Radiation sparing treatment of rectal cancer

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Options

- Radiation >Chemotherapy>Surgery> Chemotherapy
- Chemotherapy>Radiation>Surgery> Chemotherapy
- Total neoadjuvant chemo+radiation > Surgery
- Chemotherapy > Surgery > Chemotherapy
- Total neoadjuvant chemo+radiation> NO SURGERY/OBSERVATION

Radiation

- Chemoradiation has been standard of care for rectal cancer for decades and along with changes in surgical technique (emphasis on excising and intact TME plane) had reduced the risk of recurrence in the pelvis for locally advanced rectal therapy to <10%
- Radiation has toxicity
  - Increased technical difficulty of the surgery
  - Potentially increased anastomotic leak rate (however meta-analyses have shown no difference)
  - Decreased functionality of the rectum- radiation proctitis
  - Risk of injury to the small bowel, bladder, and skin

Pelvic Radiation Side Effects

- German study looking at combined chemoradiation pre/post surgery
- Bladder toxicity: 33% women, 35% men
- Skin toxicity: 75% women, 80% men
- Intestinal toxicity: 74% omen, 85% men

Wolff HA, Conradi LC, Beissbarth T, Leha A, Hohenberger W, Merkel S, Fietkau R, Raab HR, Tschmelitsch J, Hess CF, Becker H, Wittekind C, Sauer R, Rödel C, Liersch T; German Rectal Cancer Study Group. Gender affects acute organ toxicity during radiochemotherapy for rectal cancer: long-term results of the German CAO/ARO/AIO-94 phase III trial. Radiother Oncol. 2013 Jul;108(1):48-54. doi: 10.1016/j.radonc.2013.05.009. Epub 2013 Jun 11. PMID: 23768685.

Can we avoid radiation?

- PROSPECT Trial
- Included patients:
  - T2 N1
  - T3 N0
  - T3 N1
- 2 groups:
  - Intervention: 6 cycles FOLFOX >restage, if greater than 20% response> OR> +/- 6 cycles FOLFOX (recommended)
  - Chemorad: 50.4 Gy+FU over 28 days>OR> +/-8 cycles FOLFOX (recommended)

