of anastomotic fistula (RR = 0.49, 95%CI = 0.35–0.68; *P* = 0.000) and temporary colostomy (RR = 0.69, 95%CI = 0.58–0.83; *P* = 0.000). Moreover, Neo-CT without radiotherapy resulted in a higher sphincter preservation rate (RR =1.07, 95%CI = 1.01–1.13; *P* = 0.029) (Figure 4).

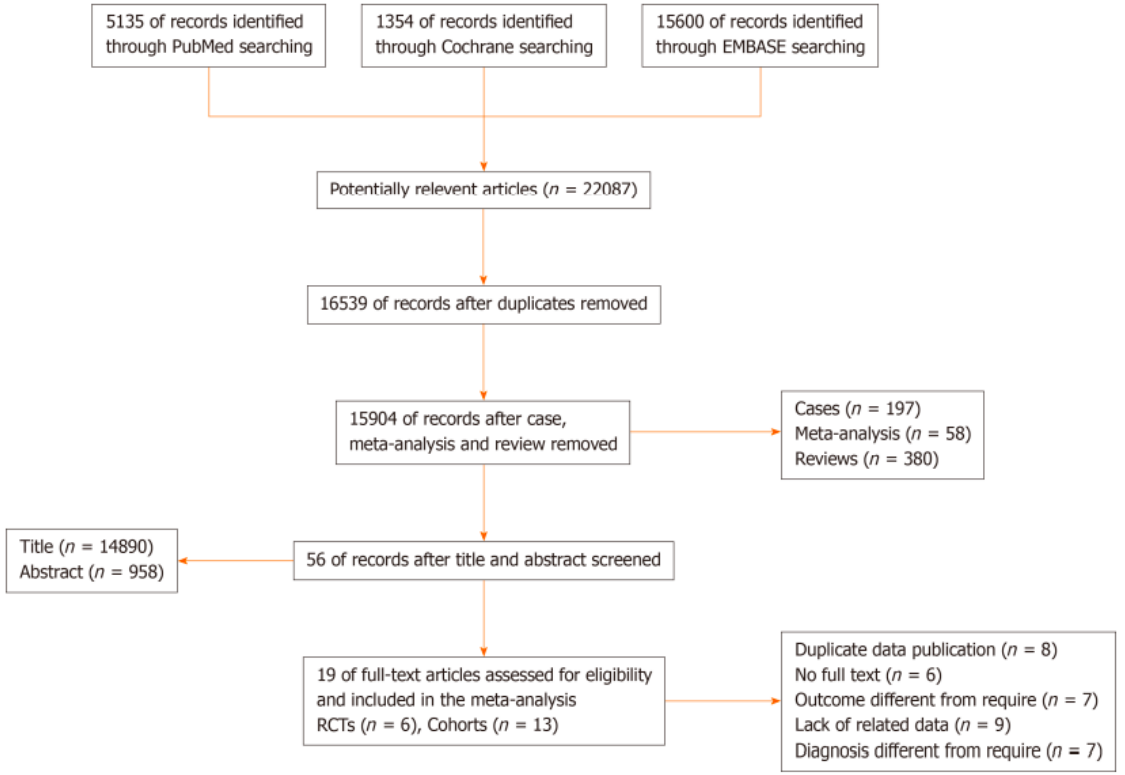


Figure 1 Flow diagram. RCT: Randomized controlled trial.

Neoadjuvant chemotherapy without radiation as a potential alternative treatment for locally advanced rectal cancer: A meta-analysis

Pei Wu, Hui-Mian Xu, Zhi Zhu *World J Gastrointest Oncol* 2021 September 15; 13(9): 1196-1209

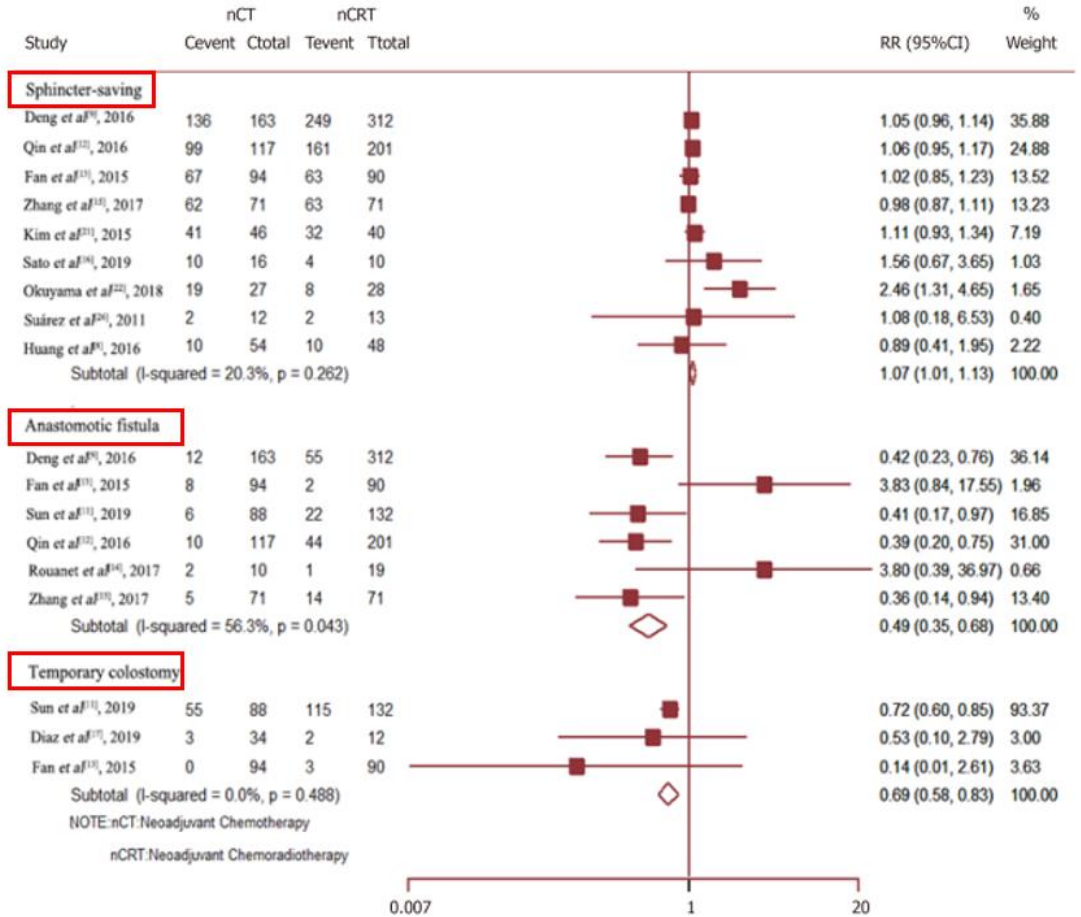


Figure 4 Neoadjuvant chemoradiotherapy was associated with lowering incidences of anastomotic fistula and temporary colostomy and increasing the sphincter preservation rate. CI: Confidence interval; nCRT: Neoadjuvant chemoradiotherapy; nCT: Neoadjuvant chemotherapy; RR: Risk ratio.

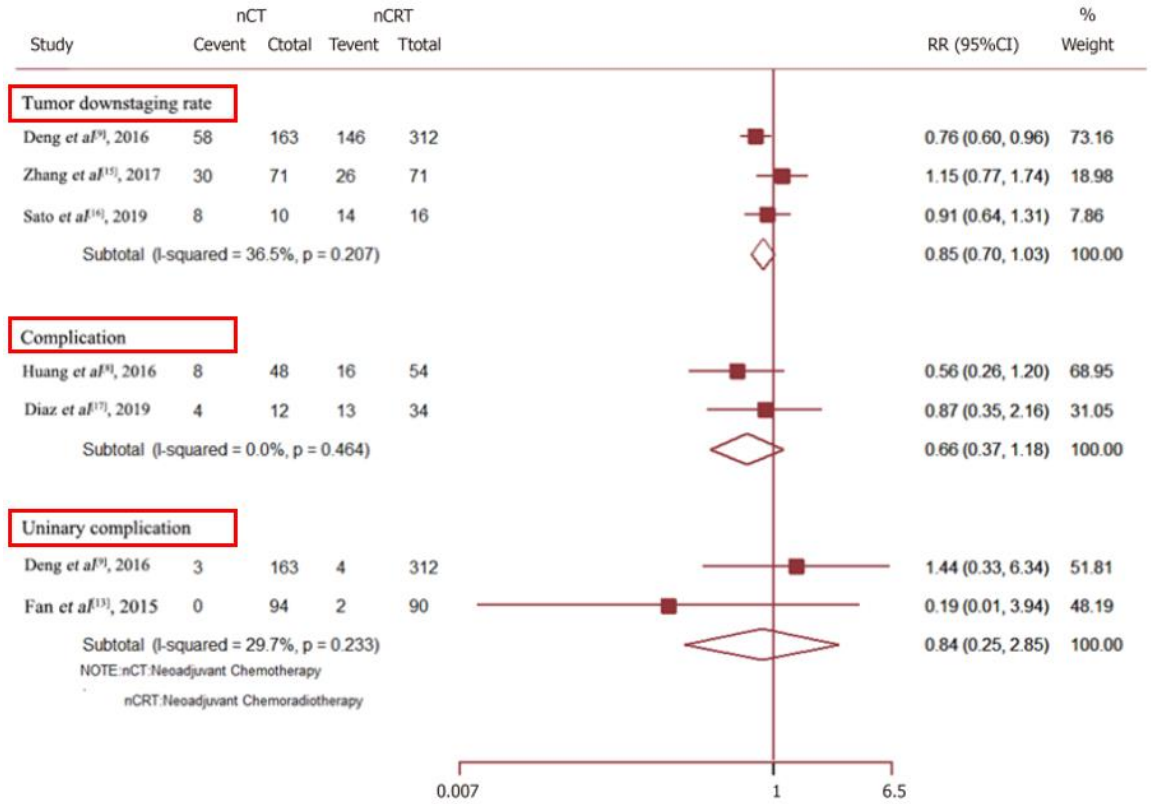
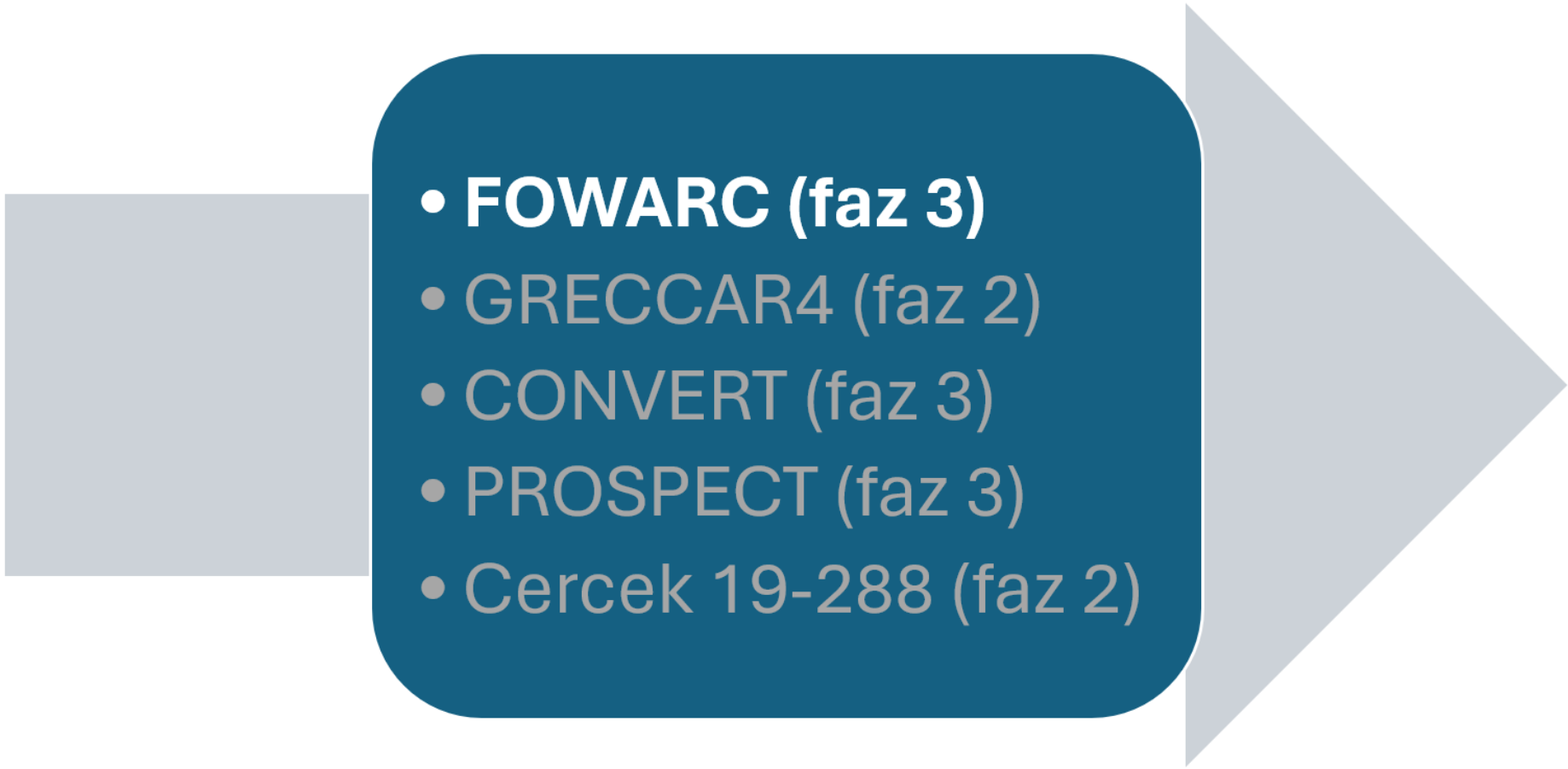


Figure 5 There were no significant differences in the tumor downstaging rate, overall complications, and urinary complications between the neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy groups. CI: Confidence interval; nCRT: Neoadjuvant chemoradiotherapy; nCT: Neoadjuvant chemotherapy; RR: Risk ratio.

Radyoterapisiz Çalışmalar



Clinical Trial > J Clin Oncol. 2019 Dec 1;37(34):3223-3233. doi: 10.1200/JCO.18.02309. Epub 2019 Sep 26.

Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial

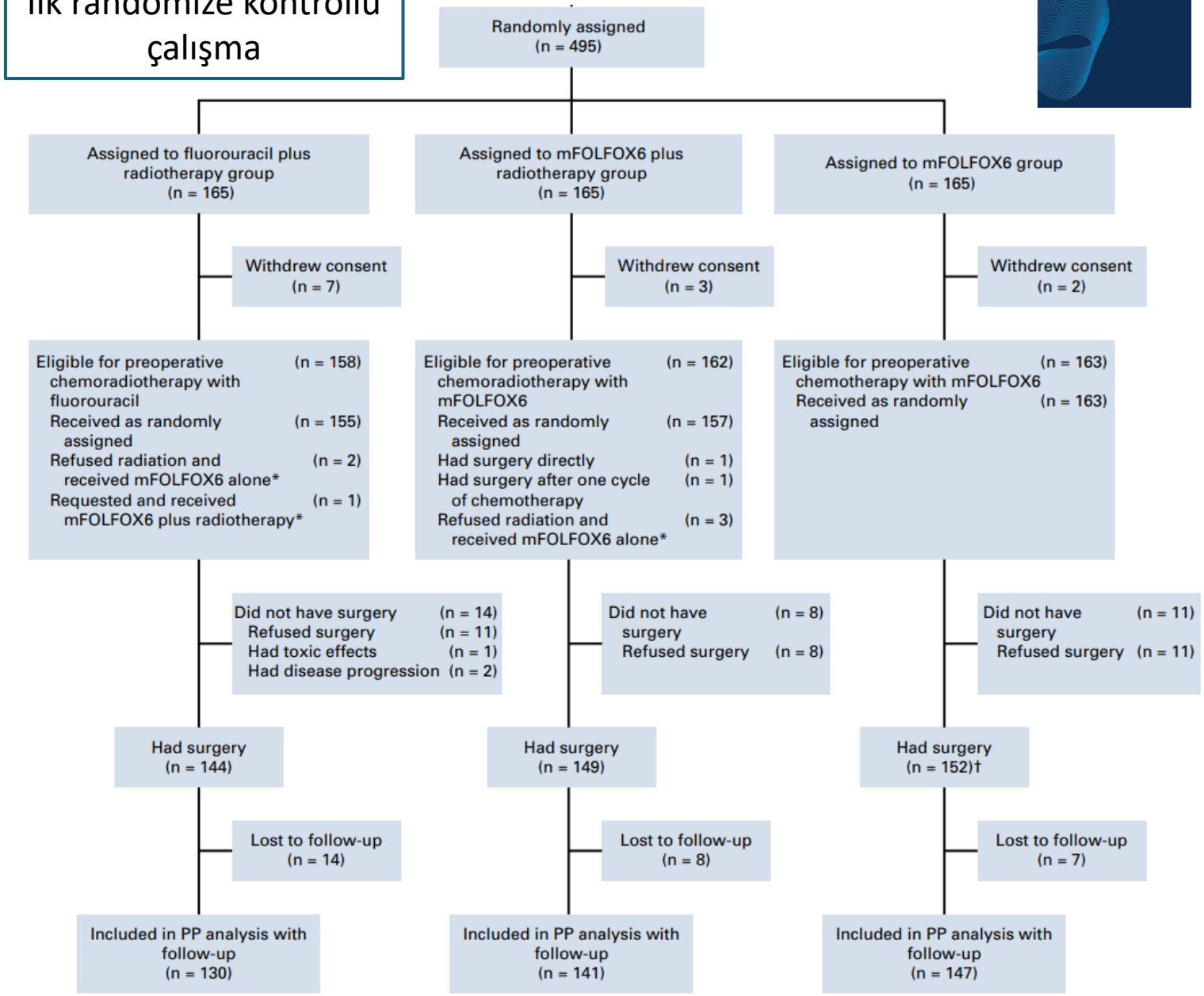
Yanhong Deng [1], Pan Chi [2], Ping Lan [1], Lei Wang [1], Weiqing Chen [3], Long Cui [4], Daoda Chen [5],

İlk randomize kontrollü çalışma

METHODS

Study Design and Patients

The FOWARC study (ClinicalTrials.gov identifier: NCT01211210) was a multicenter, randomized, phase III study conducted at 15 hospitals in China in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was registered for curative resection. Tumors were clinically confirmed as stage II (T3 to 4N0) or stage III (T1 to 4N1 to 2) with a positive node defined as 1.0 cm or larger in diameter on imaging and with a distal border located less than 12 cm from the anal verge. Patients also were required to have an Eastern Cooperative Oncology Group performance status of 1 or less and adequate hematologic, liver, and renal function. Key exclusion criteria were metastatic disease, prior radiotherapy or chemotherapy, the presence of other cancers, clinically significant cardiac disease, and known peripheral neuropathy. All participants provided written informed consent.



