

CRITICS-II: A multicenter randomized phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer.

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Background: Radical surgery remains the cornerstone of cure in non-metastatic resectable gastric cancer, but survival is poor. Perioperative chemotherapy, postoperative chemoradiotherapy and postoperative chemotherapy improve outcomes, yet compliance, especially postoperatively, is low. Preoperative treatment offers better patient compliance, induces downstaging and increases R0 resections. The CRITICS-II trial compared three preoperative regimens while omitting adjuvant treatment: chemotherapy (arm 1), chemotherapy followed by chemoradiotherapy (arm 2) and chemoradiotherapy (arm 3), aiming to identify the most effective and safe strategy for phase III testing in alignment with ongoing therapeutic developments. **Methods:** In this multicenter phase II study, patients with clinical stage IB-IIIc (TNM8) resectable gastric adenocarcinoma were randomized between: (arm 1) 4 cycles docetaxel+oxaliplatin+capecitabine (DOC), (arm 2) 2 cycles DOC followed by chemoradiotherapy (45Gy/25 fractions + weekly paclitaxel/carboplatin) or (arm 3) chemoradiotherapy. Primary endpoint was 1-year event-free survival (EFS); $\leq 60\%$ deemed insufficient, $\geq 75\%$ deemed sufficiently active. Secondary endpoints included toxicity, complications, surgical outcomes, percentage R0 resections, tumor regression grade, recurrence, overall survival (OS), compliance and health-related quality of life. Translational studies will address predictive and prognostic biomarkers. **Results:** Between 2017 - 2024, 201 patients from 16 Dutch participating centers were randomized. Median follow up is 40.4 months. For primary and secondary endpoints: see table. **Conclusions:** Preoperative chemotherapy alone failed the EFS threshold, showed lowest survival and high toxicity, and was excluded from further evaluation. Both arm 2 and 3 were sufficiently active; survival favored arm 2, toxicity/compliance favored arm 3. Considering postoperative complications and pathological response rates, arm 2 ("total neoadjuvant" chemotherapy + chemoradiotherapy) emerged as the preferred candidate for further study, especially in the context of organ sparing approaches. Clinical trial information: NCT02931890. Research Sponsor: Dutch Cancer Society.

Parameter (%)	Arm 1 (CT; n=68)	Arm 2 (CT+CRT; n=65)	Arm 3 (CRT; n=68)
1-year EFS (95% CI)	68 (58-80)	84 (75-94)	78 (69-88)
1-year OS (95% CI)	74 (64-85)	89 (81-97)	84 (76-93)
Preoperative compliance	81	65	84
Max. gr 3-5 any toxicity	56	55	43
Preoperative Surgery	91	92	93
Complete resection (R0)	98	91	93
Pathological complete response	8	20	13
Postoperative complications, any Clavien-Dindo gr 3-5			
General	3	7	8
Postoperative complications, any Clavien-Dindo gr 3-5			
Infectious	0	4	10
Postoperative complications, any Clavien-Dindo gr 3-5			
Surgical	8	12	15
Postoperative in-hospital deaths	3	4	5