PROSPECT TRIAL

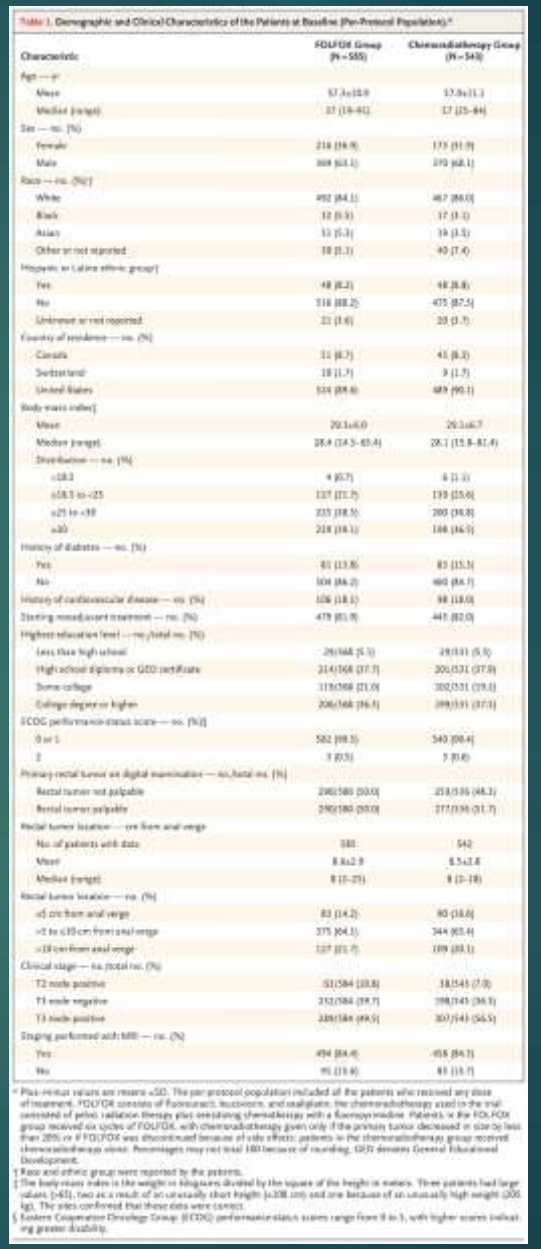


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Per-Protocol Population).*

Characteristic	FOLFOX Group (N = 585)	Chemoradiotherapy Group (N = 543)
Age — yr		
Mean	57.3±10.9	57.9±11.1
Median (range)	57 (18–81)	57 (25–84)
Sex — no. (%)		
Female	216 (36.9)	175 (31.9)
Male	369 (63.1)	370 (68.1)
Race — no. (%)†		
White	492 (84.1)	467 (86.0)
Black	32 (5.5)	17 (3.1)
Asian	11 (1.9)	19 (3.5)
Other or not reported	50 (8.5)	40 (7.4)
Hispanic or Latino ethnic group†		
Yes	48 (8.2)	48 (8.8)
No	516 (88.2)	475 (87.5)
Unknown or not reported	21 (3.6)	20 (3.7)
Country of residence — no. (%)		
Canada	51 (8.7)	45 (8.3)
Switzerland	10 (1.7)	9 (1.7)
United States	524 (89.6)	489 (90.1)
Body-mass index‡		
Mean	29.3±6.0	29.1±6.7
Median (range)	28.4 (14.5–65.4)	28.1 (15.8–81.4)
Distribution — no. (%)		
<18.5	4 (0.7)	6 (1.1)
≥18.5 to <25	137 (23.7)	139 (25.6)
≥25 to <30	225 (38.5)	200 (36.8)
≥30	218 (38.1)	198 (36.5)
History of diabetes — no. (%)		
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	26/468 (5.5)	19/511 (3.7)
High school diploma or GED certificate	214/468 (37.7)	201/511 (37.9)
Some college	119/468 (21.0)	102/511 (19.1)
College degree or higher	206/468 (36.5)	199/511 (37.1)
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)	258/536 (48.1)
Rectal tumor palpable	290/580 (50.0)	277/536 (51.7)
Rectal tumor location — cm from anal verge		
No. of patients with data	580	542
Mean	8.8±2.9	8.5±2.8
Median (range)	9 (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	52/584 (10.8)	38/545 (7.0)
T3 node negative	252/584 (39.7)	198/545 (36.3)
T3 node positive	280/584 (49.5)	307/545 (56.5)
Staging performed with MRI — no. (%)		
Yes	494 (84.4)	458 (84.3)
No	91 (15.6)	85 (15.7)

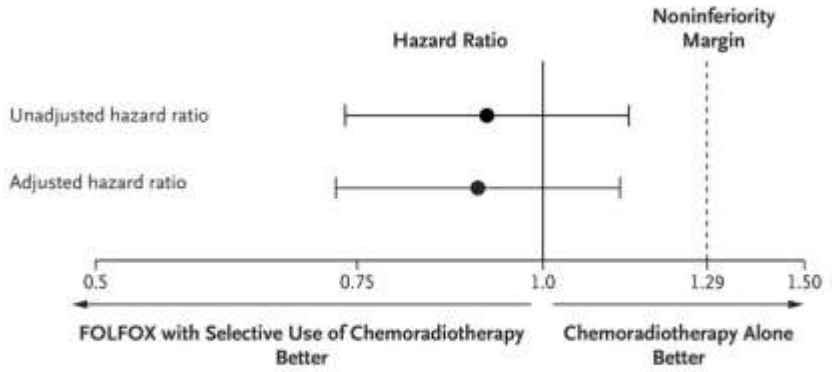
* Plus–minus values are means ±SD. The per-protocol population included all the patients who received any dose of treatment. FOLFOX consists of fluorouracil, leucovorin, and oxaliplatin; the chemoradiotherapy used in the trial consisted of pelvic radiation therapy plus oxaliplatin-containing chemotherapy with a fluoropyrimidine. Patients in the FOLFOX group received six cycles of FOLFOX, with chemoradiotherapy given only if the primary tumor decreased in size by less than 20% or if FOLFOX was discontinued because of side effects; patients in the chemoradiotherapy group received chemoradiotherapy alone. Percentages may not total 100 because of rounding. GED denotes General Educational Development.

† Race and ethnic group were reported by the patients.

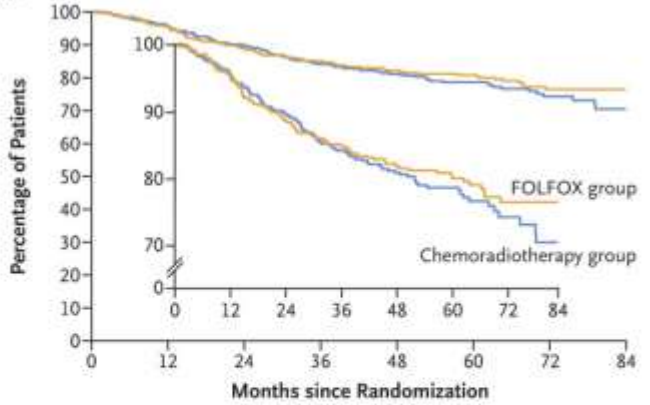
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Three patients had large values (>61), two as a result of an unusually short height (≤108 cm) and one because of an unusually high weight (205 kg). The sites confirmed that these data were correct.