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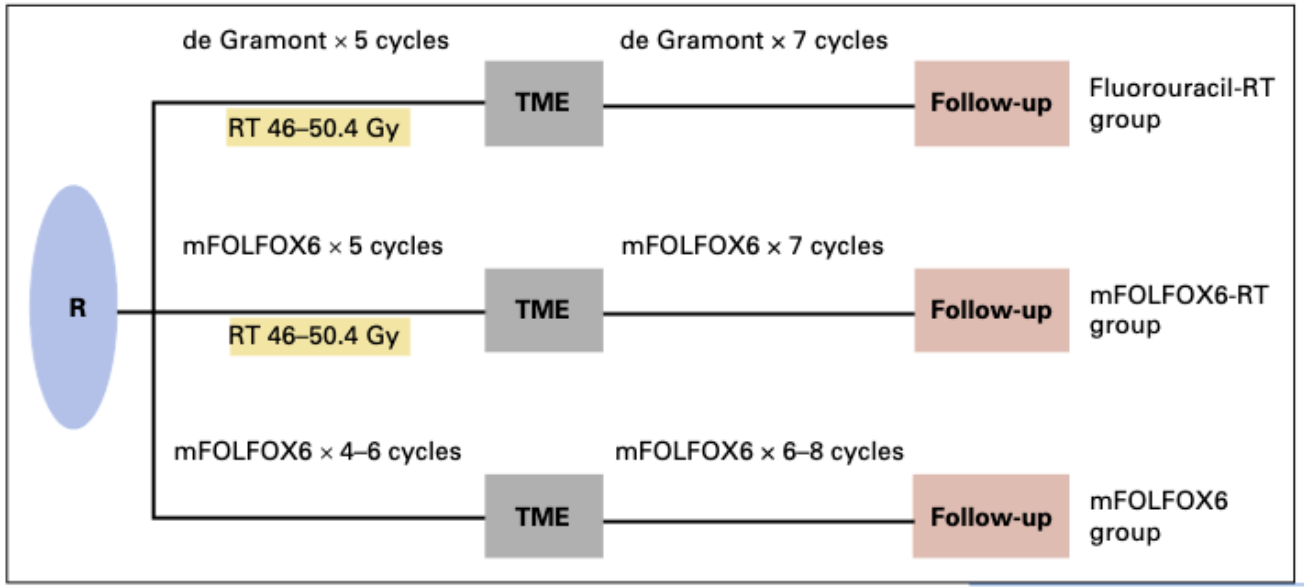

Fig 1. Study design. The de Gramont regimen consisted of leucovorin 400 mg/m^2 intravenously followed by fluorouracil 400 mg/m^2 intravenously and fluorouracil 2.4 g/m^2 by 48-h continuous intravenous infusion. mFOLFOX6 consisted of the de Gramont regimen with the addition of oxaliplatin 85 mg/m^2 intravenously on day 1 of each chemotherapy cycle. Radiotherapy was delivered in 23 to 28 fractions over 5 to 6 weeks for a total dose of 46 to 50.4 Gy. R, randomization; RT, radiotherapy; TME, total mesorectal excision.

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Study Treatments

Radiotherapy. Radiotherapy was delivered at 1.8 to 2.0 Gy per day from Monday to Friday for a total of 23 to 25 fractions over 5 to 6 weeks (total dose, 46.0 to 50.4 Gy). Radiation was delivered with a minimum energy of 6-MV photons through a three-field or four-field box technique to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes.

Study Measurements and End Points

The primary end point was 3-year DFS, defined as the time between random assignment and the occurrence of macroscopically nonradical surgery, locoregional recurrence or metastasis, or death as a result of any cause. Secondary end points were locoregional recurrence, OS, relapse-free survival, and quality of life. Quality-of-life data will be reported in another article. All resection specimens were examined

TABLE 1. Baseline Demographic and Clinical Characteristics (intention-to-treat population)

Characteristic	Fluorouracil Plus Radiotherapy No. (%)	mFOLFOX6 Plus Radiotherapy No. (%)	mFOLFOX6 No. (%)
No. of patients	165	165	165
Mean age, years (SD)	54.0 (11.9)	52.2 (11.8)	54.1 (12.1)
Male sex	103 (62.4)	114 (69.1)	108 (65.5)
Clinical T category			
cT4b	14 (8.5)	14 (8.5)	5 (3.0)
cT4a	43 (26.1)	42 (25.5)	45 (27.3)
cT3	100 (60.6)	106 (64.2)	114 (69.1)
cT2	8 (4.8)	3 (1.8)	1 (0.6)
Clinical N category			
cN2a	36 (21.8)	33 (20.0)	35 (21.2)
cN2b	8 (4.8)	14 (8.5)	8 (4.8)
cN1	84 (50.9)	88 (53.3)	76 (46.1)
Clinical stage III	128 (77.6)	135 (81.8)	119 (72.1)
Mean tumor length, cm (SD)	4.3 (1.8)	4.3 (1.5)	4.3 (1.6)
Distance from anal verge, cm			
> 10	5 (3.0)	7 (4.2)	9 (5.5)
5-10	70 (42.4)	75 (45.5)	86 (52.1)
< 5	90 (54.5)	83 (50.3)	70 (42.4)
Mean distance, cm (SD)	5.3 (2.3)	5.4 (2.5)	6.0 (2.6)
Mesorectal fascia involvement	32 of 101 (31.7)	38 of 107 (35.5)	33 of 105 (31.4)

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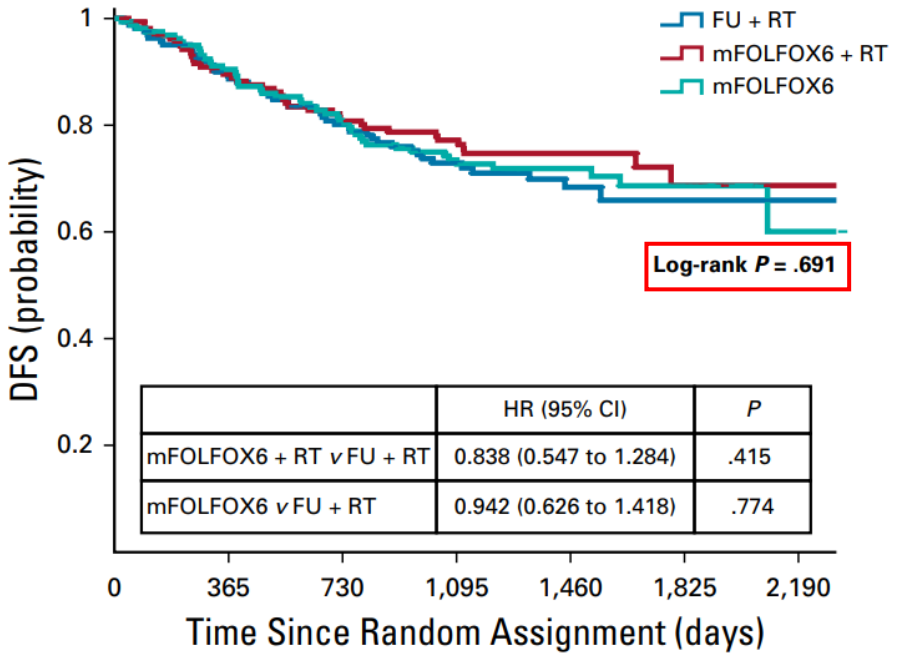
Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial

Yanhong Deng [1], Pan Chi [2], Ping Lan [1], Lei Wang [1], Weiqing Chen [3], Long Cui [4], Daoda Chen [5],

(modified ITT population). Surgery was performed in 141, 149, and 152 patients in each group, respectively. As previously reported,[15] a higher pCR rate was observed in the mFOLFOX6 plus radiotherapy group (27.5%) compared with the fluorouracil plus radiotherapy group (14.0%) or mFOLFOX6 group (6.5%).

Median follow-up was 45.2 months (range, 1 to 83 months). In the ITT population, macroscopically nonradical surgery, locoregional recurrence or metastasis, or death as a result of any cause was observed in 131 patients (46 events in the fluorouracil plus radiotherapy group, 39 in the mFOLFOX6 plus radiotherapy group, and 46 in the mFOLFOX6 group). No significant between-group differences were found in terms of liver or lung metastases. At 3 years, the probability

A



No. at risk:

FU + RT	165	135	118	80	41	13	4
mFOLFOX6 + RT	165	133	119	94	52	17	4
mFOLFOX6	165	141	125	98	54	22	5

terms of liver or lung metastases. At 3 years, the probability of DFS was 72.9% (SD, 3.6%), 77.2% (SD, 3.4%), and 73.5% (SD, 3.6%) in the fluorouracil plus radiotherapy, mFOLFOX6 plus radiotherapy, and mFOLFOX6 groups, respectively ($P = .709$ by log-rank test; Fig 2A). Relative to the fluorouracil plus radiotherapy group, the HR for DFS was 0.838 (95% CI, 0.547 to 1.284; $P = .415$) for the mFOLFOX6 plus radiotherapy group and 0.942 (95% CI, 0.626 to 1.418; $P = .774$) for the mFOLFOX6 group, and median DFS was not reached. In a multivariable analysis,

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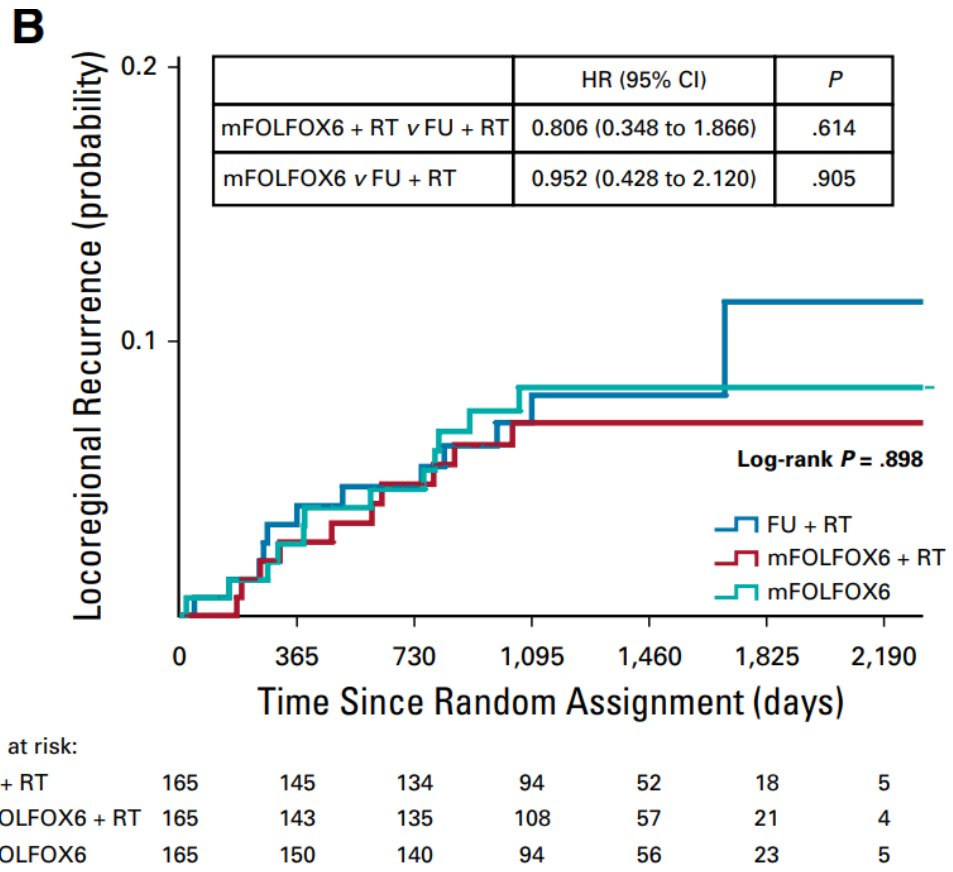

At 3 years, the probability of local recurrence after R0/1 resection was 8.0% (SD, 2.4%), 7.0% (SD, 2.1%), and 8.3% (SD, 2.3%) in the fluorouracil plus radiotherapy, mFOLFOX6 plus radiotherapy, and mFOLFOX6 groups, respectively (log-rank $P = .873$; Fig 2B). Relative to the fluorouracil plus radiotherapy group, the HR for local recurrence was 0.806 (95% CI, 0.348 to 1.866; $P = .614$) for the mFOLFOX6 plus radiotherapy group and 0.952 (95% CI, 0.428 to 2.120; $P = .905$) for the mFOLFOX6 group. In

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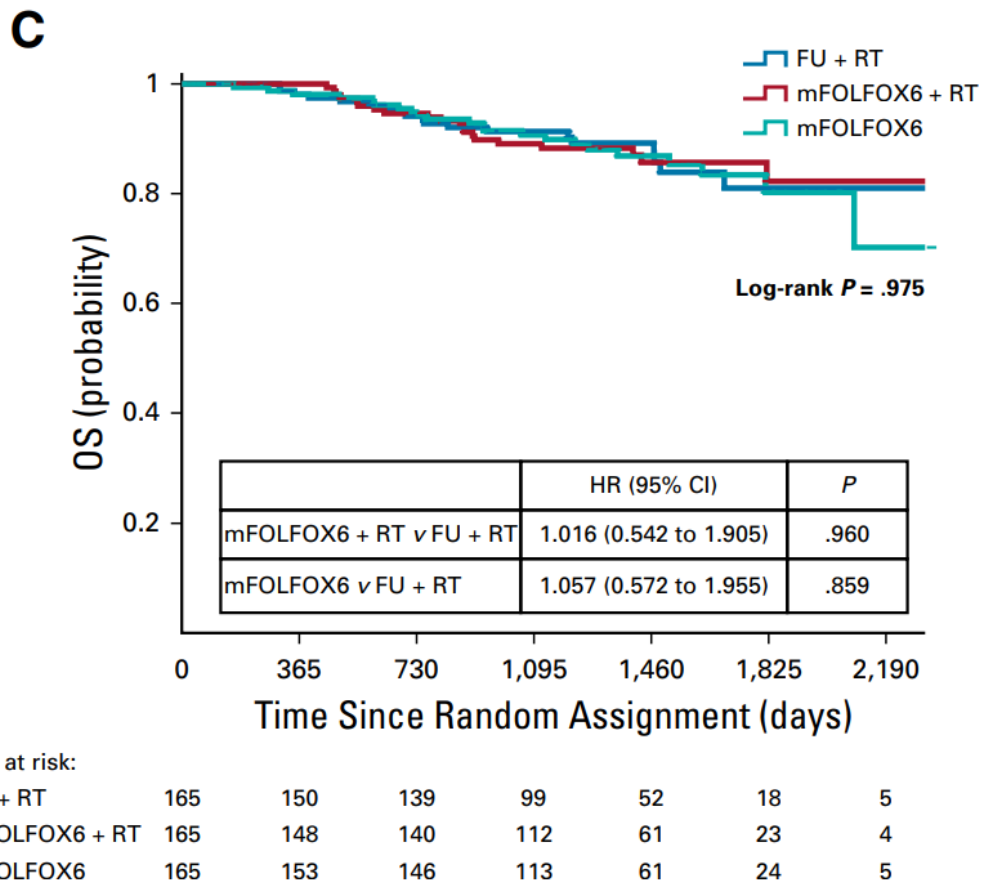

Overall, 61 patients died during the study: 19, 20, and 22 in the fluorouracil plus radiotherapy, mFOLFOX6 plus radiotherapy, and mFOLFOX6 groups, respectively. The

probability of OS at 3 years was 91.3% (SD, 2.3%), 89.1% (SD, 2.6%), and 90.7% (SD, 2.4%) in each group, respectively (intergroup $P = .971$ by the log-rank test; Fig 2C). Relative to the fluorouracil plus radiotherapy group, the HR for OS was 1.106 (95% CI, 0.542 to 1.905; $P = .960$) for the mFOLFOX6 plus radiotherapy group and 1.057 (95% CI, 0.572 to 1.955; $P = .859$) for the mFOLFOX6 group. Similar

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Yanhong Deng [1], Pan Chi [2], Ping Lan [1], Lei Wang [1], Weiqing Chen [3], Long Cui [4], Daoda Chen [5],

TABLE 2. Anal Function Findings in Patients With No Stoma at Last Follow-Up

Finding	Fluorouracil Plus Radiotherapy	mFOLFOX Plus Radiotherapy	mFOLFOX	*P**
No. of patients	61	70	89	
Stool frequency, per day				.000
0-3	24 (39.3)	26 (37.1)	64 (71.9)	
4-5	17 (27.9)	20 (58.6)	10 (11.2)	
6-9	12 (19.7)	21 (30.0)	14 (15.7)	
≥ 10	8 (13.1)	3 (4.3)	1 (1.1)	
Wexner score > 8	25 (41)	25 (35.7)	16 (18)	.005
Solid incontinence	18 (29.5)	14 (20.0)	6 (6.7)	.001
Liquid incontinence	20 (32.8)	11 (15.7)	7 (7.9)	.000
Gas incontinence	10 (16.4)	5 (7.1)	2 (2.2)	.006
Day incontinence	24 (39.3)	24 (34.3)	20 (22.5)	.068
Night incontinence	20 (32.8)	19 (27.1)	8 (9.0)	.001
Anal blood loss	2 (3.3)	6 (8.6)	3 (3.4)	.252
Use of pads	19 (31.1)	18 (25.7)	8 (9.0)	.002

Anal function data were collected for patients with no stoma and no local recurrence who had available data at the most recent follow-up: 60, 67, and 88 patients in the fluorouracil plus radiotherapy, mFOLFOX6 plus radiotherapy, and mFOLFOX6 groups, respectively. Although not representative of the entire patient cohort, in this subpopulation of patients, those who had not received radiotherapy had better anal function in terms of the number of defecations per day, Wexner score, and liquid and nocturnal incontinence (Table 2).

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Author/year/ reference	No patients	Randomized Groups	Radiation Schedule	Major Findings
Omission of RT and/or Chemotherapy				
FOWARC; (Deng et al., 2019)	495	5 cycles of 5-FU/LV followed by lcRT and TME vs. 5 cycles of mFOLFOX6 followed by lcRT and TME vs. 4–6 cycles of mFOLOFX6 followed by surgery	1.8 Gy/fraction x 23 days or 2 Gy/fraction x 28 days	Pathologic CR: 14% vs. 27.5% vs. 6.5% No other significant differences

To our knowledge, this randomized controlled study is the first to report a comparison between chemoradiotherapy and chemotherapy alone in the neoadjuvant setting for locally advanced rectal cancer. Although our trial design did not allow for a noninferiority comparison between mFOLFOX6 without radiation and standard chemoradiation, the results showed no significant difference in DFS or locoregional recurrence for patients who received mFOLFOX6 without routine use of radiation and those who received fluorouracil plus radiotherapy. Given these

In summary, the final results from the FOWARC study show that mFOLFOX6 with or without radiation did not significantly improve 3-year DFS relative to fluorouracil plus radiation in patients with locally advanced rectal cancer. However, although the study was not set up to detect noninferiority among treatment arms, no difference in outcomes was found between patients who received mFOLFOX6 without radiotherapy and those who received standard fluorouracil plus radiotherapy, which warrants additional investigation to clarify the role of radiotherapy in neoadjuvant treatment of locally advanced rectal cancer. Long-term follow-up also is required to establish any differences in OS.

