Radiotherapy in Gastric Cancer: Is it still a thing in NACT era? Role in adjuvant setting?

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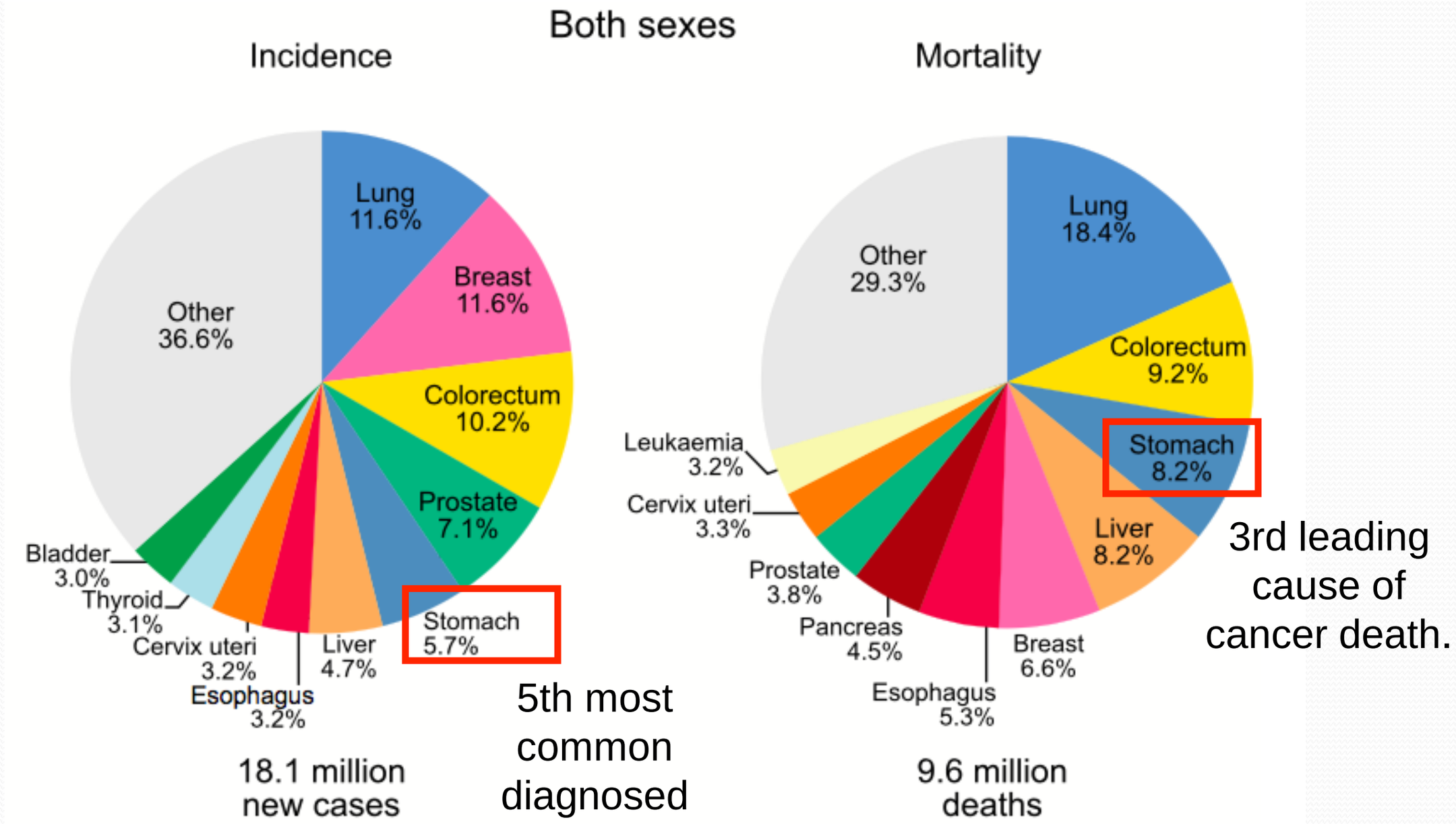
ACKNOWLEGEMENTS

Dr. Pragyat Thakur (Asst. Prof) HBCH,MULLANPUR & SANGRUR



Stomach cancer is responsible for over 1,000,000 new cases in 2018 and an estimated 783,000 deaths (equating to 1 in every 12 deaths globally).

Reference: GLOBOCAN 2018

Surgery: primary curative modality

Complete tumor resection (Total/subtotal or partial gastrectomy)
and
D2 regional lymph node resection (atleast 16 lymph nodes)

For very early T stage (Tis and T1a) - endoscopic dissection successfully used

Failure after curative surgery

Local failure in tumor bed and/or regional lymph node
distant failure by hematogenous or peritoneal routes

After complete resection, 38–94% of patients developed locoregional recurrence.
(McNeer et al, 1951; Gunderson and Sosin, 1982; Wisbeck et al, 1986; Landry et al, 1990)

<u>79%</u> may suffer recurrences within 2 years, and the median time to death after recurrence is only half a year.
(D'Angelica M et al, 2004)

So, adjuvant local treatment seems necessary.

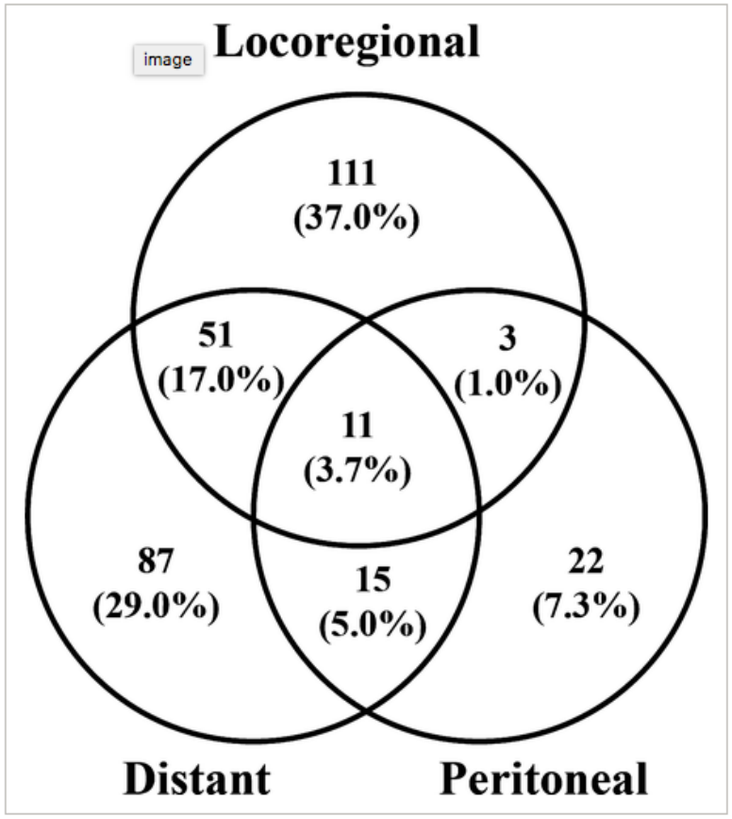


Figure 1 Open in figure viewer | PowerPoint

Patterns of recurrence in 300 patients after curative resection. Values in parentheses are percentages