§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

A Analysis of Noninferiority for Disease-free Survival



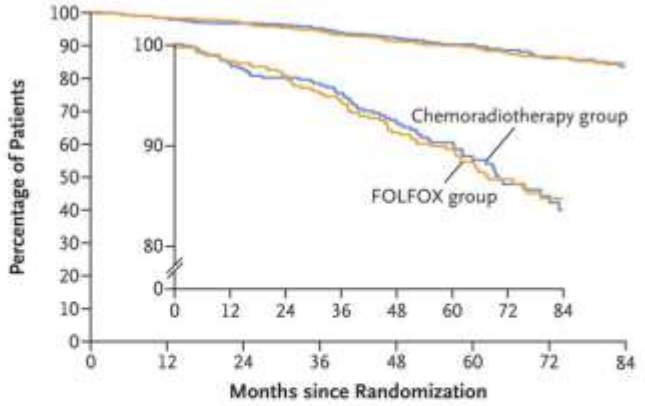
B Disease-free Survival



No. at Risk								
FOLFOX group	585	543	489	443	342	200	97	42
Chemoradiotherapy group	543	500	456	395	295	181	80	37

Group	No. of Events/ Total No.	Hazard Ratio (90.2% CI)	5-Year Estimate	Stratified P Value for NI
			percent	
FOLFOX group	114/585	0.92 (0.74–1.14)	80.8 (77.9–83.7)	0.005
Chemoradiotherapy group	113/543	Reference	78.6 (75.4–81.8)	—

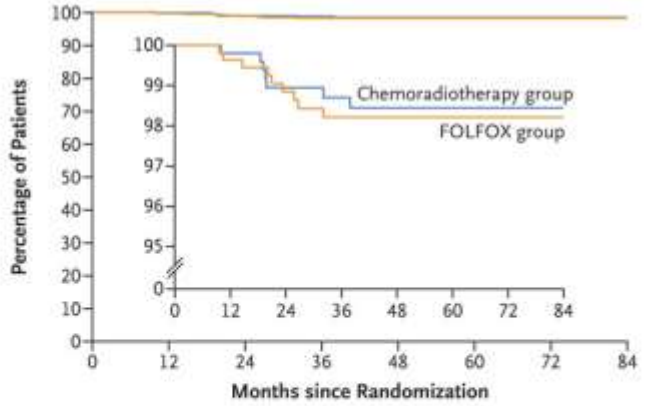
C Overall Survival



No. at Risk								
FOLFOX group	585	565	551	531	429	287	212	120
Chemoradiotherapy group	543	527	513	486	380	273	182	107

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	74/585	1.04 (0.74–1.44)	89.5 (87.0–92.2)
Chemoradiotherapy group	67/543	Reference	90.2 (87.6–92.9)

D Freedom from Local Recurrence



No. at Risk								
FOLFOX group	585	542	483	438	339	195	95	39
Chemoradiotherapy group	543	499	455	389	289	175	78	36

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

Table 2. Surgical and Pathological Secondary and Exploratory End Points in Patients in the Per-Protocol Population Who Underwent Surgery.

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 (0.2)
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)
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)

* An R0 (complete) resection was defined as a surgical specimen with no tumor identified within 1 mm of any surgical margin and no macroscopic evidence of residual tumor.
† Pathological complete response was confirmed if the surgical pathology report showed no evidence of tumor.
‡ The end of neoadjuvant therapy was defined as the start date of the last cycle of FOLFOX plus 2 weeks for patients who received neoadjuvant FOLFOX only and as the end date of preoperative radiation treatment for patients in either group who received neoadjuvant chemoradiotherapy.
§ A histologic grade of G1 indicates well differentiated, G2 moderately differentiated, G3 poorly differentiated, G4 undifferentiated or anaplastic, and GX not assessable.
¶ A margin of 1 mm or less was considered positive in accordance with the *Cancer Staging Manual* of the American Joint Committee on Cancer, 7th edition; greater than 1 mm but no greater than 3 mm is considered negative (but close to positive), and greater than 3 mm is considered negative.
‖ Tumor regression grades range from 0 to 3, with higher grades indicating greater degrees of pathological response.

Mid Rectal tumors are good candidates for avoiding radiation

- Avoids radiation side effects
- Non-inferior oncologic outcomes
- Less onerous treatment regimen
- Technically less challenging surgery

Thank You!