Long-term outcome of neoadjuvant mFOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: A multicenter, randomized phase III trial.

Jianwei Zhang, Pan Chi, Ping Lan, Long Cui, Hongbo Wei, Ren Zhao, Zhongcheng Huang, Hao Zhang,

Gastrointestinal Cancer—Colorectal and Anal | May 31, 2023

Background: Pevisous results of phase III FOWARC trial demonstrated that mFOLFOX6, with or without radiation, did not significantly improve survival versus fluorouracil with radiation in patients with locally advanced rectal cancer at 3 yeas. Here, we presented the data of long-term disease free survival (DFS) and overall survival (OS). **Methods:** In this multicenter, phase III trial, patients with stage II/III rectal cancer were randomly assigned (1:1:1) to receive 5 cycles of infusional fluorouracil (leucovorin 400 mg/m2, fluorouracil 400 mg/m2, and fluorouracil 2.4 g/m2 over 48 hours) plus radiotherapy (46.0 to 50.4 Gy delivered in 23 to 25 fractions during cycles 2 to 4) followed by surgery and seven cycles of infusional fluorouracil adjuvant treatment, mFOLFOX6 plus radiotherapy, or four to six cycles of mFOLFOX6 followed by surgery and six to eight cycles of mFOLFOX6. **Results:** Totally, 495 patients were enrolled,165 pateints in each group. 445 patients underwent surgery. After a median follow-up of 9.5 years, DFS events were observed in 56, 54, and 55 patients in fluorouracil plus radiotherapy, mFOLFOX6 plusradiotherapy, and mFOLFOX6 goups. The 10-year DFS rate were 55.5%, 63.0% and 62.8% (P = 0.934 by the log-rank test). OS evets were reported in 39, 38, and 40 patientts in the 3 group. The 10-year OS rate was 66.2%, 73.2% and 73.0% (P = 0.919 by the log-rank test), respectively. **Conclusions:** With long-term follow up, no significant difference in was found in survival outcome between mFOLFOX6, with and without radiation. Comparing with fluorouracil plus radiation, mFOLFOX6 plus radiation also failed to improve long-term survival. Clinical trial information: NCT01211210. Research Sponsor: Supported by National Key Clinical Discipline, China National Natural Science Foundation.

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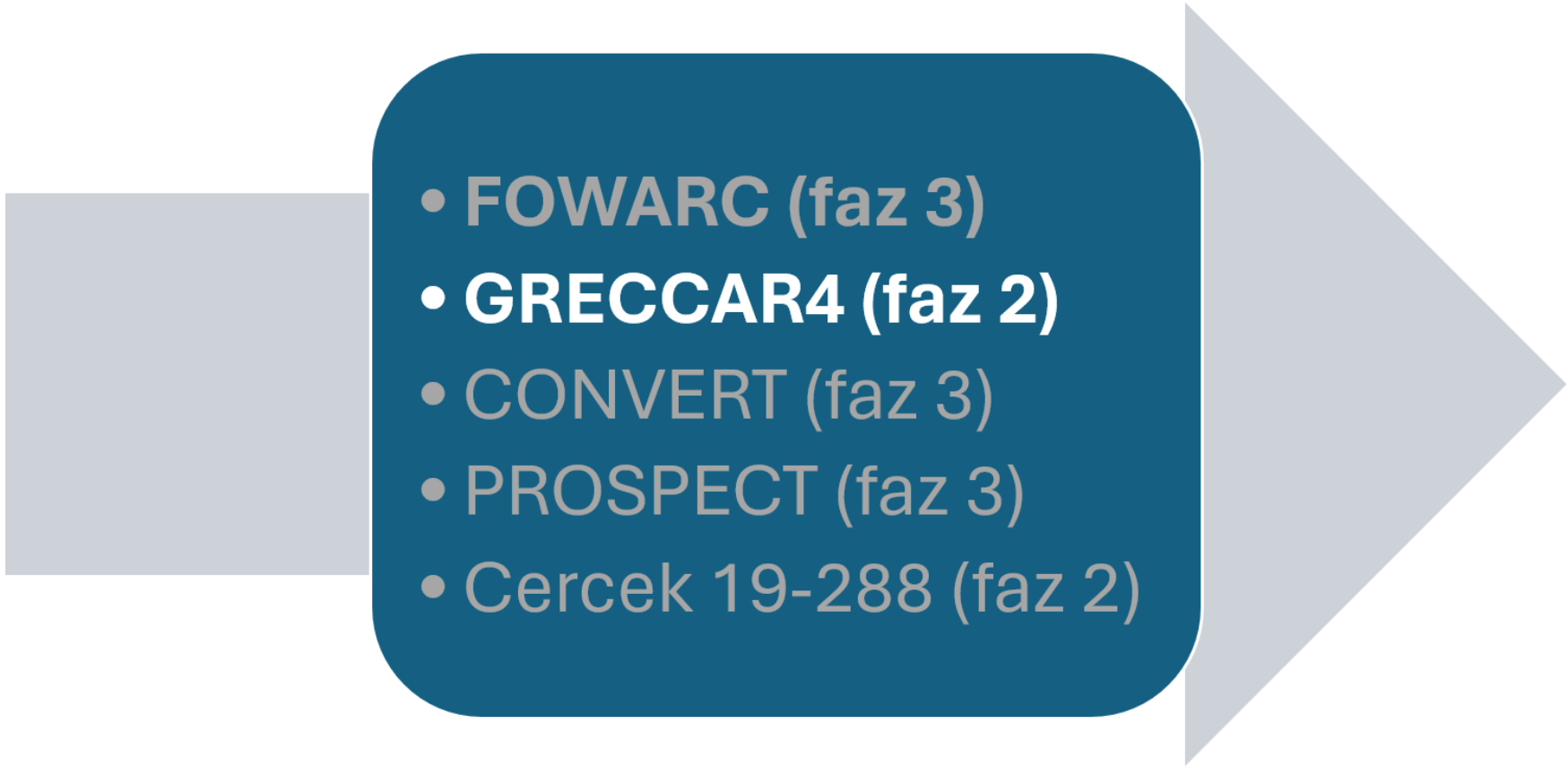

Tailored Strategy for Locally Advanced Rectal Carcinoma (**GRECCAR 4**): Long-term Results From a Multicenter, Randomized, Open-Label, Phase II Trial.

Rouanet P, Rullier E, Lelong B, Maingon P, Tuech JJ, Pezet D, Castan F, Nougaret S; GRECCAR Study Group*.

Dis Colon Rectum. 2022 Aug 1;65(8):986-995. doi: 10.1097/DCR.0000000000002153. Epub 2022

Patients: Two hundred six patients were randomly assigned to treatment: good responders after chemotherapy (≥75% tumor volume reduction) to immediate surgery (arm A) or standard radiochemotherapy (capecitabine 50) plus surgery (arm B) and poor responders to capecitabine 50 (arm C) or intensive radiochemotherapy (capecitabine 60; 60 Gy irradiation; arm D) before surgery.

Interventions: Treatment was tailored according to MRI response to induction chemotherapy.

Results: After induction treatment, 194 patients were classified as good (n = 30, 15%) or poor (n = 164, 85%) responders; they were included in arms A and B (16 and 14 patients) or C and D (113 and 51 patients). The primary objective was obtained: R0 resection rates (90% CI) in the 4 arms were 100% (74-100), 100% (85-100), 83% (72-91), and 88% (77-95). At 5 years, overall survival rates were 90% (47.3-98.5), 93.3% (61.3-99.0), 84.3% (71.0-91.8), and 86.1% (71.6-93.5); disease-free survival rates were 80% (40.9-94.6), 89.5% (64.1-97.3), 72.9% (58.5-82.9), and 72.8% (57.7-83.2); local recurrence rates were 0%, 0%, 2.1% (0.3-13.9), and 9.3% (3.6-23.0); and metastasis rates were 20% (5.4-59.1), 10.5% (2.7-35.9), 18% (31.8-94.6), and 18.8% (10.2-33.0). Late morbidity and quality-of-life evaluations showed no significant difference between arms.

Limitations: Limitations were due to the small number of patients randomly assigned in the good responder arms, especially arm A without radiotherapy.

Conclusion: Tailoring preoperative radiochemotherapy based on induction treatment response appears to be promising. Future prospective trials should confirm this strategy. See Video Abstract

- Faz 2
- T3d, CRM 1mm
- Grup A: KT (>%75 cevap) + cerrahi
- Grup B: KRT + cerrahi

A ve B kolu indüksiyona iyi cevap verenler

- Grup C: KRT + cerrahi + KT (kötü cevap verenler)
- Grup D: intensive KRT (irino+kapesitabin 60Gy) + cerrahi

Sonuç:

- Patolojik tam cevapta
- Geç morbidite QoL'da
- 5 yıllık OS'de fark yok

Limitasyon: İndüksiyon sonrası iyi cevap oranı sadece %15 (30/194)

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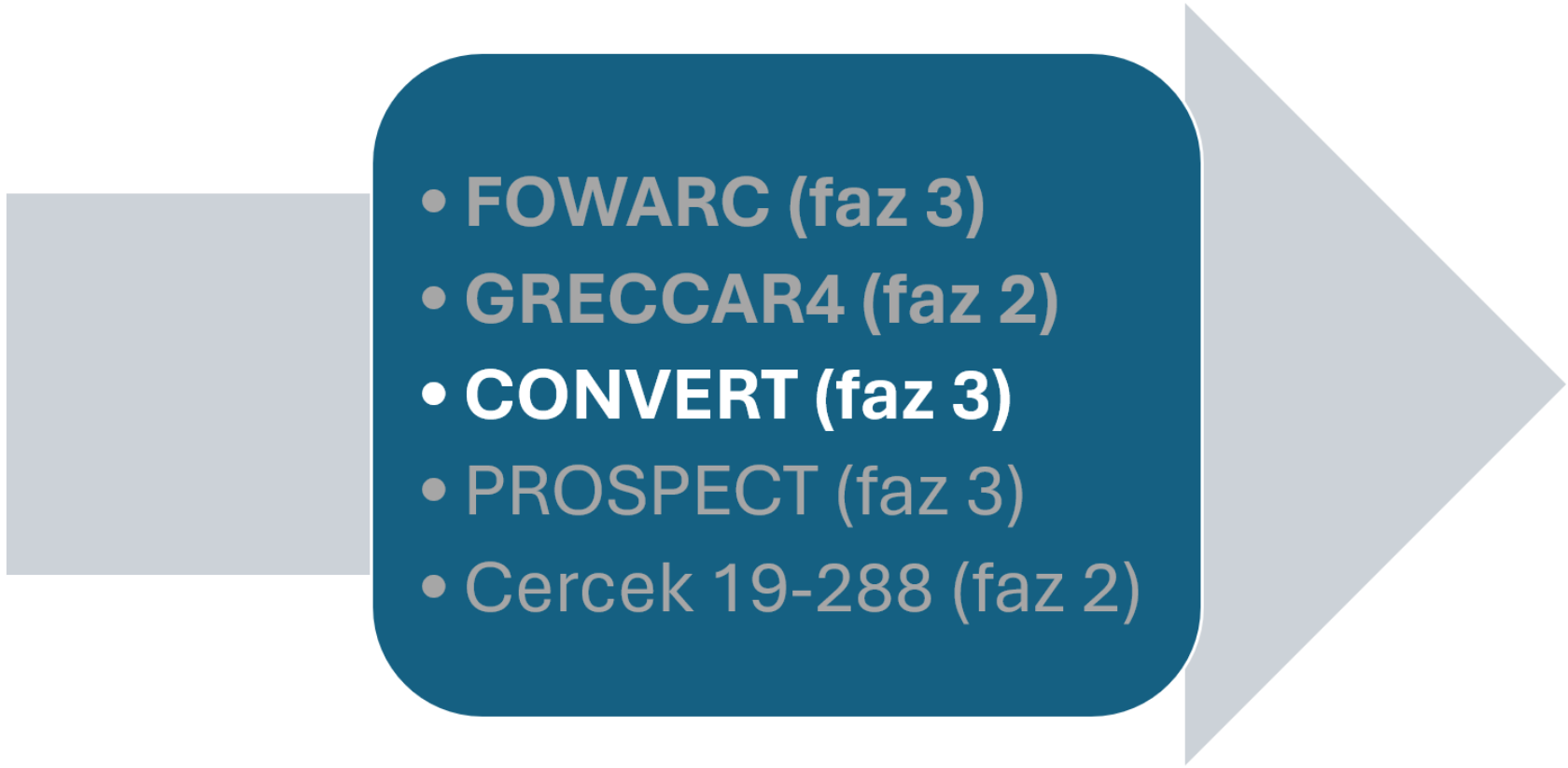
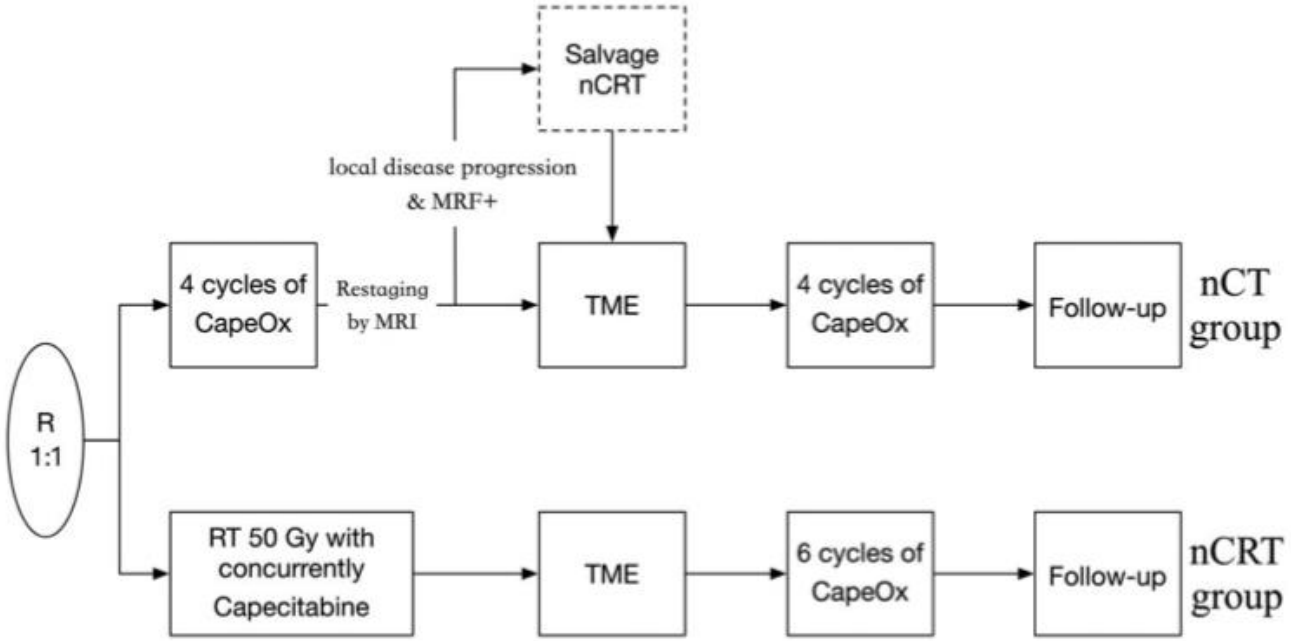


Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced **Rectal Cancer** With Uninvolved Mesorectal Fascia (**CONVERT**): Initial Results of a Phase III Trial.

Mei WJ, Wang XZ, Li YF, Sun YM, Yang CK, Lin JZ, Wu ZG, Zhang R, Wang W, Li Y, Zhuang YZ

Ann Surg. 2023 Apr 1;277(4):557-564. doi: 10.1097/SLA.0000000000005780.



- 589 hasta
- T3-4 %94-95 ; N1-2 %69-73
- İlk 10cm'de %96
- EMVI %82-78 (-)
- Klinik N(+) %69-73
- MRI'a göre lateral LN %91-87 (-)

TABLE 1. Baseline Demographic and Clinical Characteristics in the mITT Population

Characteristics	Treatment group, No. (%)	
	Neoadjuvant chemotherapy (n = 300)	Neoadjuvant chemoradiotherapy (n = 289)
Age, years		
Median(range)	60 (31-75)	60 (28-75)
Sex		
Male	188 (62·7)	177 (61·2)
Female	112 (37·3)	112 (38·8)
Clinical T category		
cT2	16 (5·3)	11 (3·8)
cT3	201 (67·0)	202 (69·9)
cT4a	83 (27·7)	76 (26·3)
Clinical N category		
cN0	92 (30·7)	77 (26·7)
cN1	147 (49·0)	133 (46·0)
cN2	61 (20·3)	79 (27·3)
Distance from the anal verge		
> 10 cm	10 (3·3)	8 (2·8)
5-10 cm	166 (55·3)	163 (56·4)
≤ 5 cm	124 (41·3)	118 (40·8)
EMVI by MRI		
Positive	52 (17·3)	63 (21·8)
Negative	248 (82·7)	226 (78·2)
Lateral lymph node by MRI		
Positive	27 (9·0)	36 (12·5)
Negative	273 (91·0)	253 (87·5)

EMVI indicates extramural venous invasion; mITT, modified intention-to-treat.

Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced **Rectal Cancer** With Uninvolved Mesorectal Fascia (**CONVERT**): Initial Results of a Phase III Trial.

Mei WJ, Wang XZ, Li YF, Sun YM, Yang CK, Lin JZ, Wu ZG, Zhang R, Wang W, Li Y, Zhuang YZ

Ann Surg. 2023 Apr 1;277(4):557-564. doi: 10.1097/SLA.0000000000005780.

Results: Of the 663 initially enrolled patients, 589 received the allocated treatment (nCT, n=300; nCRT, n=289). Pathologic complete response rate was 11.0% (95% CI, 7.8-15.3%) in the nCT arm and 13.8% (95% CI, 10.1-18.5%) in the nCRT arm (P =0.33). The downstaging (ypStage 0 to 1) rate was 40.8% (95% CI, 35.1-46.7%) in the nCT arm and 45.6% (95% CI, 39.7-51.7%) in the nCRT arm (P =0.27). nCT was associated with lower perioperative distant metastases rate (0.7% vs. 3.1%, P =0.03) and preventive ileostomy rate (52.2% vs. 63.6%, P =0.008) compared with nCRT. Four patients in the nCT arm received salvage nCRT because of local disease progression after nCT. Two patients in the nCT arm and 5 in the nCRT arm achieved complete clinical response and were treated with a nonsurgical approach. Similar results were observed in subgroup analysis.

Conclusions: nCT achieved similar pCR and downstaging rates with lower incidence of perioperative distant metastasis and preventive ileostomy compared with nCRT. CAPOX could be an effective alternative to neoadjuvant therapy in LARC with uninvolved MRF. Long-term follow-up is needed to confirm these results.