Xu et al. Cancer Medicine 2020

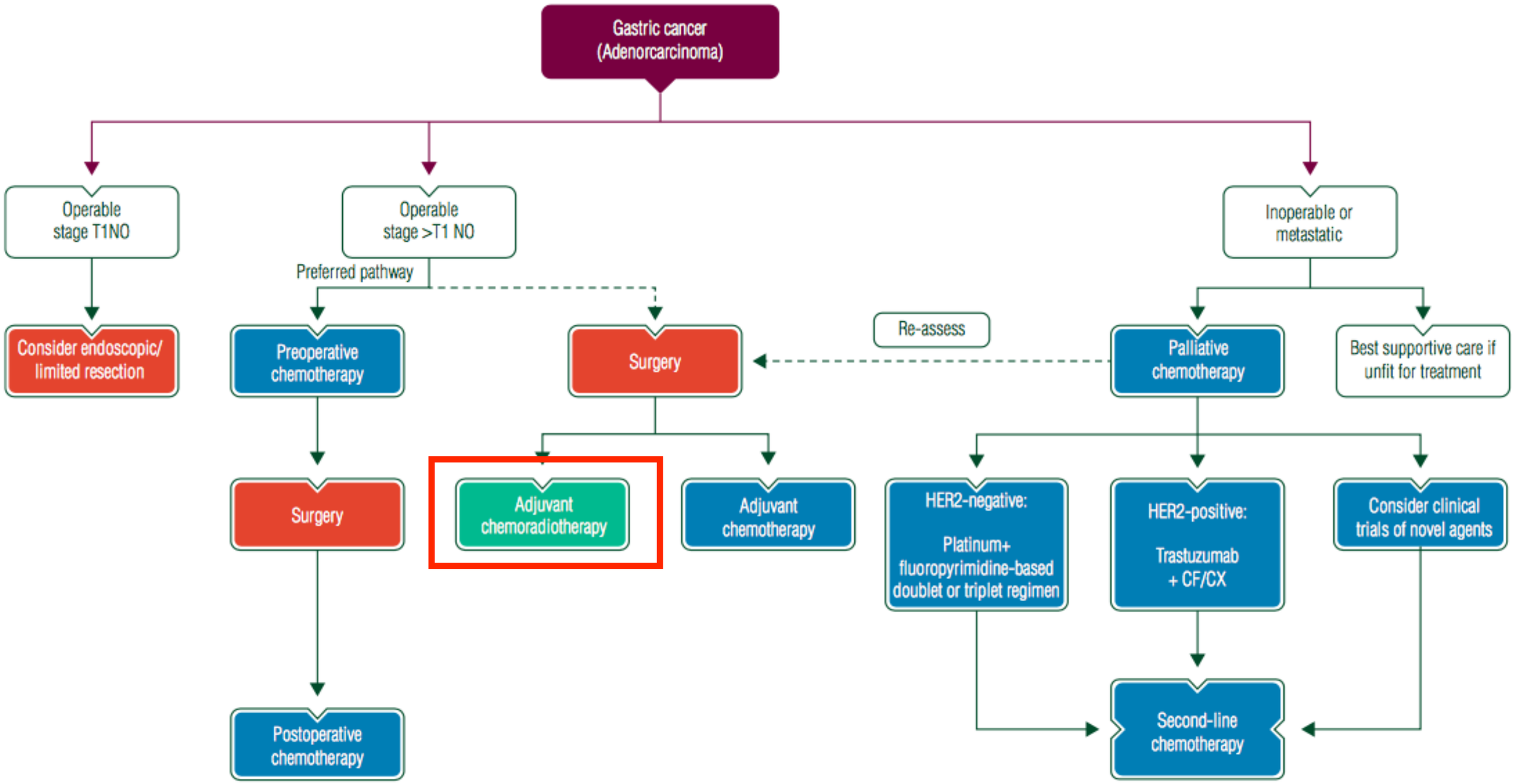


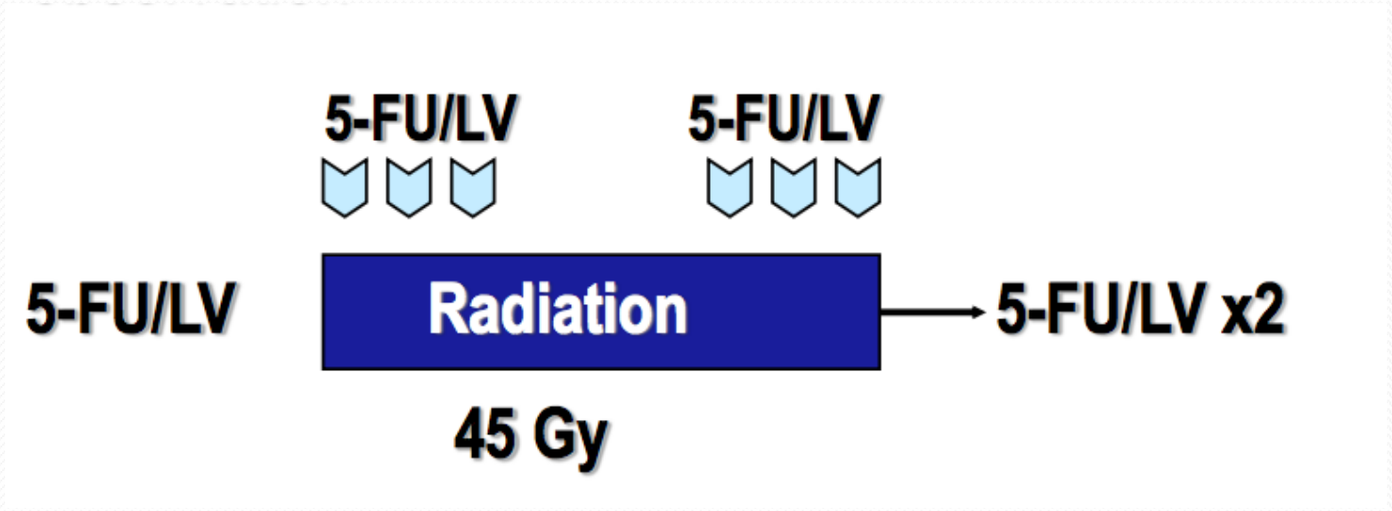
Figure 1. Gastric cancer treatment algorithm.

Smyth et al. Ann Oncol 2016

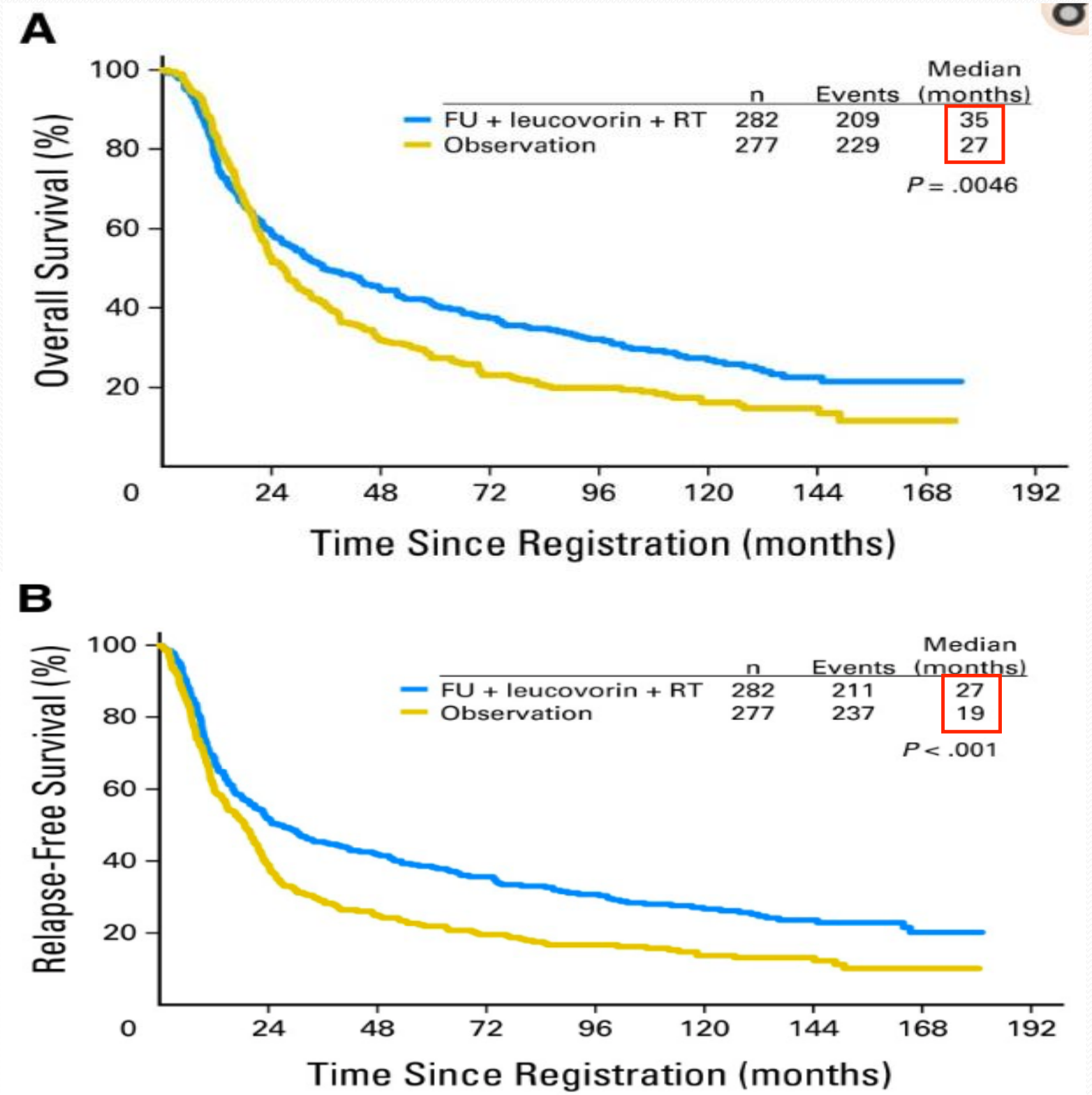
INT 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection

559 patients with primaries ≥ T3 and/or node-positive gastric cancer.
Randomized to observation versus radiochemotherapy after R0 resection.

Fluorouracil and leucovorin were administered before, during, and after radiotherapy.
Radiotherapy was given to all LRF sites to a dose of **45 Gy (1.8 Gy/fx 5 d/wk for 5 weeks)**.



Smalley et al. JCO 2012



Smalley et al. JCO 2012

Patterns of Failure by Arm

Relapse Status	Radiochemotherapy		Control(surgery alone)		Total	
	No.	%	No.	%	No.	%
No relapse*	135	48	67	24	202	36
Relapse*	147	52	210	76	357	64
Sites of relapse (% of those randomly assigned)*						
Local	7	2	21	8	28	5
Regional	62	22	109	39	171	31
Distant	46	16	49	18	95	17
Unknown site	32	11	31	11	63	11
Total	282		277		559	

*Indicates statistically significant comparisons. $P < .001$ for relapse *v* no relapse (χ^2); $P = .012$ for sites of relapse (among those with sites reported, χ^2 test for trend).

