Concurrent Chemo - Radiotherapy in Carcinoma of Stomach

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- Despite curative resection a majority of patients will develop recurrence

- Trials had failed to demonstrate an improvement in survival with adjuvant therapy compared with surgery alone

- Questions remain regarding the optimal treatment regimen and clinical trials are ongoing

- Surgery is the mainstay of treatment
- Approximately 50% of patients are not candidates for resection due to the presence of unresectable, locally advanced disease or metastases
- Even among patients undergoing gastrectomy with curative intent, 5-year survival rates range from 15% to 30% due to locoregional relapse and distant metastases
- Due to the heterogeneity in therapeutic regimens and methodologic quality of trials done, surgery has remained the standard of care.

Patterns of Failure following potentially curative surgery
Cumulative Incidence of failure (%)

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Local Failure by TNM stage	Clinical	Reoperation
T1N0	0	-
T1-2N0	19	-
T3N0	50	-
T4N0	40	-
T1-2N1-2	24	-
T3N1-2	36	-
T4N1-2	56	-

Landry et al: IJROBP:19,1357,1990
Yoo et al: Br J Surg:87,236,2000

Patterns of Failure following potentially curative surgery
Cumulative Incidence of failure (%)

Failure Site	Clinical	Reoperation
Total Local/Regional	38	67
Gastric Bed	21	54
Abdominal Scar		5
Anastomosis	25	26
Nodes	8	42
Peritoneal Seedling	23	41
Local		19
Diffuse		22
Distant	52	22

Combination of RT and CT

- **Neoadjuvant/Preoperative CTRT**
- Neoadjuvant/Perioperative CT
- **Adjuvant/Postoperative CTRT**
- Adjuvant CT

Preoperative CTRT

- Not a standard of care
- Some centres use it in T2 or node positive adenocarcinoma involving both the
- GE junction and stomach
- Pre treatment laparoscopy is mandatory to exclude patients with radiographically undetected peritoneal or liver metastasis
- Pathologic CR 25%
- 80-90% chance of complete resection with negative margins

Preoperative CTRT (RTOG 9904 trial)

Number of Patients	**43**
Stage	T2-T3 N1-N2 Lap -ve
Treatment	5FU/leucovorin/cisplatin x 2 45 Gy RT + 5FU/paclitaxel Surgery
Surgery	36 underwent surgery (7 disease progression). 50% D2 resection. pCR 26%
Toxicity	Grade 4 acute toxicity 21%.
Median Survival	23 months