TABLE 2. Pathological Findings

Variable	Treatment Group, No. (%) Neoadjuvant chemotherapy (n = 272)	Neoadjuvant Chemoradiotherapy (n = 261)	*P*
Pathologic T category	—	—	0·524
ypT0	32 (11·8)	36 (13·8)	—
ypTis	1 (0·4)	3 (1·1)	—
ypT1	15 (5·5)	11 (4·2)	—
ypT2	73 (26·8)	76 (29·1)	—
ypT3	110 (40·4)	107 (41·0)	—
ypT4	41 (15·1)	28 (10·7)	—
Pathologic N category	—	—	0·038
ypN0	200 (73·5)	214 (82·0)	—
ypN1	62 (22·8)	37 (14·2)	—
ypN2	10 (3·7)	10 (3·8)	—
Pathologic complete response	—	—	0·333
Yes	30 (11·0)	36 (13·8)	—
No	242 (89·0)	225 (86·2)	—
ypT0-2N0M0	—	—	0·265
Yes	111 (40·8)	119 (45·6)	—
No	161 (59·2)	142 (54·4)	—
Tumor regression grade	—	—	<0·001
TRG 0	30 (11·0)	36 (13·8)	—
TRG-1	33 (12·1)	60 (23·0)	—
TRG-2	98 (36·0)	103 (39·5)	—
TRG-3	111 (40·8)	58 (22·2)	—
Missing	0	4 (1·5)	—
TRG 0-1	—	—	<0·001
Yes	63 (23·2)	96 (36·8)	—
No	209 (76·8)	161 (61·7)	—
Missing	0	4 (1·5)	—

Radyoterapisiz Çalışmalar

Randomized Controlled Trial > N Engl J Med. 2023 Jul 27;389(4):322-334.
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Preoperative Treatment of Locally Advanced Rectal Cancer

Deborah Schrag [1], Qian Shi [1], Martin R Weiser [1], Marc J Gollub [1], Leonard B Saltz [1],

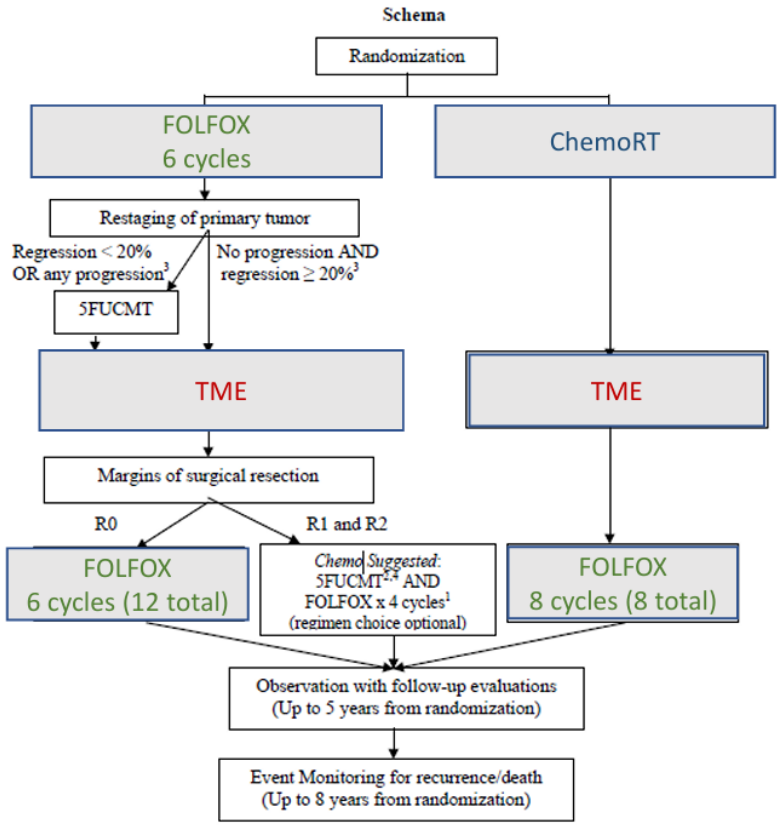
NEJM

Alliance Prospect Trial: Neoadjuvant FOLFOX and Selective Use of Chemoradiation

Phase II/III n=1100 Completed

Eligibility
T2N1,T3N0, T3N1
No distal tumors (> 5 cm from anal verge)
No N2
No T4
Tumor must be > 3mm from mesorectal fascia

Endpoints:
Time to local recurrence
Disease-Free survival



**If non-inferior, what about toxicity?

FOLFOX x 12 cycles and no RT
vs

ChemoRT + **FOLFOX x 8 cycles**

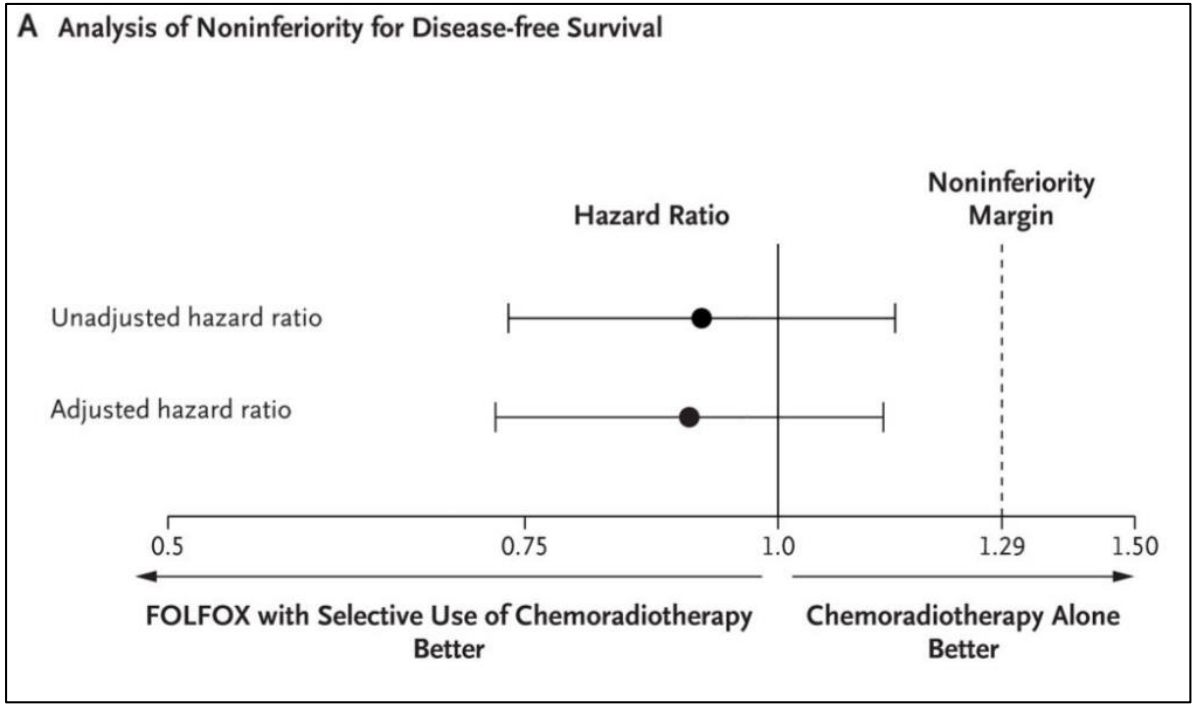
Bowel toxicity vs neuropathy tradeoffs?

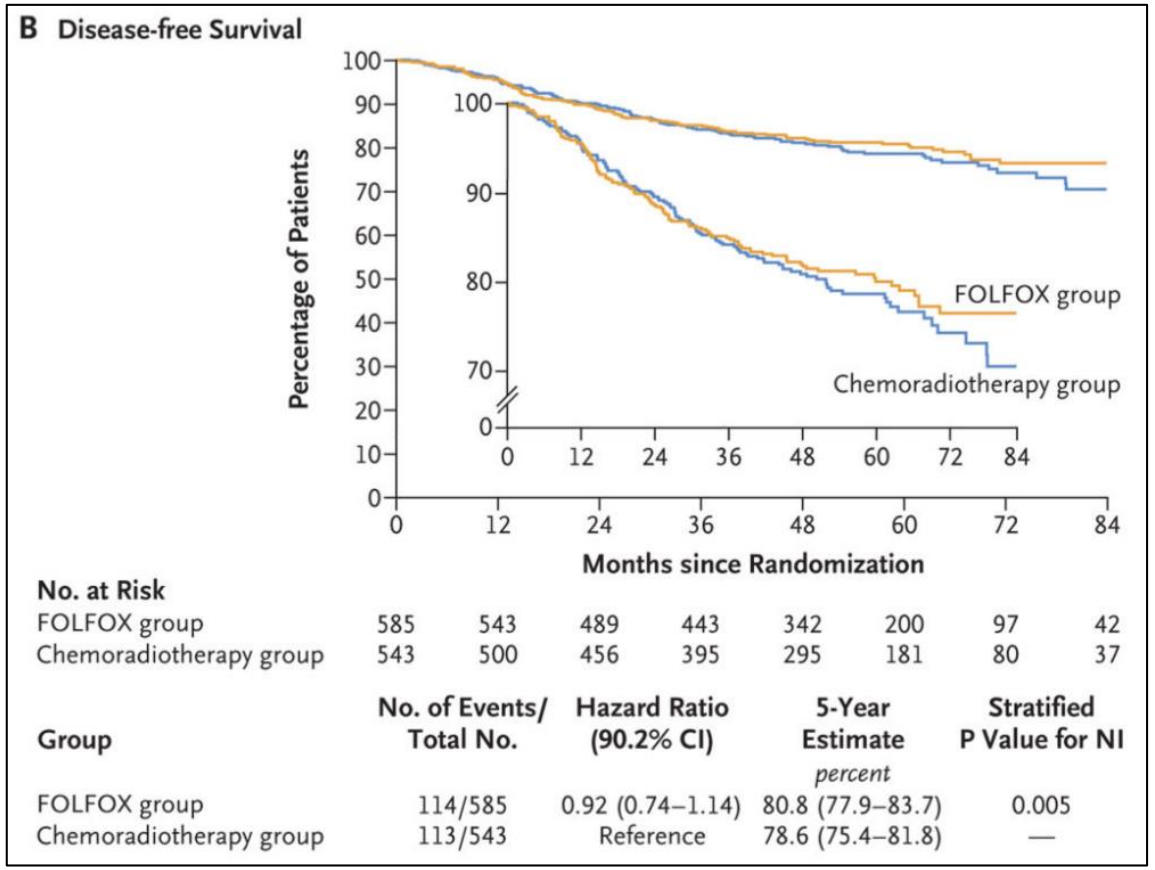
Characteristic	FOLFOX Group (N = 585)	Chemoradiotherapy Group (N = 543)
Yes	81 (13.8)	83 (15.3)
No	504 (86.2)	460 (84.7)
History of cardiovascular disease — no. (%)	106 (18.1)	98 (18.0)
Starting neoadjuvant treatment — no. (%)	479 (81.9)	445 (82.0)
Highest education level — no./total no. (%)		
Less than high school	29/568 (5.1)	29/531 (5.5)
High school diploma or GED certificate	214/568 (37.7)	201/531 (37.9)
Some college	119/568 (21.0)	102/531 (19.2)
College degree or higher	206/568 (36.3)	199/531 (37.5)
ECOG performance-status score — no. (%)[§]		
0 or 1	582 (99.5)	540 (99.4)
2	3 (0.5)	3 (0.6)
Primary rectal tumor on digital examination — no./total no. (%)		
Rectal tumor not palpable	290/580 (50.0)	259/536 (48.3)
Rectal tumor palpable	290/580 (50.0)	277/536 (51.7)
Rectal tumor location — cm from anal verge		
No. of patients with data	585	542
Mean	8.6±2.9	8.5±2.8
Median (range)	8 (2–25)	8 (2–18)
Rectal tumor location — no. (%)		
≤5 cm from anal verge	83 (14.2)	90 (16.6)
>5 to ≤10 cm from anal verge	375 (64.1)	344 (63.4)
>10 cm from anal verge	127 (21.7)	109 (20.1)
Clinical stage — no./total no. (%)		
T2 node positive	63/584 (10.8)	38/543 (7.0)
T3 node negative	232/584 (39.7)	198/543 (36.5)
T3 node positive	289/584 (49.5)	307/543 (56.5)
Staging performed with MRI — no. (%)		
Yes	494 (84.4)	458 (84.3)
No	91 (15.6)	85 (15.7)

STATISTICAL ANALYSIS

Noninferiority with respect to the primary end point required a hazard ratio for disease recurrence or death with a margin of less than 1.29, corresponding to 5-year disease-free survival that was 5 percentage points lower in the FOLFOX group than in the chemoradiotherapy group. In the original design, the prespecified acceptable maximum

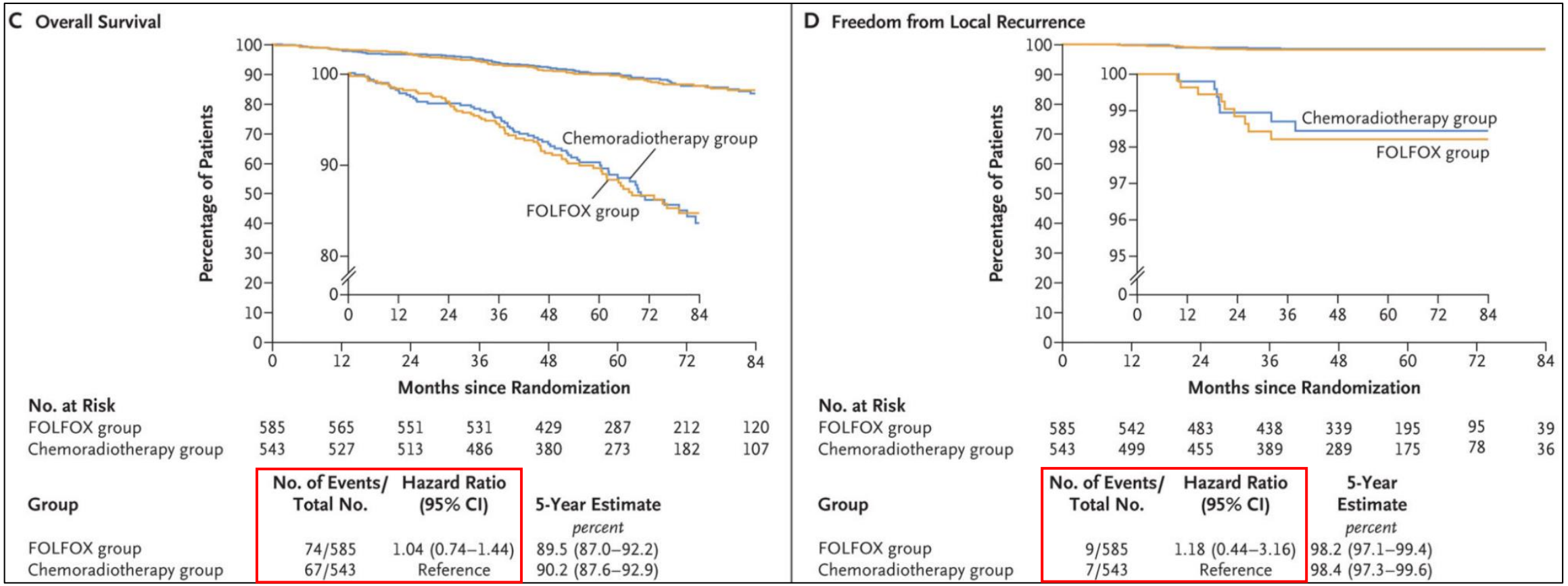
- %85 hasta orta ve üst rektumda
- %38 N0
- Hastaların %85'ine MRI evrelemesi yapılmasına rağmen T3 ve nodal alt gruplar rapor edilmemiş
- KT grubunda, hastaların %74.9'u ortalama 6 kür adjuvan FOLFOX (+)
- KRT grubundaki hastaların %77,9'u, ortalama 8 kür adjuvan FOLFOX (+)
- KT grubundaki hastaların %10,4'ü aynı zamanda KRT (+)





DISEASE-FREE SURVIVAL

FOLFOX with selective use of chemoradiotherapy was found to be noninferior to chemoradiotherapy with respect to disease-free survival (hazard ratio for disease recurrence or death, 0.92; two-sided 90.2% confidence interval [CI], 0.74 to 1.14; P = 0.005 for noninferiority), and an analysis with adjustment for age and clinical nodal status yielded consistent results (Fig. 2A and 2B). Five-year disease-free survival was 80.8% (95% CI, 77.9 to 83.7) in the FOLFOX group and 78.6% (95% CI, 75.4 to 81.8) in the chemoradiotherapy group. Figure S3 shows a comparison of disease-free survival in prespecified subgroups of interest. In a supplementary analysis of disease-free survival involving all 1194 patients who underwent randomization, the hazard ratio for disease recurrence or death was 0.91 (90.2% CI, 0.73 to 1.13; P = 0.004 for noninferiority); results were similar for patients in the per-protocol population who were later found to be ineligible. The proportional-hazards assumption was not violated (P = 0.30 by the Schoenfeld residuals method).



OVERALL SURVIVAL AND LOCAL RECURRENCE

Five-year overall survival was 89.5% in the FOLFOX group and 90.2% in the chemoradiotherapy group (hazard ratio for death, 1.04; 95% CI, 0.74 to 1.44) (Fig. 2C). Local recurrence occurred in nine patients in the FOLFOX group and seven patients in the chemoradiotherapy group; the incidence of local recurrence at 5 years was 1.8% and 1.6%, respectively (hazard ratio, 1.18; 95% CI, 0.44 to 3.16) (Fig. 2D).

Randomized Controlled Trial > N Engl J Med. 2023 Jul 27;389(4):322-334.
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PATHOLOGICAL AND SURGICAL SECONDARY END POINTS

Surgical and pathological end points are shown in Table 2. In the per-protocol population, resection was pathologically complete (R0) in 90.4% of the patients in the FOLFOX group and in 91.2% of those in the chemoradiotherapy group. Among the patients in the per-protocol population who underwent surgery, the corresponding percentages were 98.9% and 97.1%, respectively (Table 2). Among the patients in the per-protocol population who underwent surgery, 117 of 535 patients (21.9%) in the FOLFOX group and 124 of 510 (24.3%) in the chemoradiotherapy group had a complete pathological response.

End Point	FOLFOX Group (N = 535)	Chemoradiotherapy Group (N = 510)
Secondary end points		
Completeness of rectal resection — no. (%)*		
R0	529 (98.9)	495 (97.1)
R1	6 (1.1)	14 (2.7)
R2	0	1 (02)
Pathological complete response — no. (%)†		
Yes	117 (21.9)	124 (24.3)
No	418 (78.1)	386 (75.7)
Other surgical and pathological end points		
Median time from randomization to surgery (interquartile range) — wk	19.0 (17.1–21.1)	15.6 (14.6–17.0)
Median time from end of preoperative therapy to surgery (interquartile range) — wk‡	4.6 (3.1–6.3)	7.7 (6.9–9.0)
Type of surgery — no. (%)		
Abdominal perineal resection	13 (2.4)	10 (2.0)
Low anterior resection	522 (97.6)	500 (98.0)
Histologic grade — no./total no. (%)§		
G1 or G2	396/535 (74.0)	344/504 (68.3)
G3 or G4	22/535 (4.1)	27/504 (5.4)
GX	117/535 (21.9)	133/504 (26.4)
Radial margin category — no./total no. (%)¶		
≤1 mm	6/509 (1.2)	7/469 (1.5)
>1 mm but ≤3 mm	26/509 (5.1)	31/469 (6.6)
>3 mm	477/509 (93.7)	431/469 (91.9)
Pathological tumor stage after neoadjuvant therapy — no./total no. (%)		
ypT0	121/534 (22.7)	125/506 (24.7)
ypT1	56/534 (10.5)	50/506 (9.9)
ypT2	183/534 (34.3)	156/506 (30.8)
ypT3	169/534 (31.6)	173/506 (34.2)
ypT4	5/534 (0.9)	2/506 (0.4)

- G1-2 hastalık oranı %74-%68
- Gx %21.9-%26.4 ??