Peri-operative Chemotherapy: The MRC MAGIC Trial

Resectable adenocarcinoma of the stomach, OGJ or lower oesophagus n=503

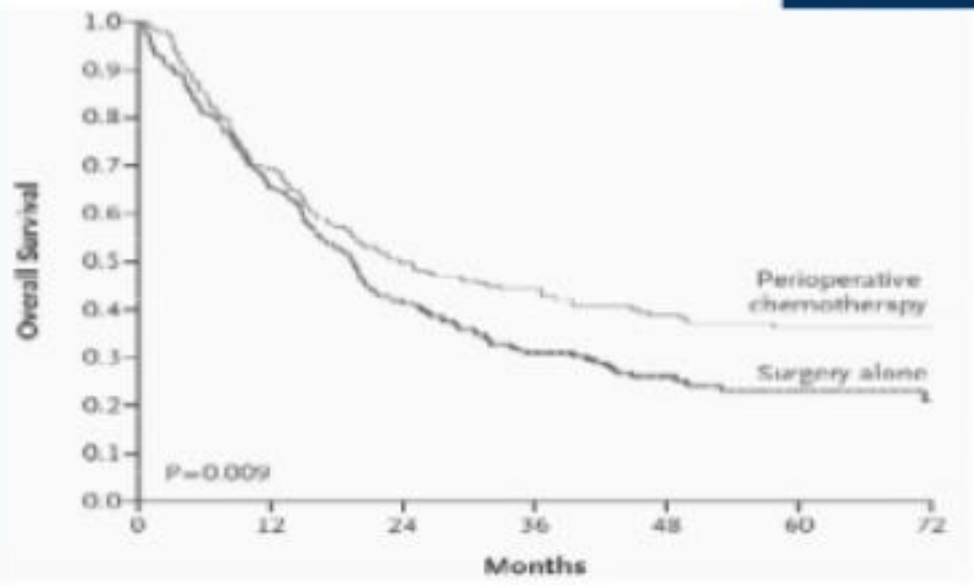
Randomised

Pre-operative ECX x3

Surgical resection within 3-6/52

Post-operative ECX x3 within 6-12/52

Surgical resection within 6/52



Median OS: 24 v 20 months
5 yr OS: 36% v 23%
13% OS benefit for ECF

HR for death 0.75, p=0.009

Pre-op chemo well tolerated (5% did not complete pre-op Rx due to toxicity)
No increase in post-op complications

Cunningham et al., NEJM 2006

- However,

- Only 42% of those enrolled were able to complete the full chemotherapy schedule

- No patient had a pathologic complete response (pCR) at the time of surgical resection, following 3 initial cycles of ECF.

VOLUME 30 · NUMBER 3 · JANUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial

Jeeyun Lee, Do Hoon Lim, Sung Kim, Se Hoon Park, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Min Gew Choi, Tae Sung Sohn, Jae Hyung Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang

RANDOMIZED

458 patients

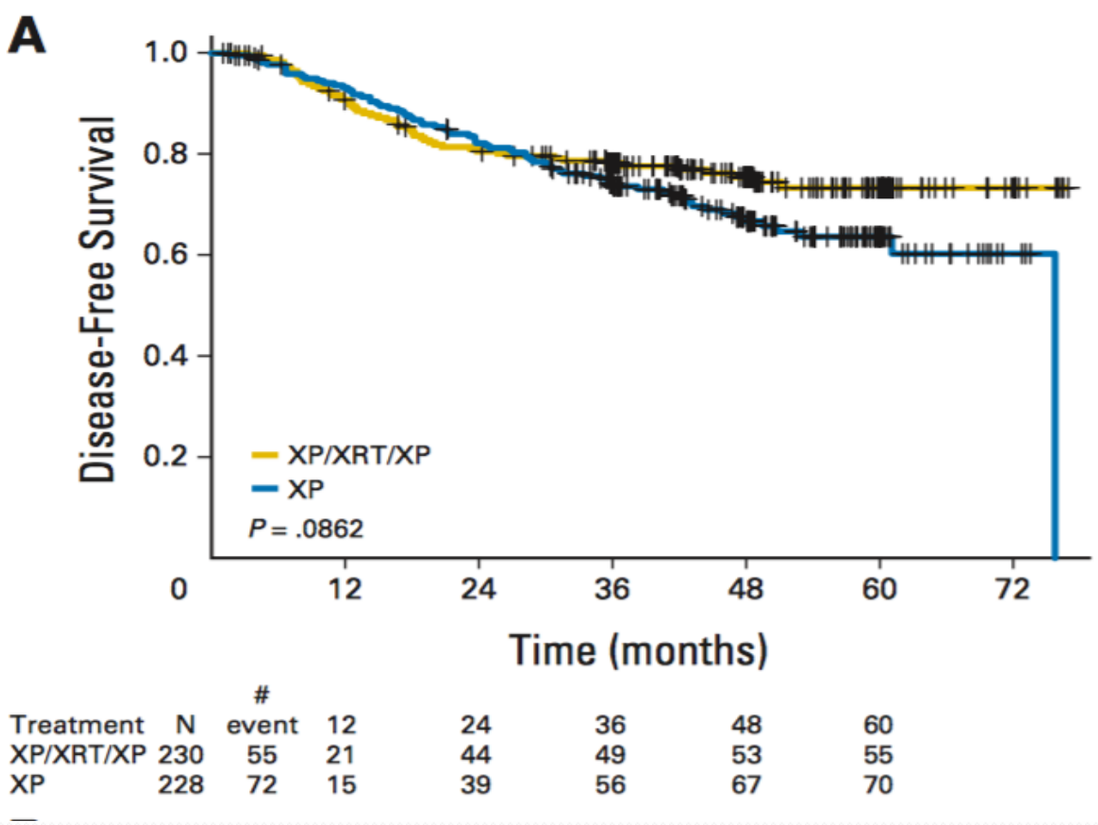
SURGERY WITH D2 LN DISSECTION

CAPECITABINE AND CISPLATIN 6 CYCLES

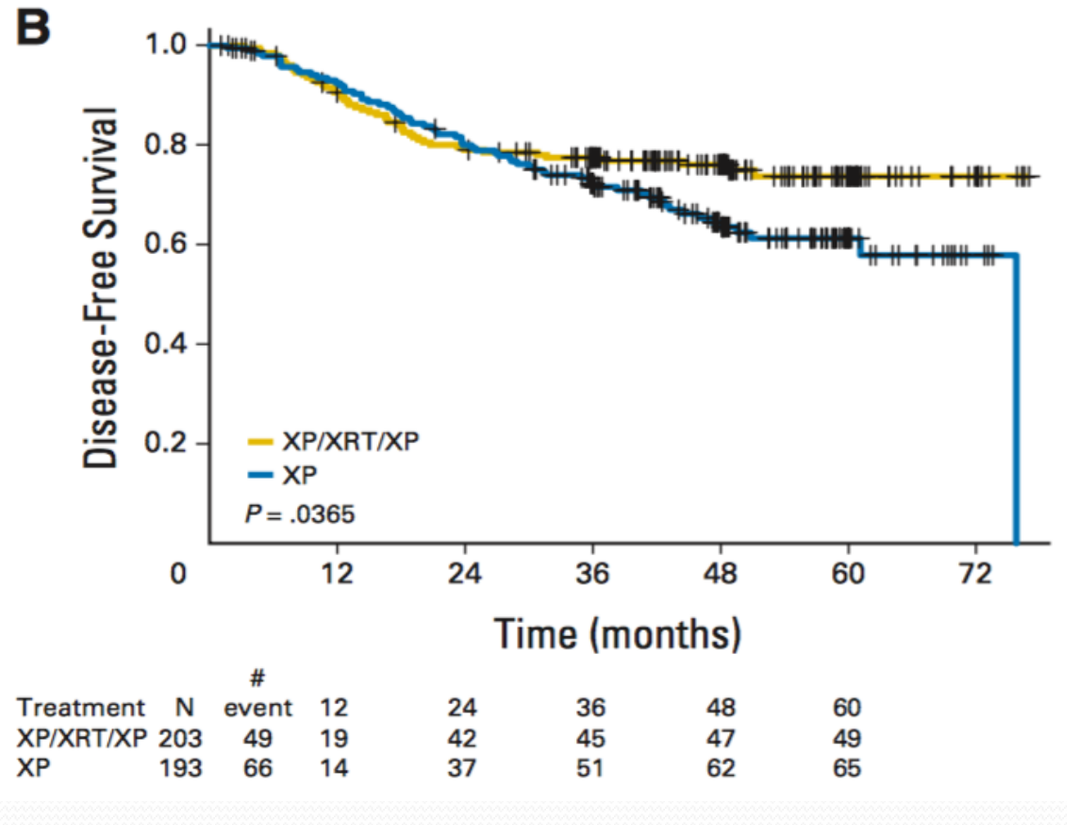
CAPECITABINE AND CISPLATIN 2 CYCLES

XPRT 45Gy IN 25#

CAPECITABINE AND CISPLATIN 2 CYCLES

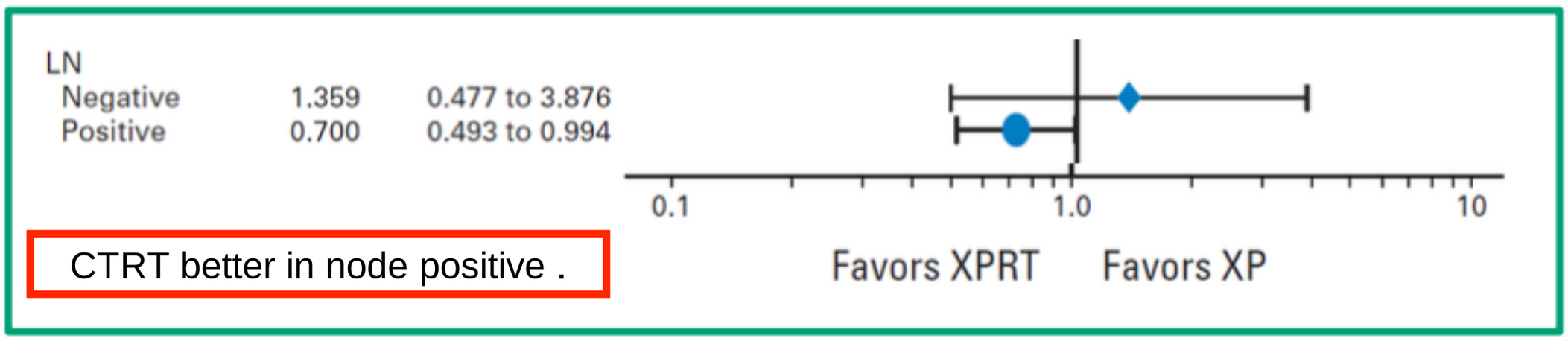


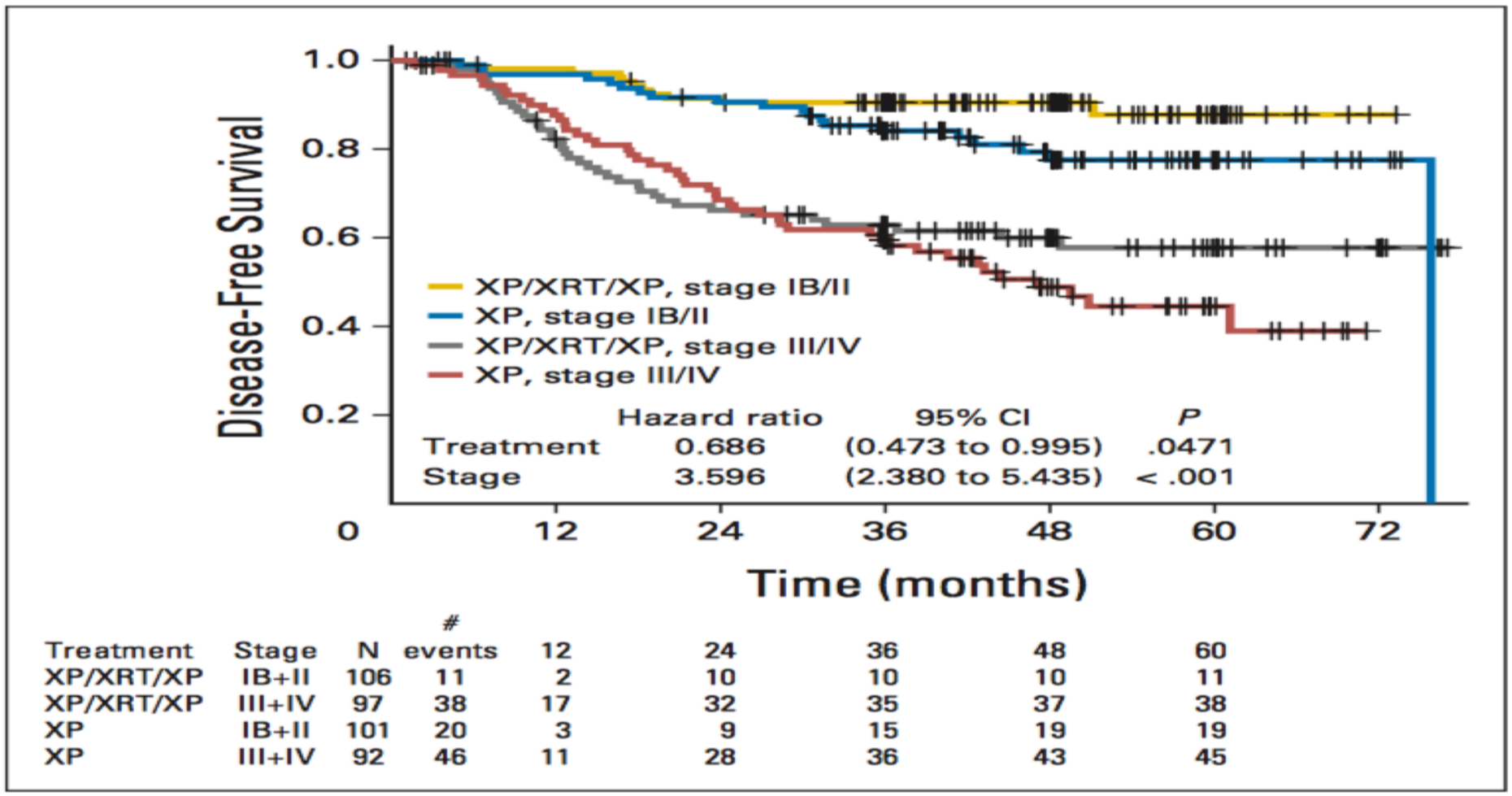
Treatment	N	# event	12	24	36	48	60
XP/XRT/XP	230	55	21	44	49	53	55
XP	228	72	15	39	56	67	70



Treatment	N	# event	12	24	36	48	60
XP/XRT/XP	203	49	19	42	45	47	49
XP	193	66	14	37	51	62	65

Fig 2. Disease-free survival in (A) all patients and (B) lymph node–positive patients. XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.





Treatment	Stage	N	# events	12	24	36	48	60
XP/XRT/XP	IB+II	106	11	2	10	10	10	11
XP/XRT/XP	III+IV	97	38	17	32	35	37	38
XP	IB+II	101	20	3	9	15	19	19
XP	III+IV	92	46	11	28	36	43	45

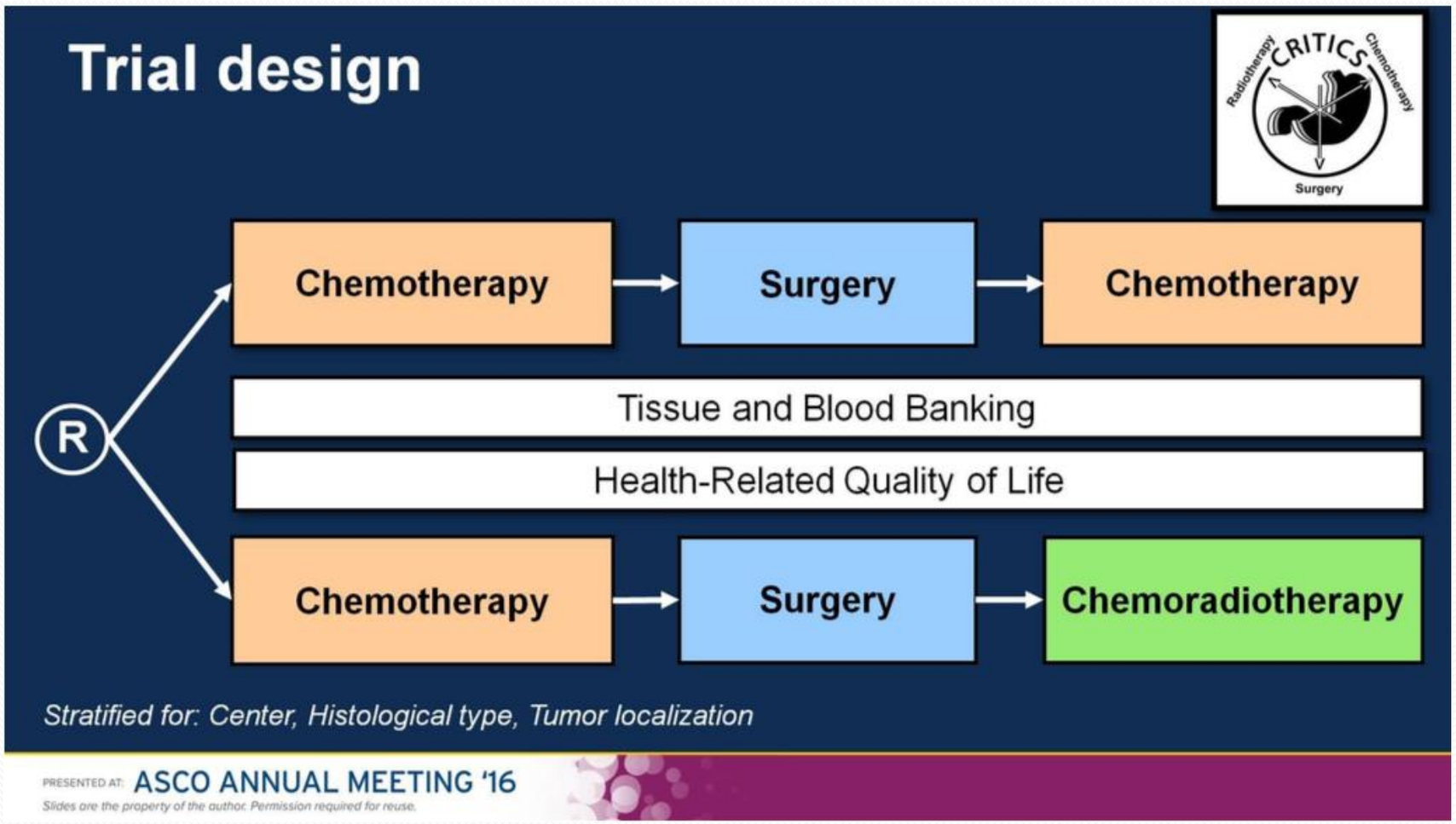
Fig 3. Disease-free survival according to stage (multivariate analysis). XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