Rationale of Adjuvant Therapy

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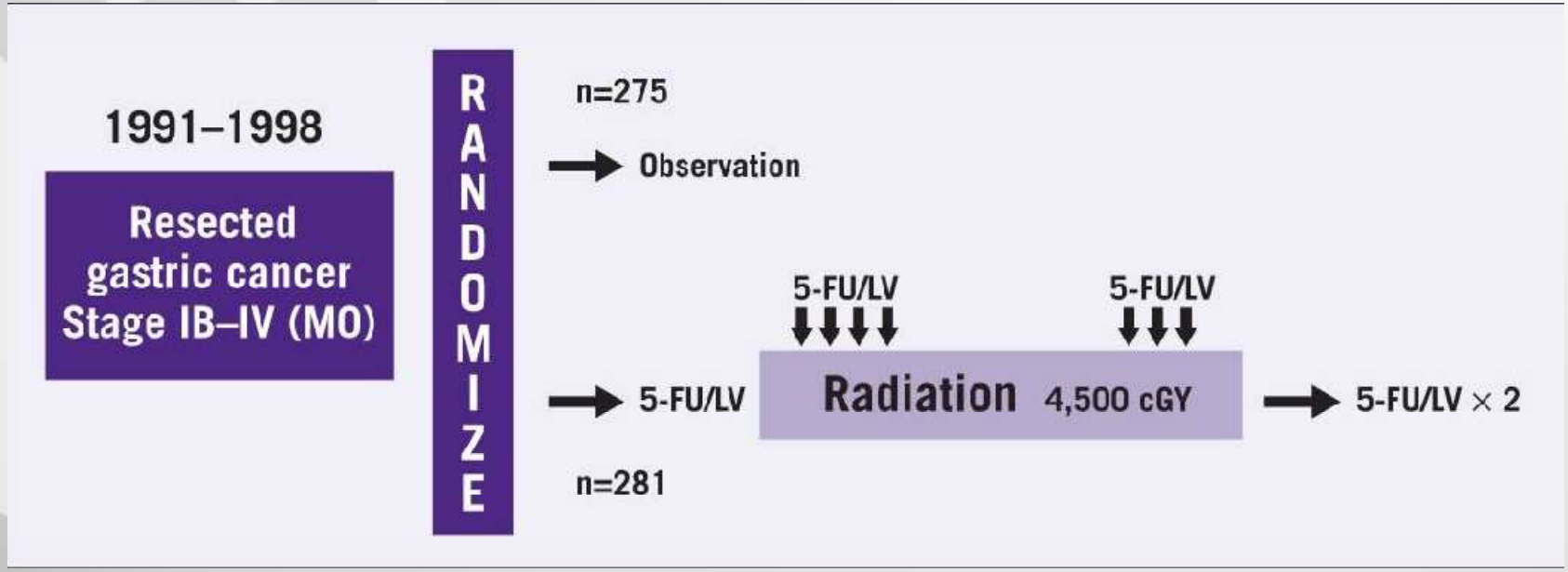
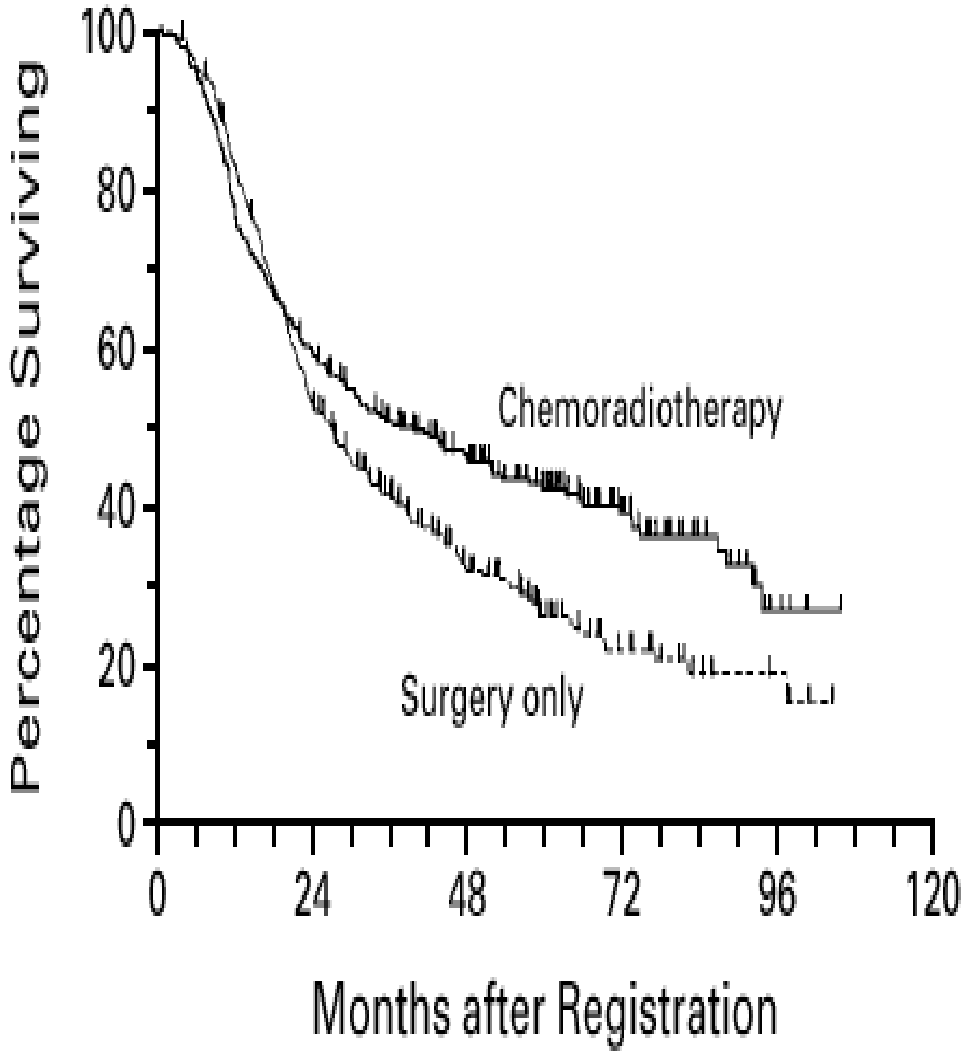
- Patterns of failure following potentially curative surgery
- Failure assessed by clinical methods, re-operation methods or both
- Clinical methods use physical exam,and radiological studies and re-operation methods use second look surgery every 6 months (more accurate but not commonly used)
- Incidence of local failure increases with increasing penetration of the wall and positive lymph nodes
- Local failure is significant even with R0 resections