- CRM >3mm %93.7-%91.9

- ypT0 %22.7- %24.7;
- ypT3 %31.5- %34.2;

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End Point	FOLFOX Group (N = 535)	Chemoradiotherapy Group (N = 510)
Pathological node status after neoadjuvant therapy — no. (%)		
ypN0	400 (74.8)	390 (76.5)
ypN1	108 (20.2)	104 (20.4)
ypN2	27 (5.0)	16 (3.1)
Pathological metastatic status — no./total no. (%)		
M0	520/521 (99.8)	494/499 (99.0)
M1a	1/521 (0.2)	5/499 (1.0)
Tumor regression grade — no./total no. (%)//		
Pathological complete response or grade 0	123/533 (23.1)	127/510 (24.9)
Grade 1	161/533 (30.2)	200/510 (39.2)
Grade 2	146/533 (27.4)	151/510 (29.6)
Grade 3	103/533 (19.3)	32/510 (6.3)

- ypN+ %25.2 - %23.5

- LCKRT; tam cevap oranları %15;
- preop KT; %5-10
- PROSPECT de %23.1- %24.9

Yüksek riskli hastalar RT aldığı düşünürse %2 lik lokal-bölgesel nüx şaşırtıcı değil

Rectal Cancer Update: Which Treatment Effects Are the Least “Brutal”?

Andrzej P. Wojcieszynski, MD,* Michael D. Chuong, MD,† Maria Hawkins, MD,‡ Krishan R. Jethwa, MD,§

International Journal of Radiation Oncology, Biology, Physics, 2024-01-01, Volume 118, Issue 1, Pages 1-7,

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS

- Uluslararası standartlara göre yaklaşık %90 hasta cT3 (düşük risklidir)
- Hastaların %85'ine MRI evrelemesi yapılmasına rağmen T3 ve nodal alt gruplar rapor edilmemiştir (bu hastalar erken veya orta dereceli kanserler olarak yeniden sınıflandırılmalı)
- Çoğu hastanın TME ile tedavi edilebileceği ve sfinkter fonksiyonunun korunabileceği için, bu çalışmada çok sayıda hastaya KT ve RT tedavisi (over-treatment?) nedeniyle gereksiz toksisiteye maruz bırakılmış olabilir !!!

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SAFETY

Details of clinician-reported toxic effects during neoadjuvant therapy (Table S2A) showed a higher incidence of severe (grade ≥3) adverse events in the FOLFOX group than in the chemoradiotherapy group (41.0% vs. 22.8%). However, the treatment period was twice as long in the FOLFOX group (minimum of 12 weeks, vs. 5.5 weeks in the chemoradiotherapy group). Neuropathy was more frequent and severe in the FOLFOX group than in the chemoradiotherapy group, and diarrhea was more frequent and severe in the chemoradiotherapy group than in the FOLFOX group. In the FOLFOX group, the most frequent grade 3 or higher toxic effects of neoadjuvant therapy were neutropenia, pain, and hypertension, reported by clinicians for 20.3%, 3.1%, and 2.9% of the patients, respectively. In the chemoradiotherapy group, the most frequent grade 3 or higher toxic effects reported by clinicians were lymphopenia, diarrhea, and hypertension, in 8.3%, 6.4% and 1.7% of the patients, respectively.

Among the patients who received any adjuvant therapy (Table S2B), severe (grade ≥3) postoperative adverse events occurred in a lower percentage of patients in the FOLFOX group than in the chemoradiotherapy group (25.6% vs. 32.6%). The most commonly reported postoperative grade 3 or higher toxic effects were neutropenia (in 3.9% of the patients), diarrhea (in 2.7%), and hyponatremia (in 2.3%) in the FOLFOX group and diarrhea (in 5.2%), dehydration (in 4.3%), and lymphopenia (in 4.3%) in the chemoradiotherapy group. No unanticipated toxic effects of either FOLFOX or chemoradiotherapy were observed.

Rectal Cancer Update: Which Treatment Effects Are the Least "Brutal"?

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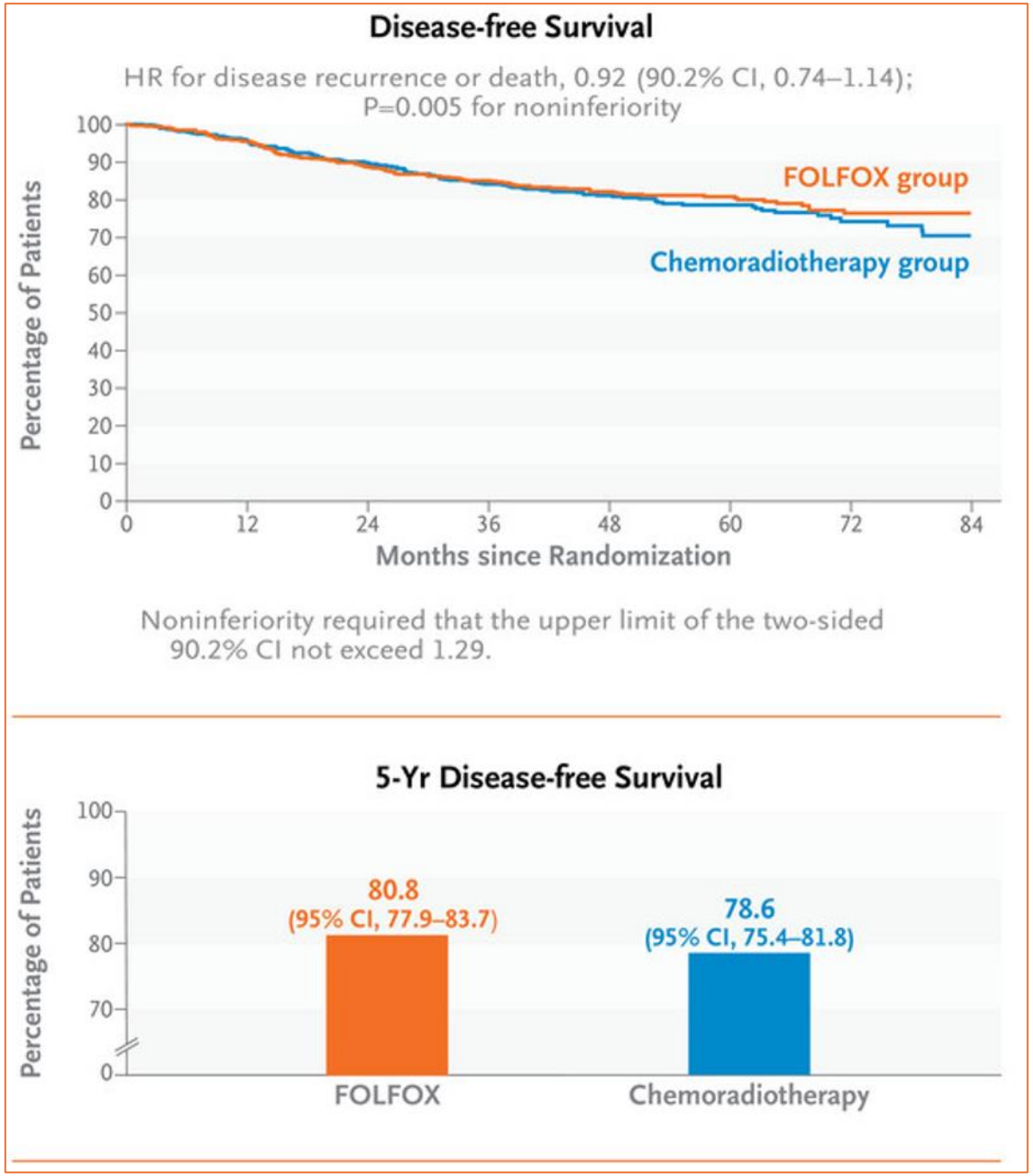
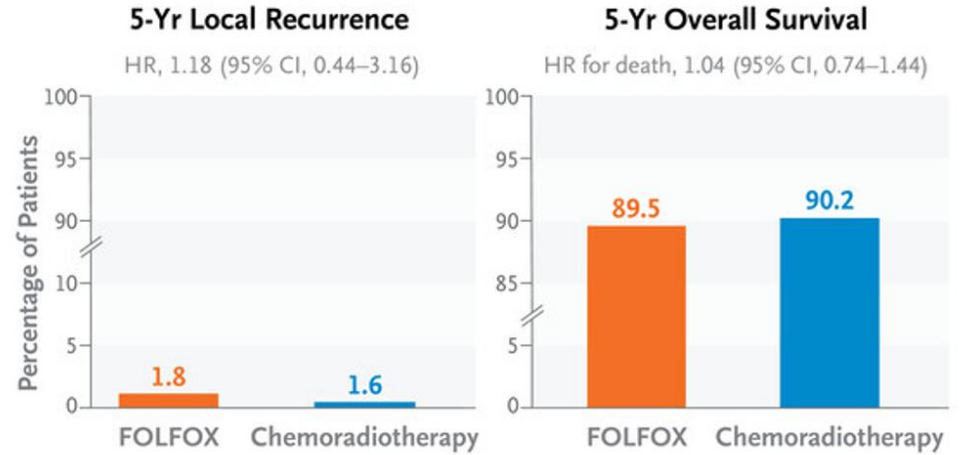
Finally, acute grade 3 or higher toxicity was significantly higher in the FOLFOX versus chemoradiation treatment arm, 41% versus 23%. Postoperative toxicity was slightly higher in the chemoradiation arm, likely reflective of the receipt of postoperative FOLFOX. These differences mostly resolved with extended follow. Notably, overall QoL was similar in both treatment arms. These toxicity differences may assist in counseling patients on an ideal treatment strategy. Perhaps the most compelling scenario to consider omission of radiation therapy would be a young premenopausal woman interested in future childbearing options. Data have suggested that in the absence of ovarian transposition surgery, up to 100% of women who undergo preoperative radiation therapy for rectal cancer will experience premature ovarian failure.[33] It is also possible that even if a woman were to have preserved ovarian endocrine function, the uterus would no longer be implantable or have the capacity to maintain a term pregnancy. In such a scenario, the use of chemotherapy to allow omission of radiation therapy may allow a patient to achieve their family planning goals.





CONCLUSIONS

In patients with locally advanced rectal cancer amenable to sphincter-sparing surgery, neoadjuvant FOLFOX chemotherapy with selective use of chemoradiotherapy was noninferior to neoadjuvant chemoradiotherapy for disease-free survival, and nearly 90% of patients in the FOLFOX group were able to avoid chemoradiotherapy.

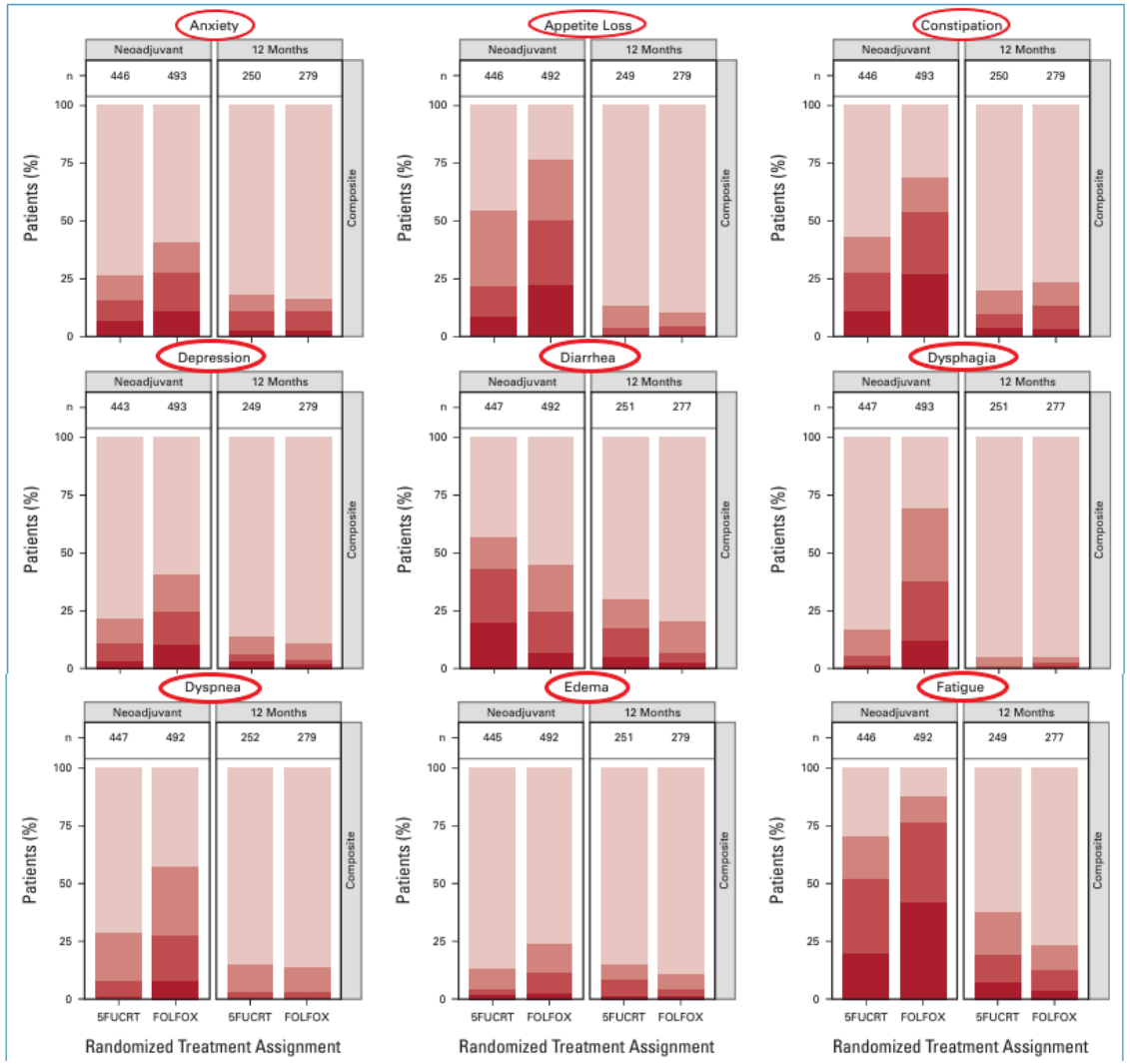
LIMITATIONS AND REMAINING QUESTIONS

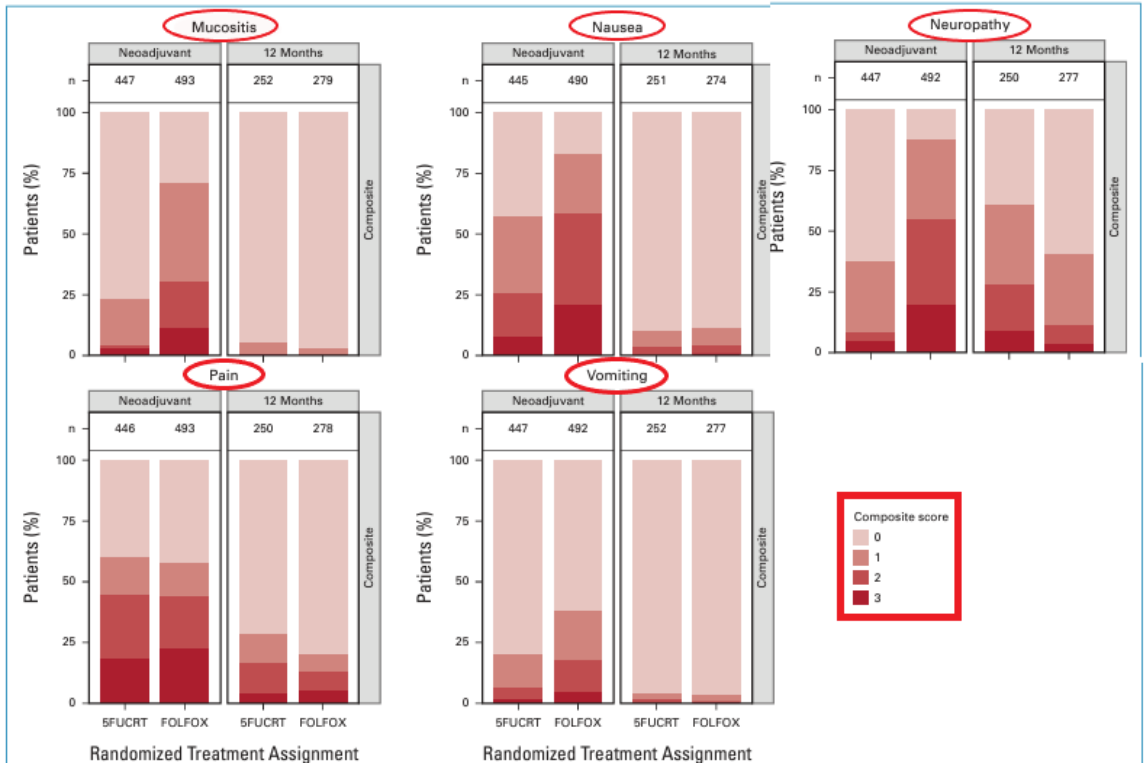
- Because of the eligibility criteria used in the trial, the generalizability of the findings to high-risk patients may be limited.
- Further research is needed to determine whether distinctive molecular features predict responsiveness to chemotherapy as compared with radiation.
- Longer follow-up is required to evaluate the magnitude of late effects of pelvic radiation.

Patient-Reported Outcomes During and After Treatment for Locally Advanced Rectal Cancer in the PROSPECT Trial (Alliance N1048)

Ethan Basch, MD, MSc, FASCO[1]; Amylou C. Dueck, PhD[2]; Sandra A. Mitchell, PhD[3]; Harvey Mamon, MD, PhD[4]; Martin Weiser, MD[5]

J Clin Oncol. 2023 Jul 20;41(21):3724-3734.





- PROSPECT çalışmasının New England Journal of Medicine'de yayınlandığı gün, ilgili QoL verileri Journal of Clinical Oncology'de yayınlandı.
- Hekim tarafından bildirilen tedavi toksisitesini bildiren diğer birçok çalışmanın aksine PROSPECT, hasta tarafından bildirilen sonuçları (PRO'lar) kullandı

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Ethan Basch, MD, MSc, FASCO[1]; Amylou C. Dueck, PhD[2]; Sandra A. Mitchell, PhD[3]; Harvey Mamon, MD, PhD[4]; Martin Weiser, MD[5]

J Clin Oncol. 2023 Jul 20;41(21):3724-3734.