Postoperative CRT with capecitabine and cisplatin did not appear to significantly decrease disease recurrence after a D2 LND compared with adjuvant chemotherapy alone.

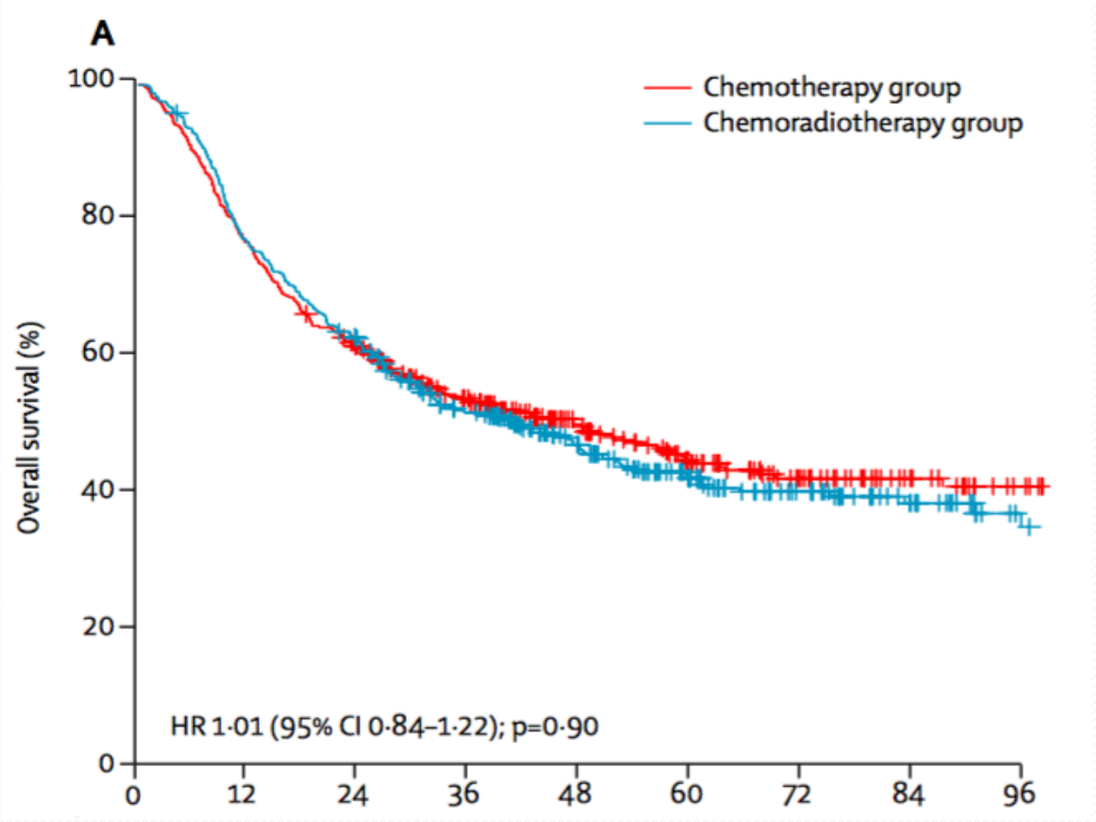
A subgroup analysis of patients with lymph node-positive disease found a significant increase in 3-year disease-free survival (DFS) in the postoperative CRT group.

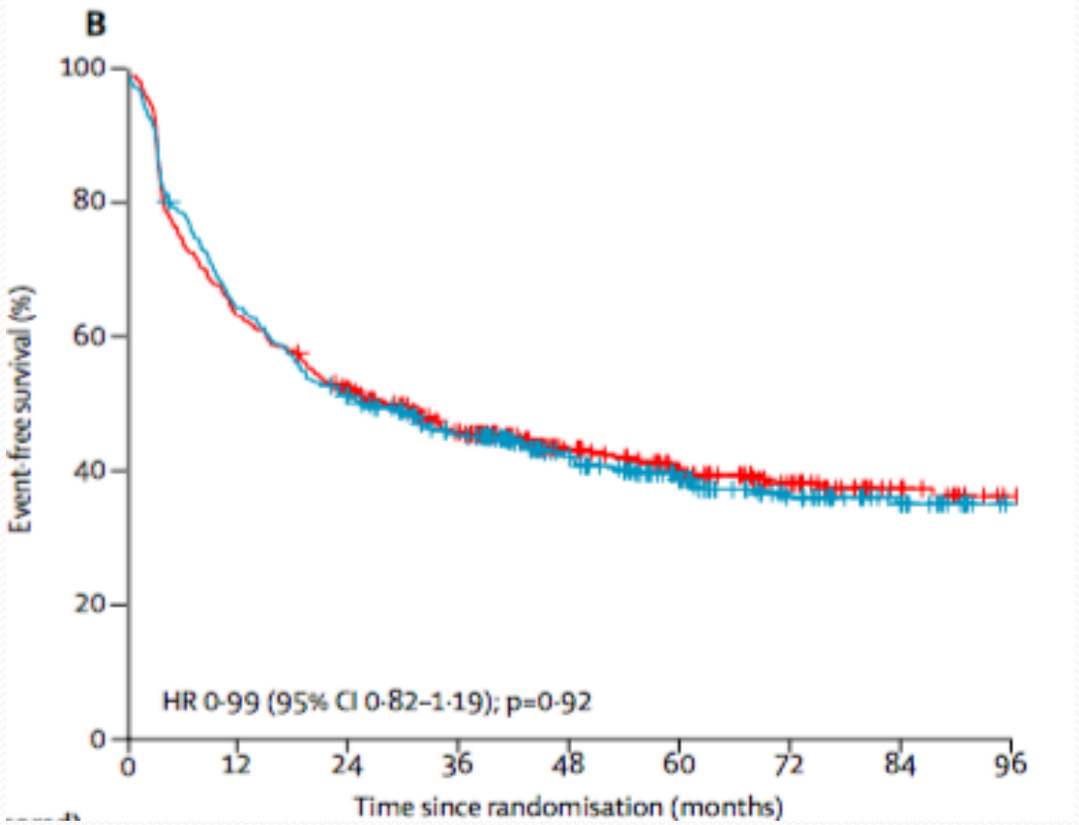
Patients with positive resection margins after surgery were excluded from the trial.

Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial



788 patients were randomly assigned to chemotherapy and chemoradiotherapy.





- The 5-year OS was approximately 41% in both arms (better than MAGIC and Intergroup 0116 trials).
- Grade 3 hematologic toxicity was slightly higher in the perioperative chemotherapy arm (44% vs 34%).
- Patients in both arms had difficulty completing protocol treatment (47% for perioperative chemotherapy, 52% for adjuvant chemoradiotherapy).