INT 0116: Treatment Schema



INT 0116: 5 year survival by T and N status

Characteristic	CTRT (%)	Surgery Only (%)
Nodal Status		
N0	60	44
N1-N3	50	37
N > 4	30	17
Stage		
T1-T2	56	38
T3	38	20



INT 0116: Updated 10 yr Results

Overall survival (OS) and relapse-free survival (RFS) data demonstrate continued strong benefit from postoperative radiochemotherapy.

The hazard ratio (HR) for OS is 1.32 (95% CI, 1.10 to 1.60; P = .0046). The HR for RFS is 1.51 (95% CI, 1.25 to 1.83; P < .001).

Adjuvant radiochemotherapy produced substantial reduction in both overall relapse and locoregional relapse. There were significantly fewer local and regional recurrences in the chemoradiotherapy group but no difference in the rates of distant recurrences. Can we conclude from these findings that the underlying survival benefit of chemoradiotherapy is principally a consequence of preventing locoregional recurrences?

Second malignancies were observed in 21 patients with radiotherapy versus eight with observation (P = .21).

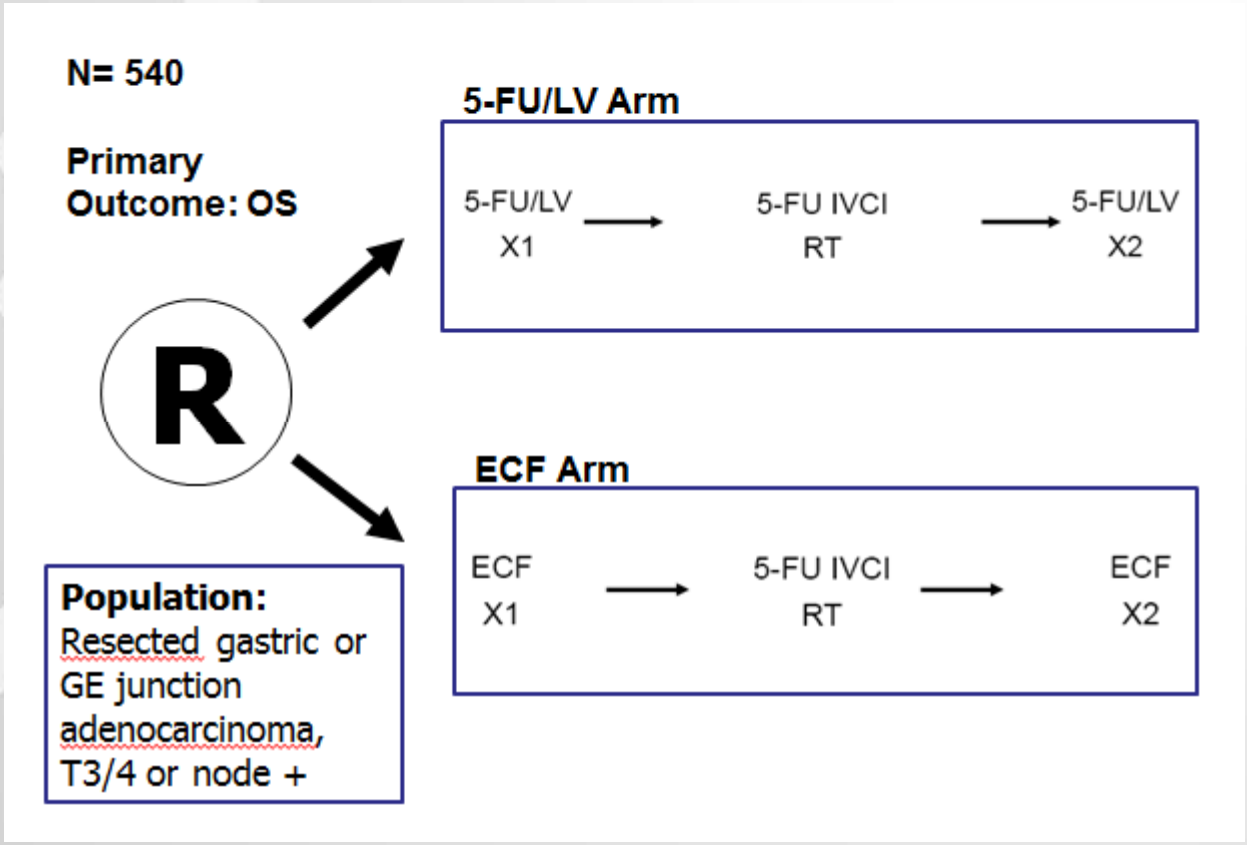
Subset analyses show robust treatment benefit in most subsets, with the exception of patients with diffuse histology who exhibited minimal nonsignificant treatment effect.