Knowledge Generated

During neoadjuvant treatment, patients receiving FOLFOX experienced less diarrhea and better bowel function, whereas those receiving 5FUCRT had less anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting. In contrast, at 6, 12, and 18 months after treatment, patients receiving FOLFOX had less fatigue and neuropathy and better sexual function, compared with 5FUCRT. Overall quality of life remained similar between treatment groups during and after treatment.

Relevance *(A.H. Ko)*

As treatment paradigms evolve for locally advanced rectal cancer, the quality of life and toxicity data from this large PROSPECT trial—as reported directly by patients—can help inform decision-making and counseling patients in deciding between neoadjuvant FOLFOX or fluorouracil-based chemoradiation.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

Rectal Cancer Update: Which Treatment Effects Are the Least "Brutal"?

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY • BIOLOGY • PHYSICS
ONCOLOGY SCAN

Andrzej P. Wojcieszynski, MD,* Michael D. Chuong, MD,† Maria Hawkins, MD,‡ Krishan R. Jethwa, MD,§

International Journal of Radiation Oncology, Biology, Physics, 2024-01-01, Volume 118, Issue 1, Pages 1-7,

- PROSPECT çalışmasında hedef de-escalation; Ancak QoL verileri ile bu doğrulanamadı
- FOLFOX ile grade ≥ 3 toksisite, KRT'nin neredeyse iki katı (%22.8 vs %41)
- Uzun dönem takipte, KRT kolunda yorgunluk ve nöropati anlamlı derecede daha kötü
- Platin bazlı KT'nin tersine pelvik radyasyon tedavisinin periferik nöropati ilişkisi (-)
- Bu farkın nedeni adjuvan KT ile ilişkili olabilir
- Sonuç olarak klinisyenler ve hastalar neoadjuvan tedavi seçeneği olarak KRT daha iyi tolere edildi
- Ancak daha uzun takipte toksisite profillerinin nasıl değişebileceği henüz bilinmiyor.

The rise of negative portrayals of radiation oncology: A textual analysis of media news

Dominik Wawrzuta [a,*], Justyna Klejdysz [b,c], Marzanna Chojnacka [a]

Radiotherapy and Oncology 190 (2024) 110008

A B S T R A C T

Background and Purpose: There has been growing concern about the media's negative portrayal of radiation oncology in recent years. Our study shows changes in media sentiment toward radiotherapy over the years, identifies prevalent themes, and analyzes their shifts over time.

Materials and Methods: We analyzed articles about radiation oncology published in The New York Times since the journal's inception in 1851. Initially, we collected 30 427 articles containing the keywords "radiation" or "radiotherapy" up to July 2023. In the next step, we selected 342 articles on radiation oncology using keyword searches, prompting the Chat GPT language model and manual assessment. Ultimately, we created a codebook summarizing the media topics related to radiotherapy and categorized the articles into these categories.

Results: Our analysis identified ten distinct categories representing media themes related to radiation oncology: five negative, three positive, and two neutral. Our findings indicate a rising negative sentiment toward radiotherapy. In the 21st century, over 50% of articles negatively described radiation oncology. The media coverage has shifted its focus away from describing scientific breakthroughs and the implementation of new techniques and toward treatment errors, toxicity, and ineffectiveness.

Conclusion: The increasing negative media sentiment surrounding radiation oncology may influence public perceptions and impact patients' decisions. Radiation oncologists should remain vigilant about this situation, ensuring the dissemination of accurate information and addressing negative portrayals.

The rise of negative portrayals of radiation oncology: A textual analysis of media news

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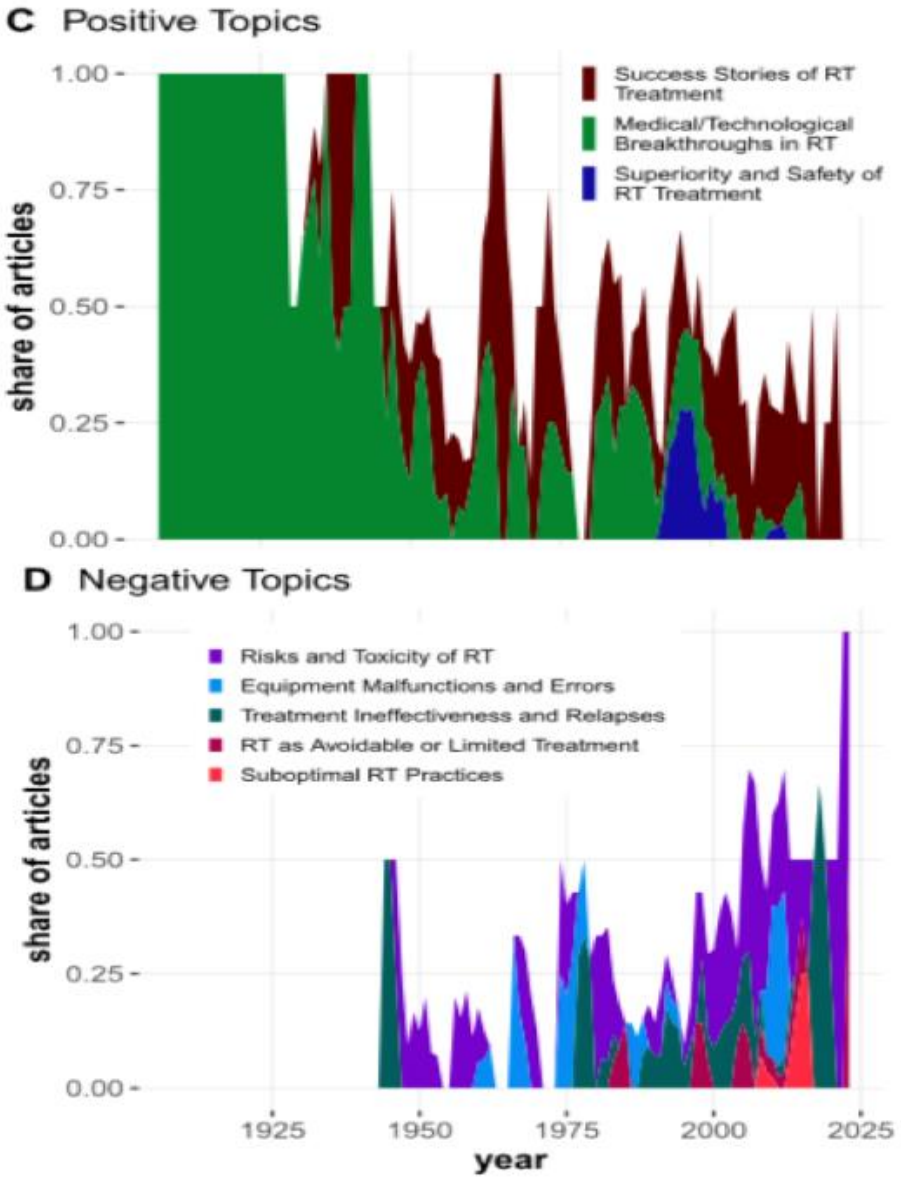

Table 1
Topics of articles on radiation oncology with examples.

Sentiment	Category	Description	Example of Headline	Count
positive	1	Success Stories of RT Treatment	Experts Say Hodgkin's Disease Can Be Controlled by Radiation	70
	2	Medical/ Technological Breakthroughs in RT	Stronger Radiation Treatment for Deep Cancer Is Made Possible With New X-Ray Shield	65
	3	Superiority and Safety of RT Treatment	Why Do So Many Women Have Breasts Removed Needlessly?	11
neutral	4	Celebrities' RT Treatment	Ex-Los Angeles Mayor Talks Of Cancer and 2002 Race	86
	5	Implementing RT in Hospitals	First Medical Proton Accelerator Being Built	48
negative	6	Risks and Toxicity of RT	Radiation Reality: Poisoned to Be Cured	49
	7	Equipment Malfunctions and Errors	Fatal Radiation Dose in Therapy Attributed to Computer Mistake	21
	8	Treatment Ineffectiveness and Relapses	Study Raises Concerns About a Faster Radiation Therapy for Breast Cancer	18
	9	RT as Avoidable or Limited Treatment	Rectal Cancer Patients Could Be Spared the Effects of Radiation	7
	10	Suboptimal RT Practices	Doctors Who Profit From Radiation Prescribe It More Often, Study Finds	3

The rise of negative portrayals of radiation oncology: A textual analysis of media news

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[1]. The article, titled "Rectal Cancer Patients Could Be Spared the Brutal Effects of Radiation" garnered significant attention, but it portrayed radiotherapy negatively despite the study's findings [2]. The depiction of radiotherapy as a "brutal treatment method" sparked controversy and debate. Both the European Society for Radiotherapy and

- "Rektal Kanserli Hastalar Radyasyonun Acımasız Etkilerinden Korunabilir"
- Hem Avrupa Radyoterapi ve Onkoloji Derneği (ESTRO) hem de Amerikan Radyasyon Onkolojisi Derneği (ASTRO), radyoterapinin rolünü ve PROSPECT çalışma sonuçlarının önemini açıklığa kavuşturmak için açıklamalar yayınladı
- Radyasyon onkolojisi topluluğunun tepkisine karşılık haber başlığından "acımasız" kelimesi kaldırıldı.

The rise of negative portrayals of radiation oncology: A textual analysis of media news

Dominik Wawrzuta [a,*], Justyna Klejdysz [b,c], Marzanna Chojnacka [a]

Radiotherapy and Oncology 190 (2024) 110008

- Dijital çağda medya genellikle sansasyonel ve dikkat çekici hikayelere öncelik veriyor, bu da bilimdeki olumlu gelişmeleri göz ardı ederken olumsuz olayların aşırı vurgulanmasına yol açıyor
- Yeni tedavi metotları bulundukça medya radyoterapinin daha az olumlu yönüne yer verme ve bunun yerine potansiyel olumsuz etkilere daha fazla odaklanma eğiliminde olabilir.
- Bu yaklaşım, bu tür haberlerin daha fazla ilgi ve okuyucu çekmesinden kaynaklanmaktadır.

PROSPECT trial adds another treatment possibility for patients with resectable rectal cancer

ESTRO

The results of the PROSPECT trial (ALLIANCE N1048) have been presented at the 2023 ASCO meeting, but their interpretation in public newspapers and social media causes significant concern amongst health care professionals, patients and the public.

Unfortunately, several newspapers reported the PROSPECT trial using provocative and misleading headlines, describing the effects of radiation as "brutal". Such inflammatory use of language not only goes beyond the evidence generated by the PROSPECT trial but also risks unnecessarily alarming a large group of patients with rectal cancer for whom radiation therapy will still form an important part of their cancer treatment with proven beneficial effects on survival and quality-of-life.

Pierfrancesco Franco, Chair, ESTRO Lower GI Focus Group

Emmanouil Fokas, Course Director, ESTRO Lower GI Course

Anna Kirby, ESTRO President

Matthias Guckenberger, ESTRO President-Elect

Ben Slotman, ESTRO Past-President

THE TIMES

FRIDAY MAY 10 2024

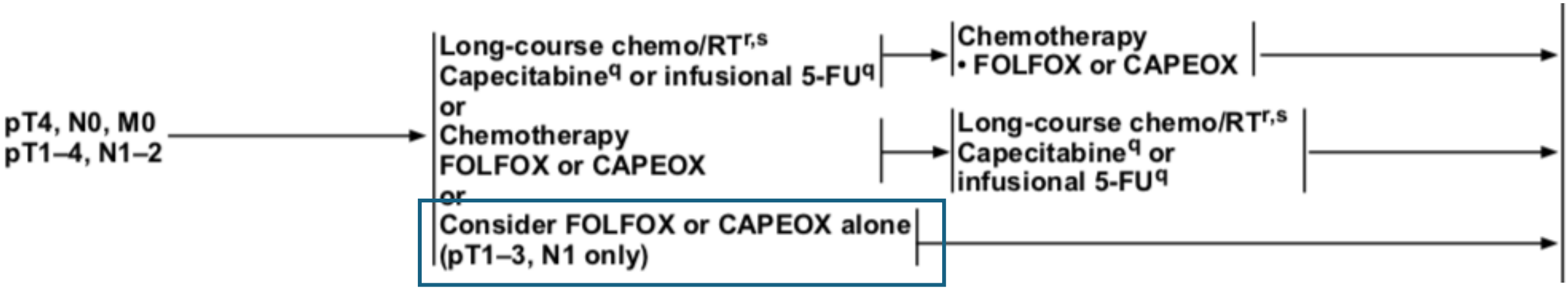
Thousands of bowel cancer patients could avoid radiotherapy

Kat Lay

... He said it was important to note that the findings would not apply to all **rectal cancer** patients, and that care of patients with that type of **cancer** was "complex ...

Monday June 5 2023 | The Times

NCCN Guidelines Version 2.2024
Rectal Cancer



Differential clinical outcomes after 3 versus 5 years in a comparison of preoperative chemotherapy with and without radiotherapy in locally advanced rectal cancer: A national cohort propensity score-matched study

Heliyon 10 (2024) e27684

Yuanxin Zhang [a,d,e,1], Rui Luo [a,d,e,1], Jinggi Peng [b,1], Zichuan He [a,d,e], Delin Tan

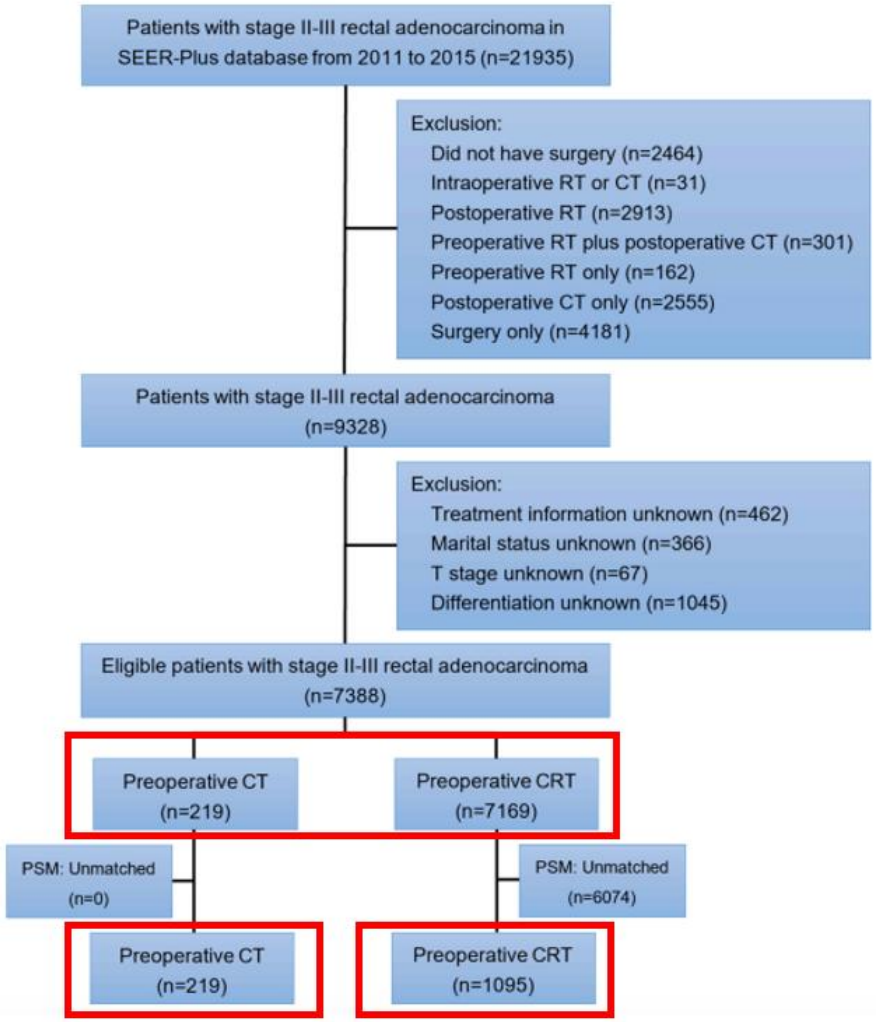


Fig. 1. Flow chart of SEER-Plus population recruitment. RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy; PSM = propensity score matching.

Characteristics	Unmatched population (n = 7388)			Matched population (n = 1314)		
	Pre CT(n = 219)	Pre CRT(n = 7169)	P value	Pre CT(n = 219)	Pre CRT(n = 1095)	P value
Sex			0.339			0.896
Female	76 (34.7)	2733 (38.1)		76 (34.7)	372 (34.0)	
Male	143 (65.3)	4436 (61.9)		143 (65.3)	723 (66.0)	
Age at diagnosis, yr			0.999			0.961
<60	111 (50.7)	3631 (50.6)		111 (50.7)	560 (51.1)	
≥60	108 (49.3)	3538 (49.4)		108 (49.3)	535 (48.9)	
Marital status[a]			0.642			0.860
Not married	89 (40.6)	2785 (38.8)		89 (40.6)	435 (39.7)	
Married	130 (59.4)	4384 (61.2)		130 (59.4)	660 (60.3)	
Race[b]			0.544			0.734
White	175 (79.9)	5838 (81.4)		175 (79.9)	886 (80.9)	
Black	15 (6.8)	545 (7.6)		15 (6.8)	83 (7.6)	
Other/unknown	29 (13.2)	786 (11.0)		29 (13.2)	126 (11.5)	
T category			0.008			0.999
T1-3	183 (83.6)	6413 (89.5)		183 (83.6)	912 (83.3)	
T4	36 (16.4)	756 (10.5)		36 (16.4)	183 (16.7)	
N category			0.702			0.725
N0	89 (40.6)	2769 (38.6)		89 (40.6)	444 (40.5)	
N1	96 (43.8)	3349 (46.7)		96 (43.8)	502 (45.8)	
N2	34 (15.5)	1051 (14.7)		34 (15.5)	149 (13.6)	
AJCC stage[c]			0.594			0.999
II	89 (40.6)	2769 (38.6)		89 (40.6)	444 (40.5)	
III	130 (59.4)	4400 (61.4)		130 (59.4)	651 (59.5)	
Histologic grade			0.648			0.559
Well/moderately	195 (89.0)	6293 (87.8)		195 (89.0)	992 (90.6)	
Poor/undifferentiated	24 (11.0)	876 (12.2)		24 (11.0)	103 (9.4)	
Tumor size, cm			0.326			0.762
<5	113 (51.6)	3332 (46.5)		113 (51.6)	554 (50.6)	
≥5	78 (35.6)	2823 (39.4)		78 (35.6)	415 (37.9)	
Unknown	28 (12.8)	1014 (14.1)		28 (12.8)	126 (11.5)	
Nodes examined[d], No.			0.336			0.330
<12	65 (29.7)	2367 (33.0)		65 (29.7)	287 (26.2)	
≥12	154 (70.3)	4802 (67.0)		154 (70.3)	808 (73.8)	