In conclusion, we did not find better efficacy of postoperative chemoradiotherapy compared with postoperative chemotherapy in patients with resectable gastric cancer treated with preoperative chemotherapy and adequate surgery. Tolerability was also similar between the two adjuvant regimens. Future explorative

Adjuvant radiotherapy improves overall survival in patients with resected gastric adenocarcinoma: A National Cancer Data Base analysis

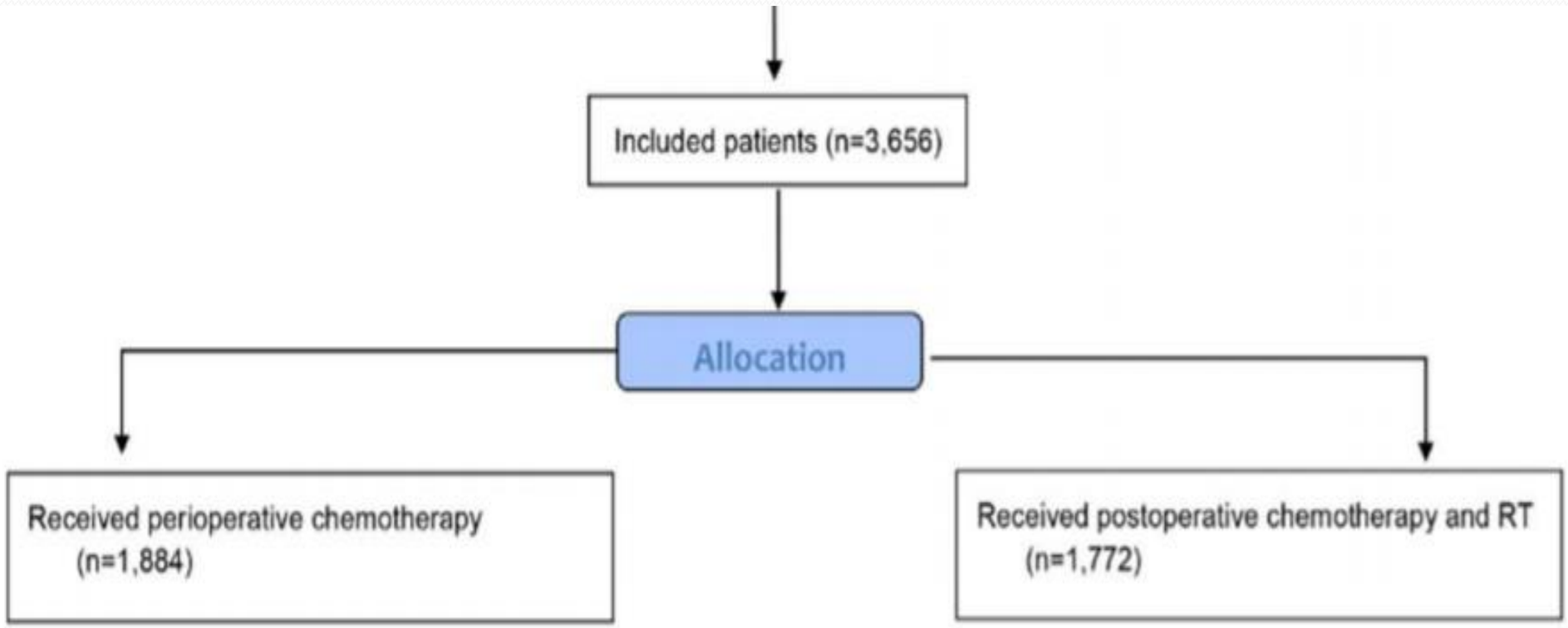
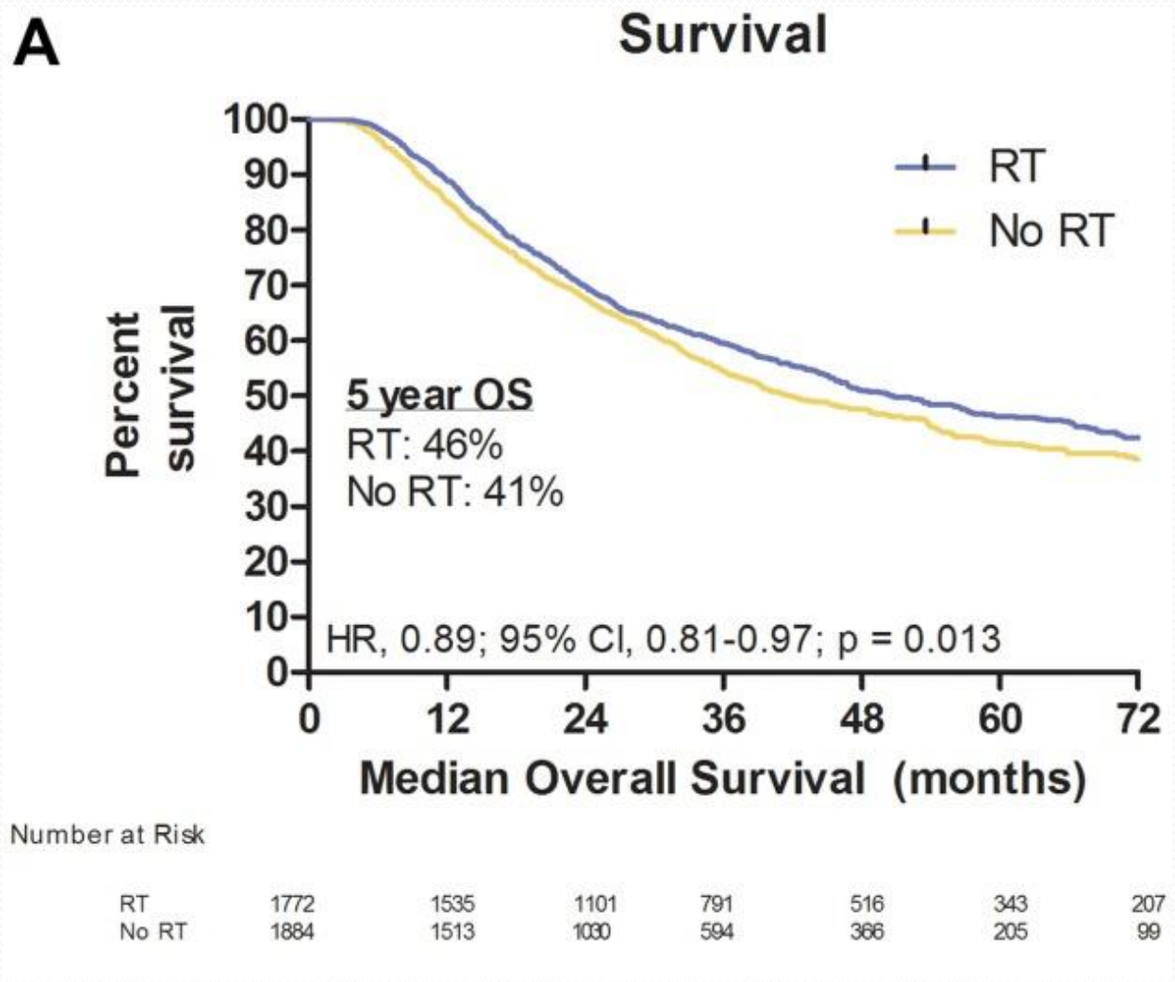


Figure 1. Cohort derivation showing case selection for the study group. cGy indicates centigrays; cT, clinical tumor classification; NCDB, National Cancer Data Base; RT, radiotherapy.

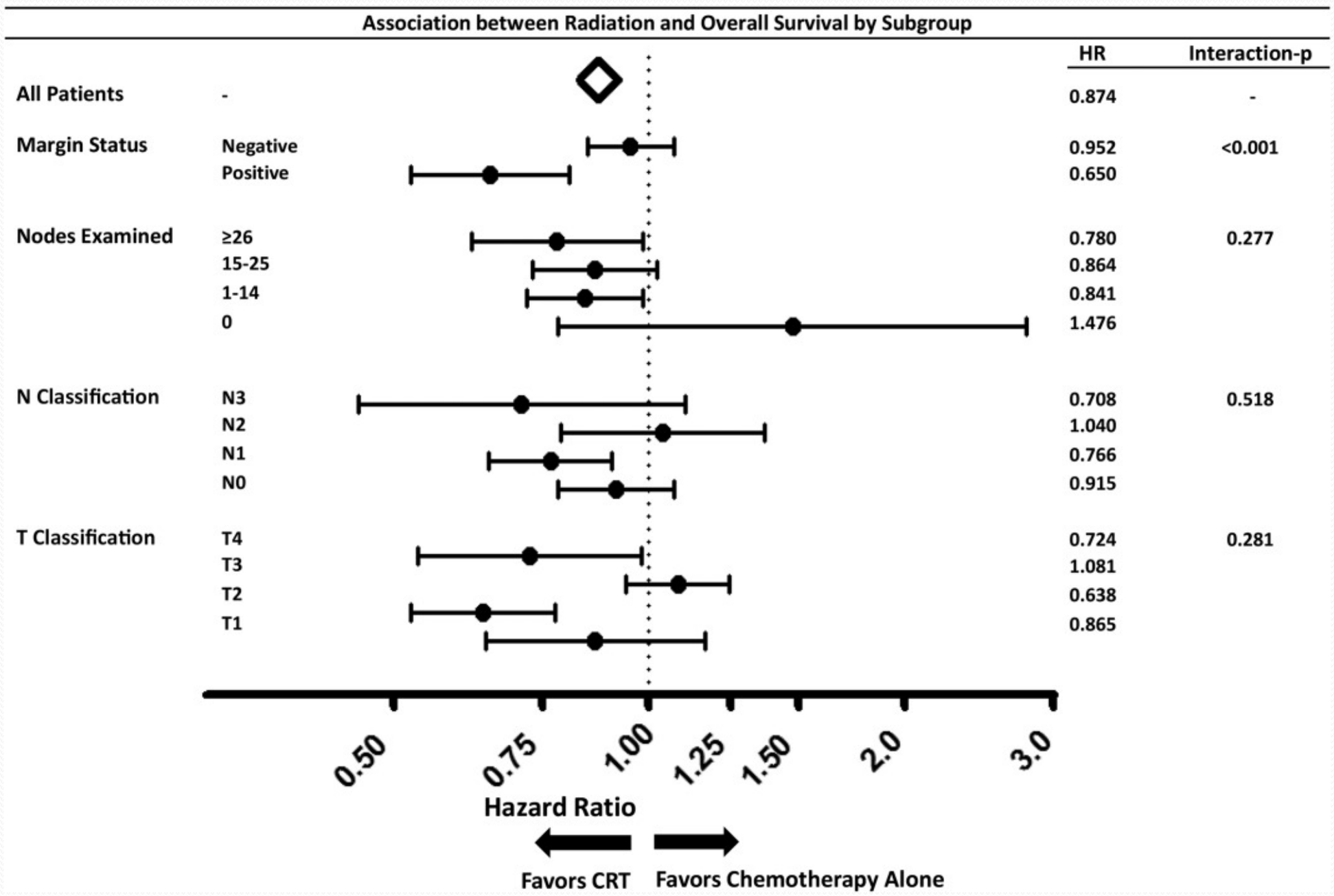
Cancer, Volume: 123, Issue: 17, Pages: 3402-3409, First published: 17 May 2017, DOI: (10.1002/cncr.30748)