Characteristics	Unmatched population (n = 7388)			Matched population (n = 1314)		
	Pre CT(n = 219)	Pre CRT(n = 7169)	P value	Pre CT(n = 219)	Pre CRT(n = 1095)	P value
Perineural Invasion[e]			0.721			0.775
Negative	164 (74.9)	5496 (76.7)		164 (74.9)	842 (76.9)	
Positive	27 (12.3)	763 (10.6)		27 (12.3)	130 (11.9)	
Unknown	28 (12.8)	910 (12.7)		28 (12.8)	123 (11.2)	
Tumor Deposits[e]			0.609			0.729
Negative	170 (77.6)	5688 (79.3)		170 (77.6)	872 (79.6)	
Positive	23 (10.5)	776 (10.8)		23 (10.5)	112 (10.2)	
Unknown	26 (11.9)	705 (9.8)		26 (11.9)	111 (10.1)	
CEA Pretreatment			0.377			0.323
Normal	86 (39.3)	2847 (39.7)		86 (39.3)	425 (38.8)	
Elevated/borderline	62 (28.3)	2278 (31.8)		62 (28.3)	360 (32.9)	
Unknown	71 (32.4)	2044 (28.5)		71 (32.4)	310 (28.3)	
Postoperative CT			0.023			0.957
No	154 (70.3)	4484 (62.5)		154 (70.3)	765 (69.9)	
Yes	65 (29.7)	2685 (37.5)		65 (29.7)	330 (30.1)	

Differential clinical outcomes after 3 versus 5 years in a comparison of preoperative chemotherapy with and without radiotherapy in locally advanced rectal cancer: A national cohort propensity score-matched study

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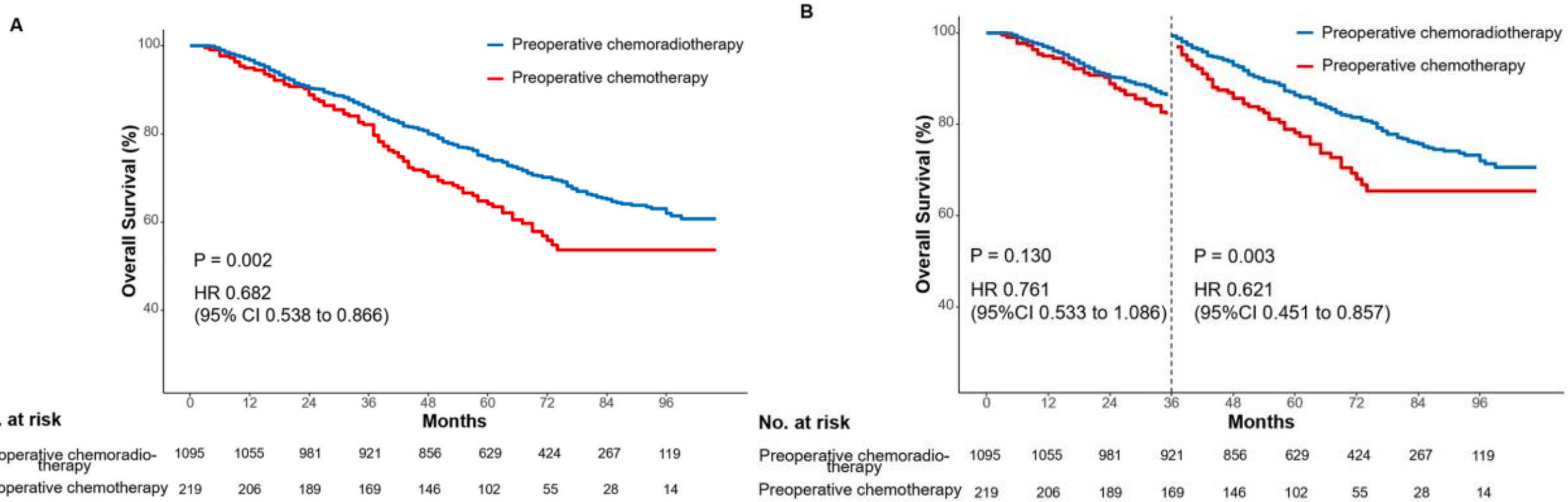
Yuanxin Zhang [a,d,e,1], Rui Luo [a,d,e,1], Jingqi Peng [b,1], Zichuan He [a,d,e], Delin Tan



In the matched population, the median follow-up was 74.0 months. The mean OS was 84.2 months in the preoperative chemoradiotherapy group and 76.4 months in the preoperative chemotherapy group. Fig. 2A illustrates that the 5-year OS was significantly different (HR 0.682, 95% CI 0.538–0.866; P = 0.002), while OS appeared similar within 3 years. The landmark analysis confirmed that survival outcomes did not differ significantly between the two groups at 3-year follow-up (HR 0.761, 95% CI 0.533–1.086; P = 0.130); however, at 3–5 years' follow-up, OS was significantly greater in the preoperative chemoradiotherapy group than in the preoperative chemotherapy group (HR 0.621, 95% CI 0.451–0.857; P = 0.003) (Fig. 2B).

Differential clinical outcomes after 3 versus 5 years in a comparison of preoperative chemotherapy with and without radiotherapy in locally advanced rectal cancer: A national cohort propensity score-matched study

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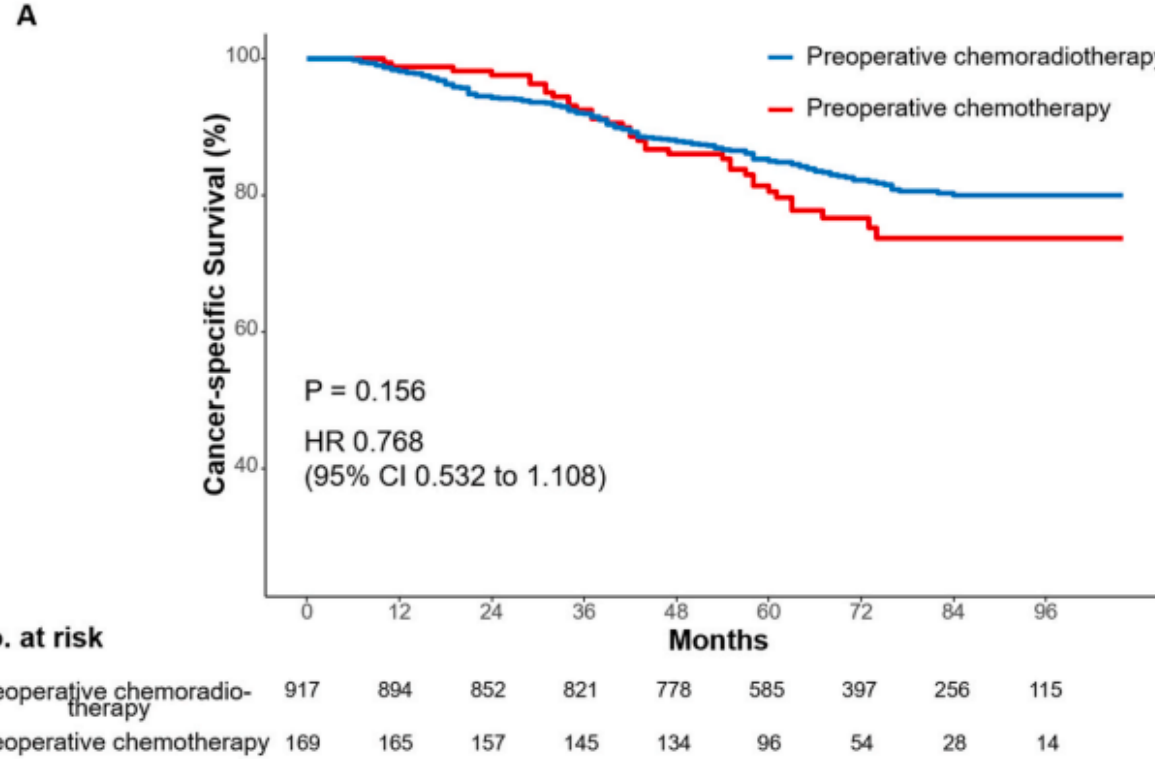

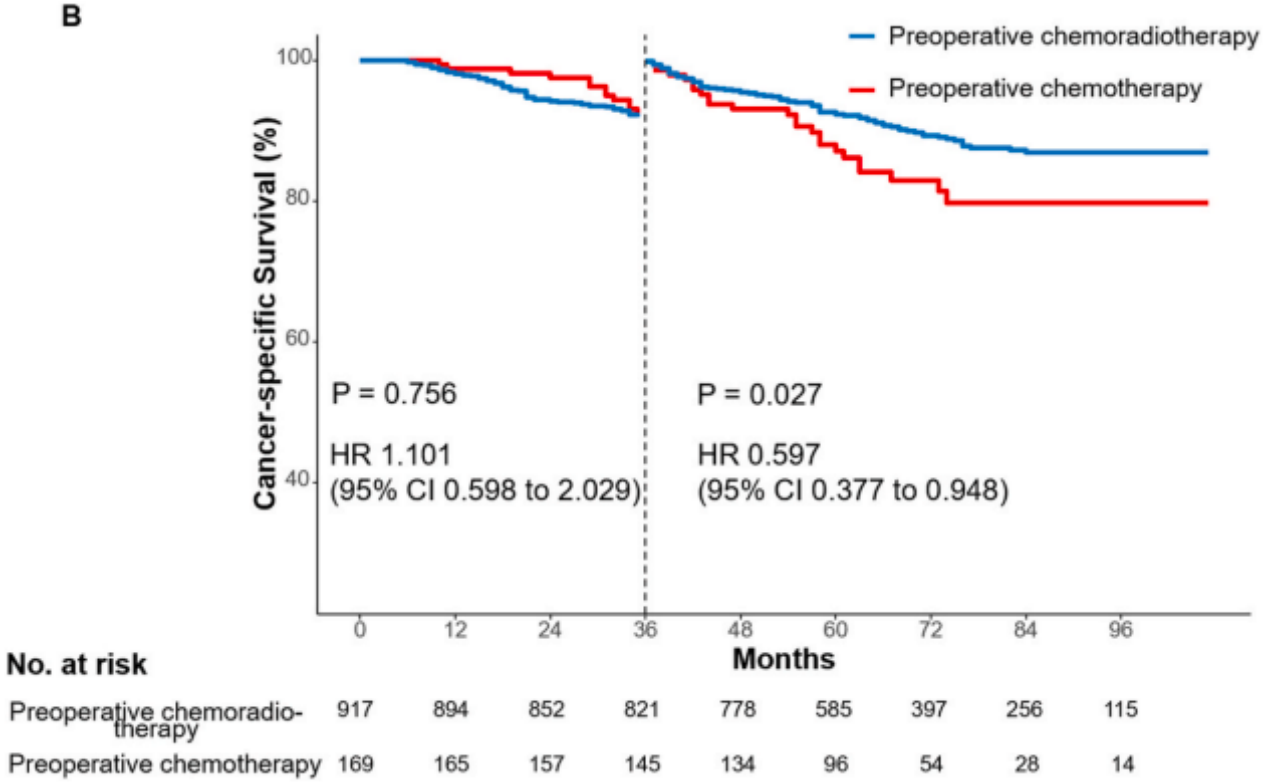

At 5-year follow-up, CSS was similar between patients who received preoperative chemoradiotherapy and preoperative chemotherapy (HR 0.768, 95% CI 0.532–1.108; P = 0.156) (Fig. 3A). This finding at 5 years is indicative of directly contrasting results for survival outcomes within 3 years versus 3–5 years. Patients in the preoperative chemoradiotherapy group had worse CSS outcomes within 3 years (HR 1.101, 95% CI 0.598–2.029; P = 0.756), but had better CSS outcomes beyond the third year (HR 0.597, 95% CI 0.377–0.948; P = 0.027) (Fig. 3B).

Differential clinical outcomes after 3 versus 5 years in a comparison of preoperative chemotherapy with and without radiotherapy in locally advanced rectal cancer: A national cohort propensity score-matched study

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Univariate and multivariate analyses of the effects of prognostic factors on overall survival in the **matched population**.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Pre treatment (Pre CRT vs. Pre CT)	0.682 (0.538–0.866)	0.002	0.707 (0.556–0.899)	0.005
Sex (Male vs. Female)	1.219 (0.990–1.501)	0.062		
Age (≥60 vs. <60 yr)	1.611 (1.326–1.958)	<0.001	1.550 (1.267–1.896)	<0.001
Marital status (Married vs. Not married)	0.720 (0.594–0.872)	0.001	0.777 (0.638–0.946)	0.012
Race (Black vs. White)	1.610 (1.179–2.199)	0.003	1.314 (0.958–1.802)	0.091
T category (T4 vs. T1-3)	2.020 (1.621–2.519)	<0.001	1.596 (1.273–2.000)	<0.001
N category		<0.001		<0.001
N0	Reference		Reference	
N1	0.942 (0.759–1.169)	0.586	1.090 (0.872–1.363)	0.448
N2	1.930 (1.488–2.503)	<0.001	1.922 (1.446–2.554)	<0.001
AJCC stage (III vs. II)	1.141 (0.936–1.390)	0.192		
Grade (Poor/undifferentiated vs. Well/moderately)	1.831 (1.395–2.403)	<0.001	1.698 (1.289–2.235)	<0.001
Tumor size (≥5 vs. <5 cm)	1.173 (0.957–1.439)	0.124		
Nodes examined (≥12 vs. <12)	0.754 (0.613–0.928)	0.008	0.774 (0.623–0.962)	0.021
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Perineural Invasion (Positive vs. Negative)	2.018 (1.565–2.602)	<0.001	1.555 (1.182–2.044)	0.002
Tumor Deposits (Positive vs. Negative)	2.050 (1.576–2.667)	<0.001	1.422 (1.064–1.901)	0.017
CEA Pretreatment (Elevated/borderline vs. Normal)	1.880 (1.489–2.374)	<0.001	1.641 (1.293–2.083)	<0.001
Postoperative CT (Yes vs. No)	0.695 (0.556–0.869)	0.001	0.732 (0.583–0.919)	0.007

Abbreviations: HR, hazard ratio; CI, confidence interval; Pre, preoperative; CRT, chemoradiotherapy; CT, chemotherapy; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen.

Univariate Cox regression analysis identified 13 underlying prognostic factors and variables with a $P < 0.05$ in the univariate analysis were selected for multivariate analysis. In the multivariable analysis, factors significantly associated with a worse 5-year OS only were preoperative chemotherapy alone, older age, unmarried status, T4, N2, poor/undifferentiated grade, less than 12 nodes examined, presence of perineural invasion, presence of tumor deposits, elevated pretreatment CEA and no use of postoperative chemotherapy (Table 2).

Radyoterapisiz Çalışmalar

- **FOWARC (faz 3)**
- **GRECCAR4 (faz 2)**
- CONVERT (faz 3)
- PROSPECT (faz 3)
- **Cercek 19-288 (faz 2)**

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

19-288

Cercek A et al. DOI: 10.1056/NEJMoa2201445

Approximately 5 to 10% of rectal adenocarcinomas are mismatch-repair deficient, and these tumors have been shown to respond poorly to standard chemotherapy regimens, including neoadjuvant chemotherapy in locally advanced rectal cancer.[12-14] Immune checkpoint blockade alone has been shown to be highly effective as first-line treatment for patients with mismatch repair–deficient metastatic colorectal cancer, as well as for patients with treatment-refractory disease, with objective response rates of 33 to 55%, clinically significant durability of response, and prolonged overall survival.[15-17]

The NEW ENGLAND JOURNAL of MEDICINE

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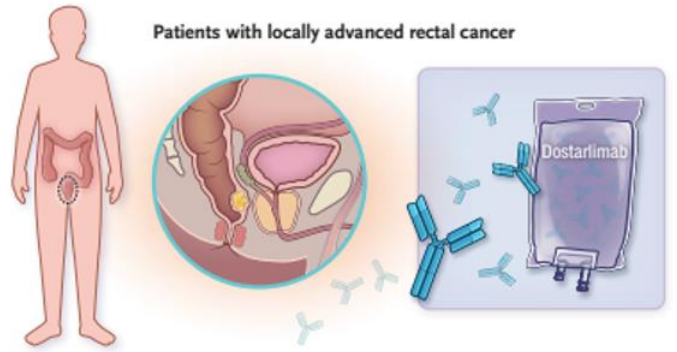
CLINICAL PROBLEM

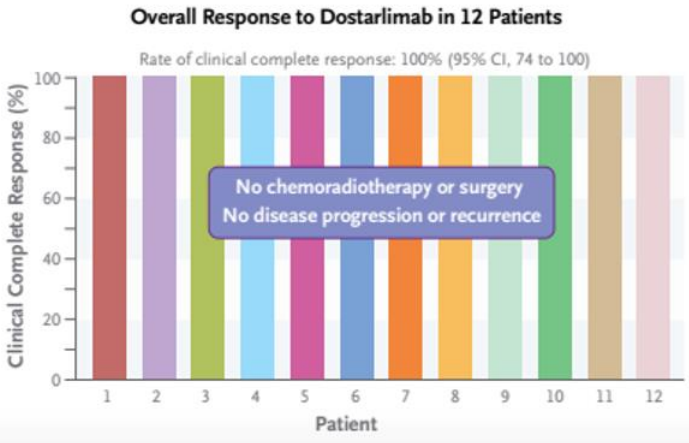
Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.





Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	
White	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic or Latinx ethnic group — no. (%)*	1 (6)
ECOG performance-status score — no. (%)†	
0	12 (75)
1	4 (25)
Tumor stage — no. (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status — no. (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge (range) — cm	5 (0.9–8.9)

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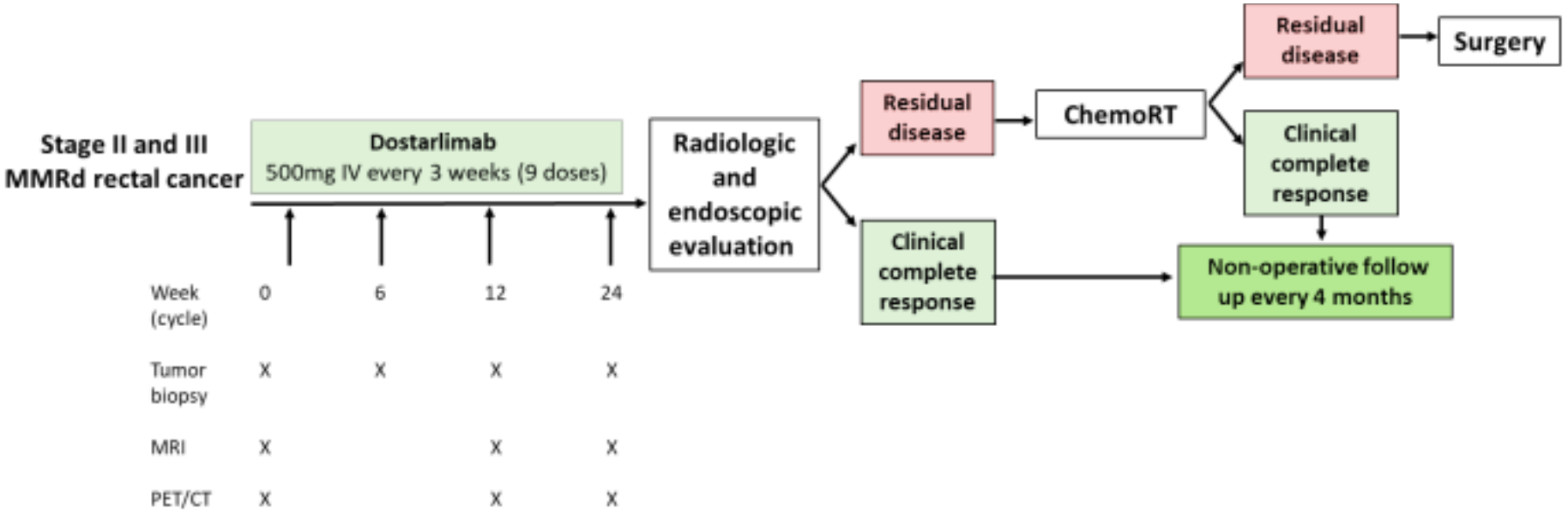

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

19-288

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

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RESULTS

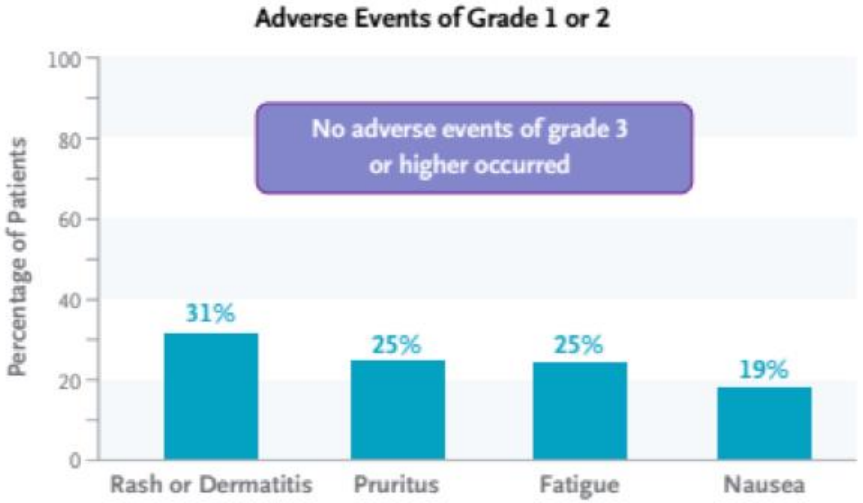
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: Full Article | NEJM Quick Take | Editorial



CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

EFFICACY

The criteria for the primary end point of overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy have been met. The percentage of patients with a clinical complete response was 100% (95% confidence interval [CI], 74 to 100) in 12 consecutive patients who have completed 6 months of therapy (Figure 1, Table 2, and Fig. S2). After completion of therapy at 6 months, the median time to rectal MRI was 16 days (range, 8 to 26), and the median time to endoscopy was 20 days (range, 14 to 28).

During the median follow-up period of 12 months, no patients have received chemoradiotherapy, and no patients have undergone surgical resection. Because none of the 12 patients who completed 6 months of dostarlimab therapy have undergone surgery, evaluation of pathological complete response will not be possible. No patients have had disease progression or recurrence, and all 16 enrolled patients are alive (Table 2 and Table S2).

Table 1 Key characteristic of trials investigating neoadjuvant systemic therapy alone without radiation in locally advanced rectal cancer

Study	ID	Design	LARC	Study group	Comparator group(s)	mFU	pCR (%)	Local control (%)	OS (%)
FOWARC[4]	NCT01211210	Phase 3	Suitable for curative resection	FOLFOX	CCRT	45.2	6.5 *vs* (14 or 27.5); *P* 0.05	3-year LRR 8.3 *vs* (8 or 7); *P* = 0.873	3-year 90.7 *vs* (91.3 or 89.1); *P* = 0.971
PROSPECT [6]	NCT01515787	Phase 3	T2N1, T3N0, T3N1	FOLFOX	CCRT	58	21.9 *vs* 24.3; *P* value NA	5-year LR 1.8% *vs* 1.6%; *P* value > 0.05	5-year 89.5 *vs* 90.2; *P* value > 0.05
GRECCAR4 [9]	NCT01333709	Phase 2 RCT	T3d with predictive CRM 1 mm	FOLFIRINOX	CCRT	65.7	(10 or 13.5) *vs* (58 or 20); *P* value NA	NA	5-year (90 or 84.3) *vs* (93.3 or 86.1); *P* value > 0.05
CONVERT [10]	NCT02288195	Phase 3	cT2N+ or cT3-4Nany uninvolved mesorectal fascia	CAPOX	CCRT	NA	11 *vs* 13.8; *P* = 0.33	NA	NA
19-288[5]	NCT04165772	Phase 2	Mismatch repair–deficient	Dostarlimab	NA	NA	NA	100	100

LARC: Locally advanced rectal cancer; LR: Local recurrence; LRR: Locoregional recurrence; mFU: Median follow up (in months); pCR: Pathological complete response; OS: Overall survival; CCRT: Concurrent chemoradiotherapy; CRM: Circumferential resection margin; NA: Not available; RCT: Randomized controlled trial.

Sonuç

- T3N0
  - İyi-orta differansiye
  - Mezorektuma 2mm den az invaze
  - Lenfatik ve venöz damar invazyonu olmayan
  - Üst rektum yerleşimli ise

Radyoterapi ihmal edilebilir

- PROSPECT çalışmalarında KT, KRT'ye göre noninferior ancak çalışmaların takip süresi kısa ve defektleri mevcut
- SEER analizine göre KRT vs KT karşılaştırıldığında 5. yılda OS ve CSS KRT lehine anlamlı
- İmmunoterapi uygun hastalarda uygulanabilir ancak hasta sayısı az olmakla beraber sonuç etkileyici

Teşekkür Ederim

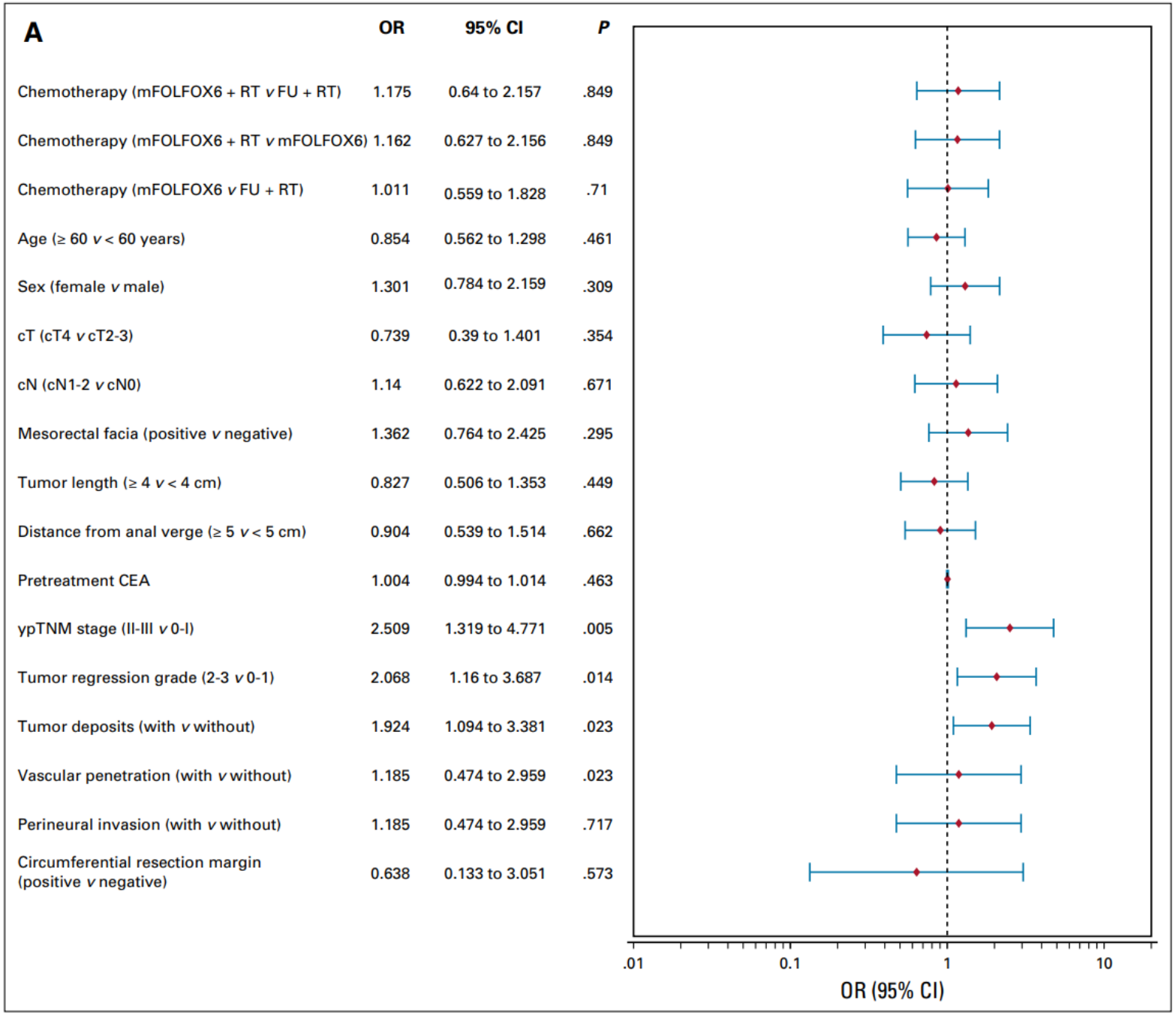


FIG 3. Multivariable analysis of the effects of prognostic factors on (A) 3-year disease-free survival and (B) locoregional recurrence. CEA, carcinoembryonic antigen; FU, fluorouracil; mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; OR, odds ratio; RT, radiotherapy.

median DFS was not reached. In a multivariable analysis, factors associated with worse DFS were ypTNM stage II or III, tumor regression grade 2 or 3, presence of tumor deposits, and presence of perineural invasion (Fig 3A).

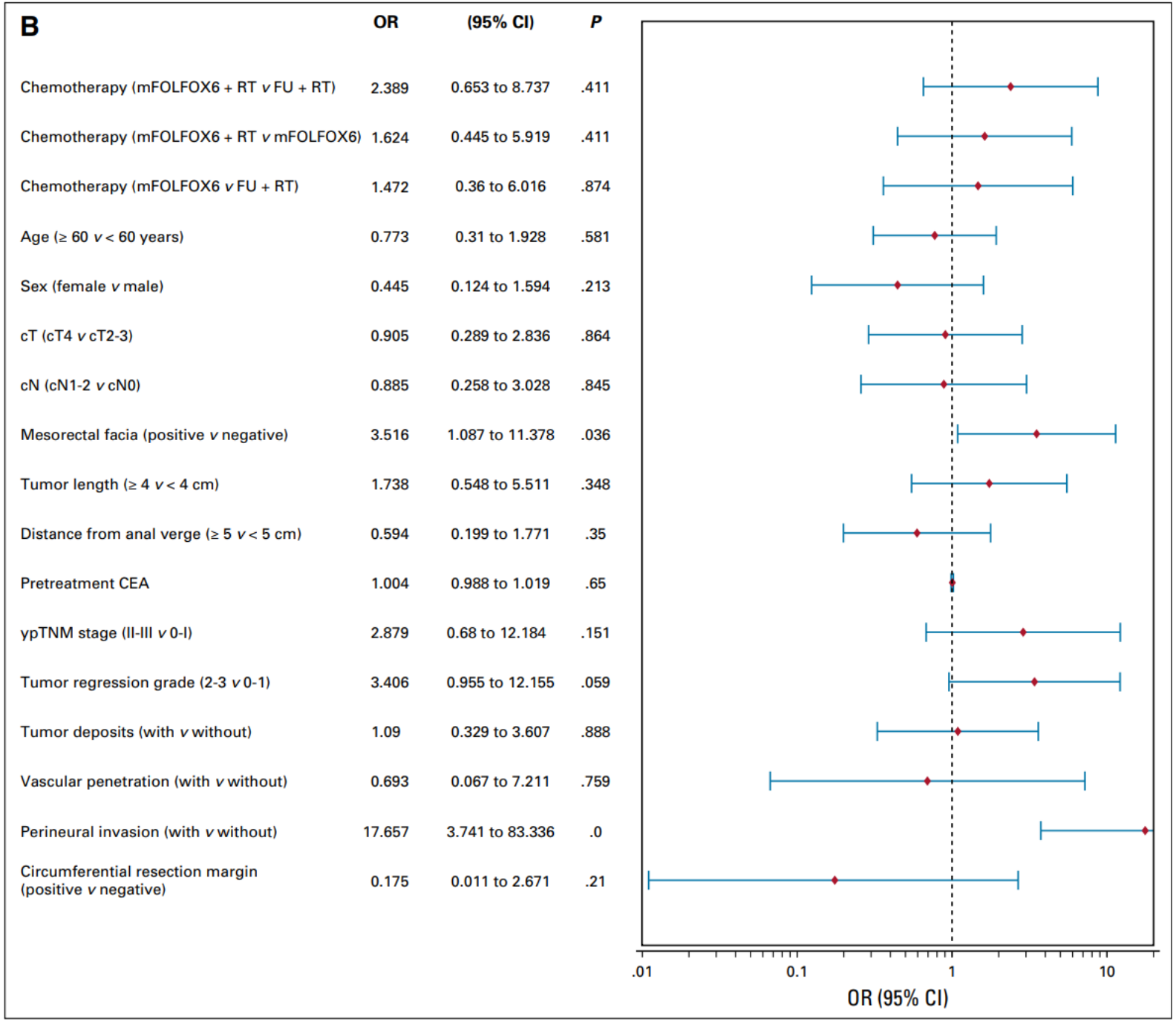


FIG 3. (Continued).

CI, 0.428 to 2.120; $P = .905$) for the mFOLFOX6 group. In a univariable analysis, mesorectal facial involvement, elevated pretreatment CEA, ypTNM stage II or III, tumor regression grade 2 or 3, presence of tumor deposits, and presence of perineural invasion were prognostic factors for worse DFS (data not shown). However, in multivariable analysis, only clinical mesorectal facial involvement and presence of perineural invasion were significantly associated with worse DFS (Fig 3B).

Author/year/ reference	No patients	Randomized Groups	Radiation Schedule	Major Findings
Omission of RT and/or Chemotherapy				
FOWARC; (Deng et al., 2019)	495	5 cycles of 5-FU/LV followed by lcRT and TME vs. 5 cycles of mFOLFOX6 followed by lcRT and TME vs. 4–6 cycles of mFOLOFX6 followed by surgery	1.8 Gy/fraction x 23 days or 2 Gy/fraction x 28 days	Pathologic CR: 14% vs. 27.5% vs. 6.5% No other significant differences
Cercek (2022-phase II) (Cercek et al., 2022)	12	One arm: Dostarlimab q3weeks followed by lcCRT with capecitabine and surgery for Mismatch Repair-Decificent rectal cancer	1.8 Gy/fraction x 28 days (planned – not performed)	Clinical CR with Dostarlimab alone: 100% Patients didn't receive further treatment during the median follow-up period of 12 months

Randomized Controlled Trial > N Engl J Med. 2023 Jul 27;389(4):322-334.
doi: 10.1056/NEJMoa2303269. Epub 2023 Jun 4.

Preoperative Treatment of Locally Advanced Rectal Cancer

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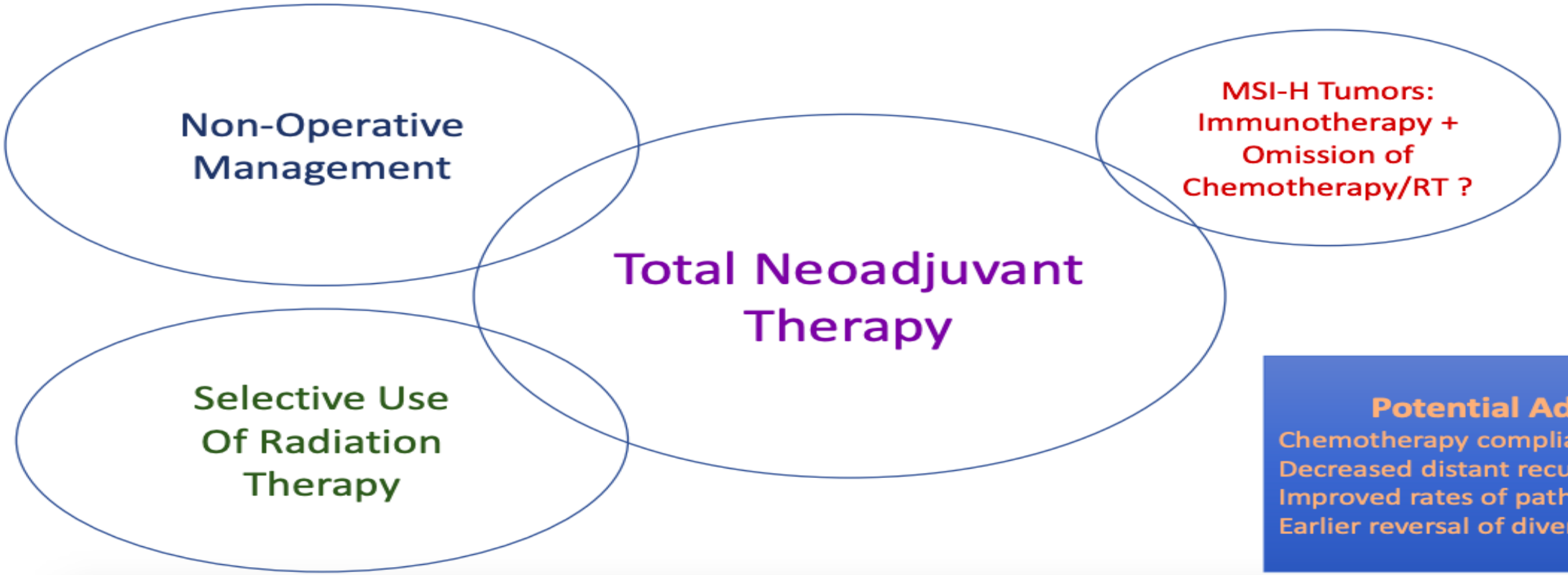
Discussion

In patients with rectal cancer that had been clinically staged as T2 node-positive, T3 node-negative, or T3 node-positive who were candidates for sphincter-sparing surgery, neoadjuvant FOLFOX and selective use of pelvic chemoradiotherapy was noninferior to the current North American standard of neoadjuvant pelvic chemoradiotherapy with respect to disease-free survival. Among the patients assigned to receive neoadjuvant FOLFOX, 89.6% were ultimately able to avoid receiving chemoradiotherapy. Overall survival was also similar with the two treatment strategies.

The percentage of patients free from local recurrence was also similar in the two groups and exceeded 98% at 5 years. The major benefit of pelvic radiation therapy that has been shown in previous clinical trials is a decrease in the risk of pelvic recurrence.[5,6,17,18] The

Newer Treatment Trends



Potential Advantages

Chemotherapy compliance?
Decreased distant recurrence?
Improved rates of pathologic response?
Earlier reversal of diverting ileostomies