Adjuvant radiotherapy improves overall survival in patients with resected gastric adenocarcinoma: A National Cancer Data Base analysis



A **5% absolute OS advantage was observed at 5 years with the use of adjuvant RT in addition to chemotherapy for patients with resected gastric cancer** (5-year OS rate: 46% [95% CI, 43%-49%] vs 41% [95% CI, 38%-44%]), which remained significant on propensity score-matched analyses.

Stumpf et al. Cancer 2017



Forest plot of the association between radiotherapy and overall survival by patient subgroup.

Role of chemoradiotherapy is less well defined in patients undergoing R1 resection because of lack of any randomized data

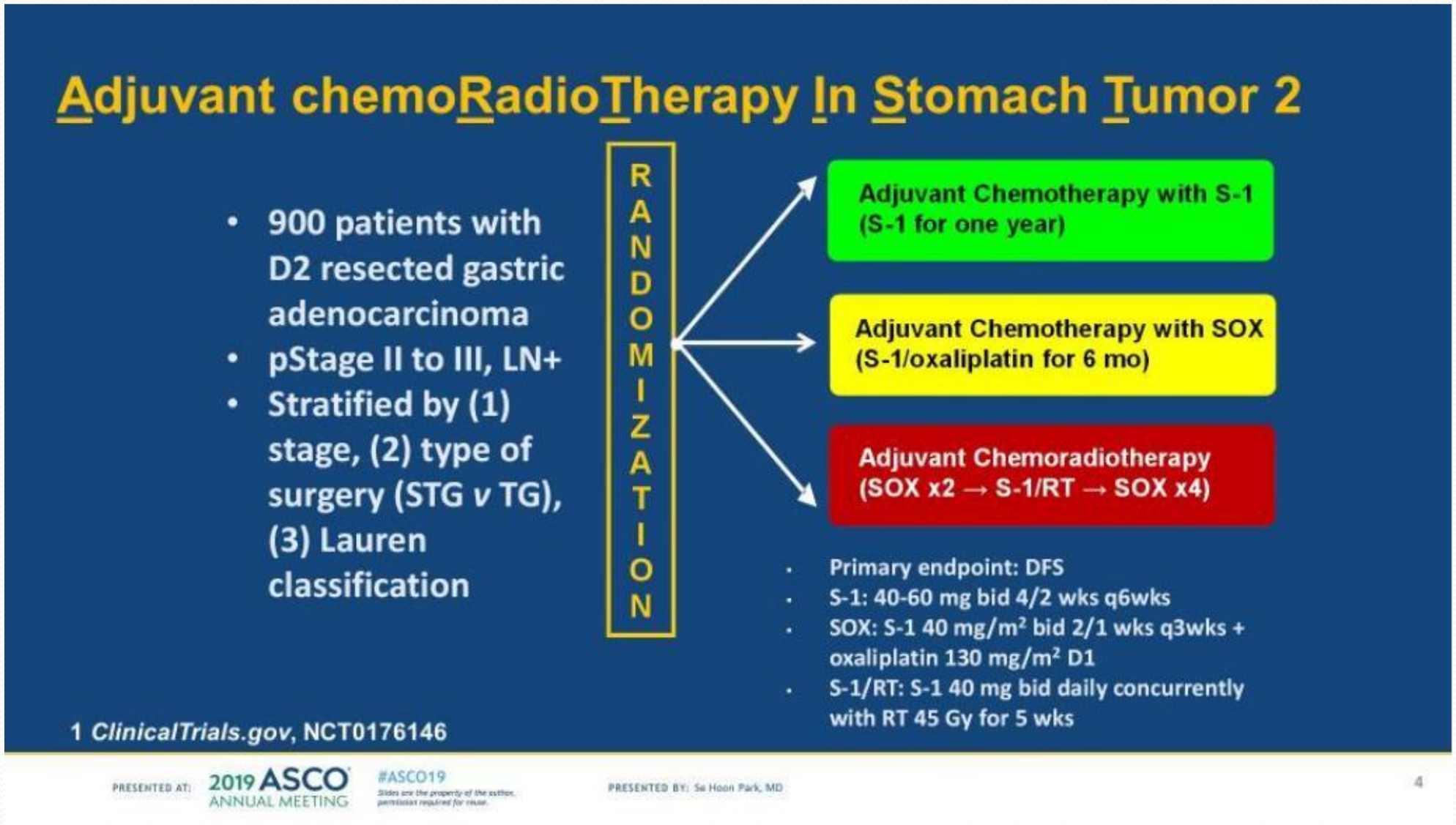
› Ann Surg Oncol. 2015 Feb;22(2):581-8. doi: 10.1245/s10434-014-4032-8. Epub 2014 Aug 28.

Does adjuvant chemoradiotherapy improve the prognosis of gastric cancer after an r1 resection? Results from a dutch cohort study

Jurriën Stiekema [1], Anouk K Trip, Edwin P M Jansen, Mieke J Aarts, Henk Boot, Annemieke Cats, Olga Balague Ponz, Patrycja L Gradowska, Marcel Verheij, Johanna W van Sandick

Conclusions: Adjuvant CRT was associated with an improved survival in patients who had undergone an R1 resection for gastric cancer.

ARTIST 2: Phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC)



Interim results:

A total of 538 patients were included for this interim efficacy analysis.

- Median age was 58 years, men constituted 65%, and stage II and III were 31% and 69%, respectively. Baseline tumor and patient characteristics were balanced between treatment arms. Adverse events were as anticipated in each arm, generally well-tolerated and manageable.

- DFS in the control arm (S-1) were significantly shorter than in SOX and SOXRT arms S-1 vs. SOX, 0.617 (P = 0.016) and S-1 vs. SOXRT, 0.686 (P = 0.057). The DFS at 3-years was found to be 65%, 78% and 73% in S-1, SOX and SOXRT arms, respectively.

- No difference in DFS between SOX and SOXRT was found (HR 0.910, P = 0.667).

- Conclusions: In patients with curatively D2-resected, stage II/III, node-positive GC, adjuvant SOX or SOXRT was effective in prolonging DFS, when compared to S-1 monotherapy.

Role of Radiotherapy in the Neoadjuvant Setting

Advantages:

- Enhance resectability
- Assess response in primary tumour
- Improve local control
- Treat micrometastases early
- Better tolerance than postoperative treatment

a. including smaller target volumes
b. removal of the irradiated normal tissue at the time of resection

There are two major phase III trials, TOPGEAR and CRITICS-II, which will assist in determining its appropriateness in gastric cancer management.

Ann Surg Oncol (2017) 24:2252–2258
DOI 10.1245/s10434-017-5830-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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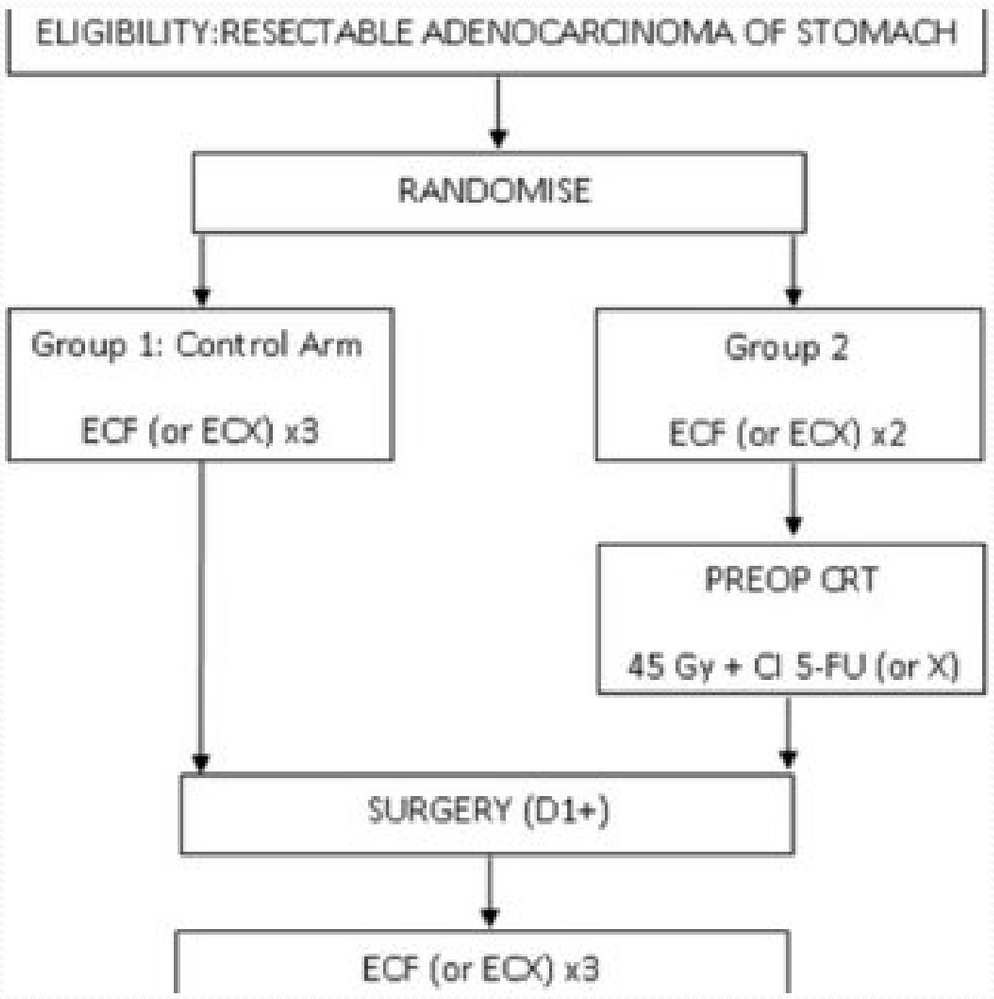
ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG



Chemoradiotherapy was to begin 2–4 weeks after the completion of cycle 2 of induction ECF.

Dose: 45 Gy in 25 fractions, 5 days per week for 5 weeks, plus
continuous infusional 5-FU 200 mg/m2/day, 7 days per week throughout the entire period of radiotherapy (or capecitabine 825 mg/m2 BD, days 1–5 each week of radiotherapy).
Radiotherapy was delivered to the entire stomach, any perigastric tumor extension, and regional lymph nodes using 3DCRT, IMRT or VMAT.

Interim results:

1. Preoperative chemoradiation is safe and feasible and does not adversely affect surgical morbidity.

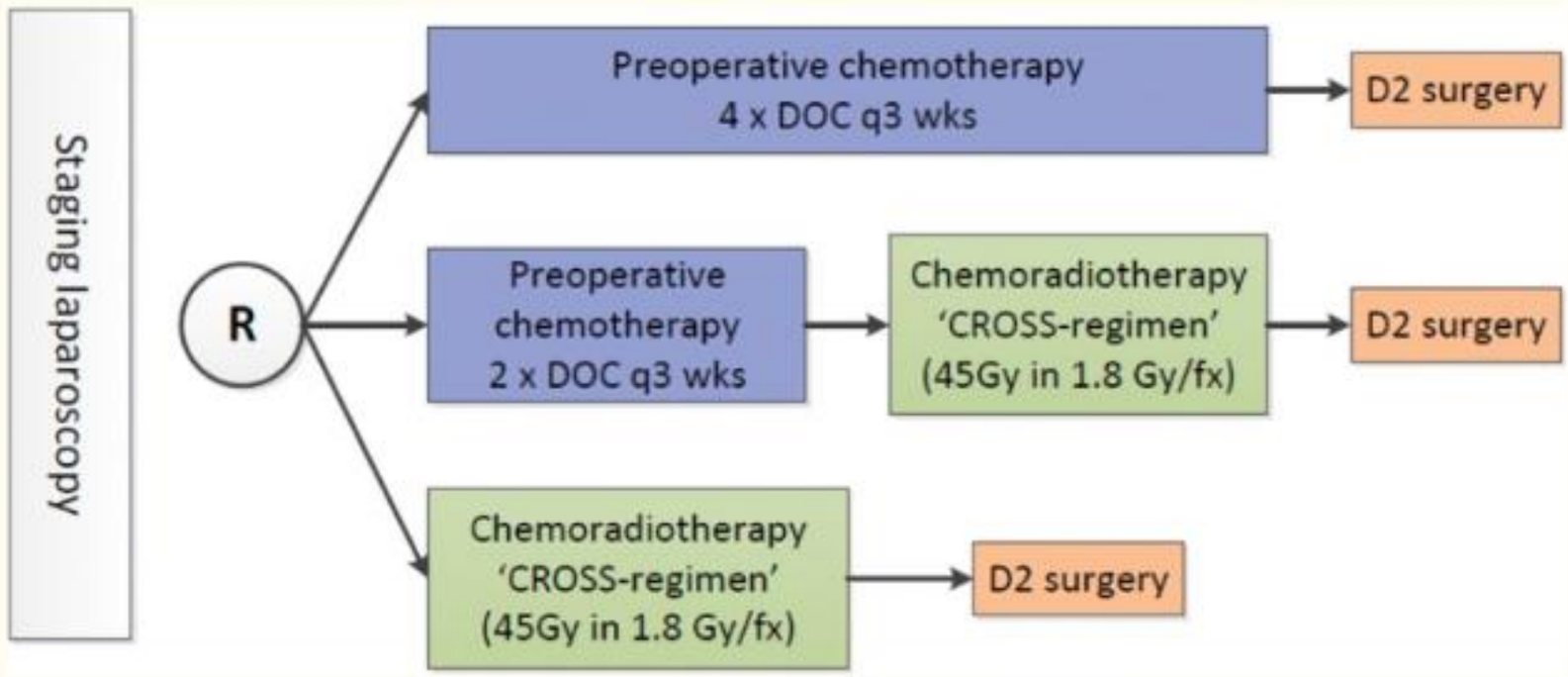
2. Demonstrates the advantage of delivering radiotherapy in the preoperative rather than postoperative setting.

3. 98% of patients were able to complete the planned protocol dose of radiotherapy, in contrast to the INT0116 postoperative chemoradiation trial, in which 17% of patients were unable to complete radiotherapy due to treatment-related toxicity.

4. Addition of preoperative abdominal irradiation to perioperative ECF did not increase the rates of major hematologic and non-hematologic toxicities, which were similar in the two groups.

BMC Cancer. 2018; 18: 877.
Published online 2018 Sep 10. doi: 10.1186/s12885-018-4770-2
PMCID: PMC6131797
PMID: 30200910

CRITICS-II: a multicentre randomised 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



Results are pending!

Our Experience…

DOI:10.31557/APJCC.2020.5.3.151

RESEARCH ARTICLE

Dosimetric Evaluation of 3-Dimensional Conformal Radiotherapy Technique in Postoperative Patients with Gastric Carcinoma: When Is IMRT Really Needed?

Rakesh Kapoor, Srinivasa GY, Namrata Das, Chinna Babu Dracham, Divya Khosla, Arun S Oinam

Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Conclusion of study:

The results of this study and subsequent comparison with existing literature suggests that 3D-CRT provides adequate homogenous target volume dose coverage and OAR protection, comparable to IMRT.

More than the radiotherapy technique, it was the anastomotic site and the tumor location that determined the OAR doses.

Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-020-00440-w

ORIGINAL RESEARCH

Clinical Outcomes and Prognostic Factors in Gastric Carcinoma Patients with Curative Surgery Followed by Adjuvant Treatment: Real-World Scenario

Rakesh Kapoor[1] · Chinna Babu Dracham[1] · Srinivasa G Y[1] · Divya Khosla[1] · Treshita Dey[1] · Arun Elangovan[1] · Renu Madan[1] · Budhi Singh Yadav[1] · Narendra Kumar[1]

Conclusion of study:

The present study demonstrated that survival in gastric carcinoma is influenced by the stage of disease and surgical margins.

In locally advanced patients, radical surgery followed by sequential chemoradiation based on a doublet/triplet regimen was an independent prognostic factor for survival.

Take Home Message

1. Preoperative RT still lacks large-scale phase III clinical trials for gastric cancer.

2. Post operative RT indicated for

a) Patients with D1 or D1 plus lymphadenectomy

b) Node positive

c) Positive margin

HOMI BHABHA CANCER HOSPITAL, SANGRUR
(A Unit of TATA MEMORIAL CENTRE, Mumbai)

CANCER IS CURABLE IF DETECTED EARLY

THANK YOU