Smalley et al : J Clin Oncol. 2012 Jul 1;30(19):2327-33.

Conclusion

- **Adjuvant radiochemotherapy produced substantial reduction in both overall relapse and locoregional relapse.**
- Second malignancies were observed in 21 patients with radiotherapy versus eight with observation (P = .21).
- Subset analyses show robust treatment benefit in most subsets, with the exception of patients with diffuse histology who exhibited minimal nonsignificant treatment effect.
- Toxicities, including second malignancies, appear acceptable, given the magnitude of RFS and OS improvement.
- LRF reduction may account for the majority of overall relapse reduction.
- **Adjuvant radiochemotherapy remains a rational standard therapy for curatively resected gastric cancer with primaries T3 or greater and/or positive** nodes

CALGB 80101



Accrual Over

CALGB: Results

	5-FU/LV (n = 280)	ECF (n = 266)	p-value
Median DFS	30.1 mos	28.2 mos	-
5Y-DFS	35%	38%	p = 0.99
Median OS	36.6 mos	37.8 mos	-
5Y-OS	41%	44%	p = 0.80

CALGB: Toxicity

	5FU/LV Grade 3/4	ECF Grade 3/4
Diarrhea	15%	7%
Mucositis	15%	7%
Dehydration	9%	4%
Grade 4 Neutropenia	33%	19%

CALGB: Conclusion

- Following curative resection of gastric or GE junction adenocarcinoma, adjuvant treatment using ECF and chemoradiation does not improve survival when compared to 5-FU/LV and chemoradiation
- ECF and chemoradiation was associated with less severe diarrhea, mucositis and neutropenia than 5-FU/LV and chemoradiation
- ECF and chemoradiation can be considered as an option for the adjuvant treatment of resected gastric cancer based on equivalent efficacy and reduced toxicity compared to the current standard of 5-FU/LV and chemoradiation
- Multidisciplinary assessment of patients with resectable gastric cancer should determine whether best treatment option is perioperative ECF or surgery followed by ECF and chemoradiation

ARTIST

Adjuvant Chemoradiation Therapy in Stomach Cancer

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To investigate the role of postoperative chemoradiotherapy therapy in patients with curatively resected gastric cancer with **D2 lymph node dissection**. This trial was designed to compare postoperative treatment with capecitabine plus cisplatin (XP) versus XP plus radiotherapy with capecitabine (XP/XRT/XP).

XP ARM: Chemotherapy Arm: Six cycles of XP (capecitabine 1,000 mg/m2 BD on days 1 to 14 and cisplatin 60 mg/m2 on day 1, repeated every 3 weeks) chemotherapy

XP/XRT/XP ARM: two cycles of XP (1000 mg/m2 BD Day 1-14): Followed by 45-Gy (1.8 Gy/#) XRT (capecitabine 1,650 mg/m2 per day for 5 weeks) and two cycles of XP (1,000 mg/m2 BD on days 1 to 14 and cisplatin 60 mg/m2 on day 1, repeated every 3 weeks)

ARTIST Trial

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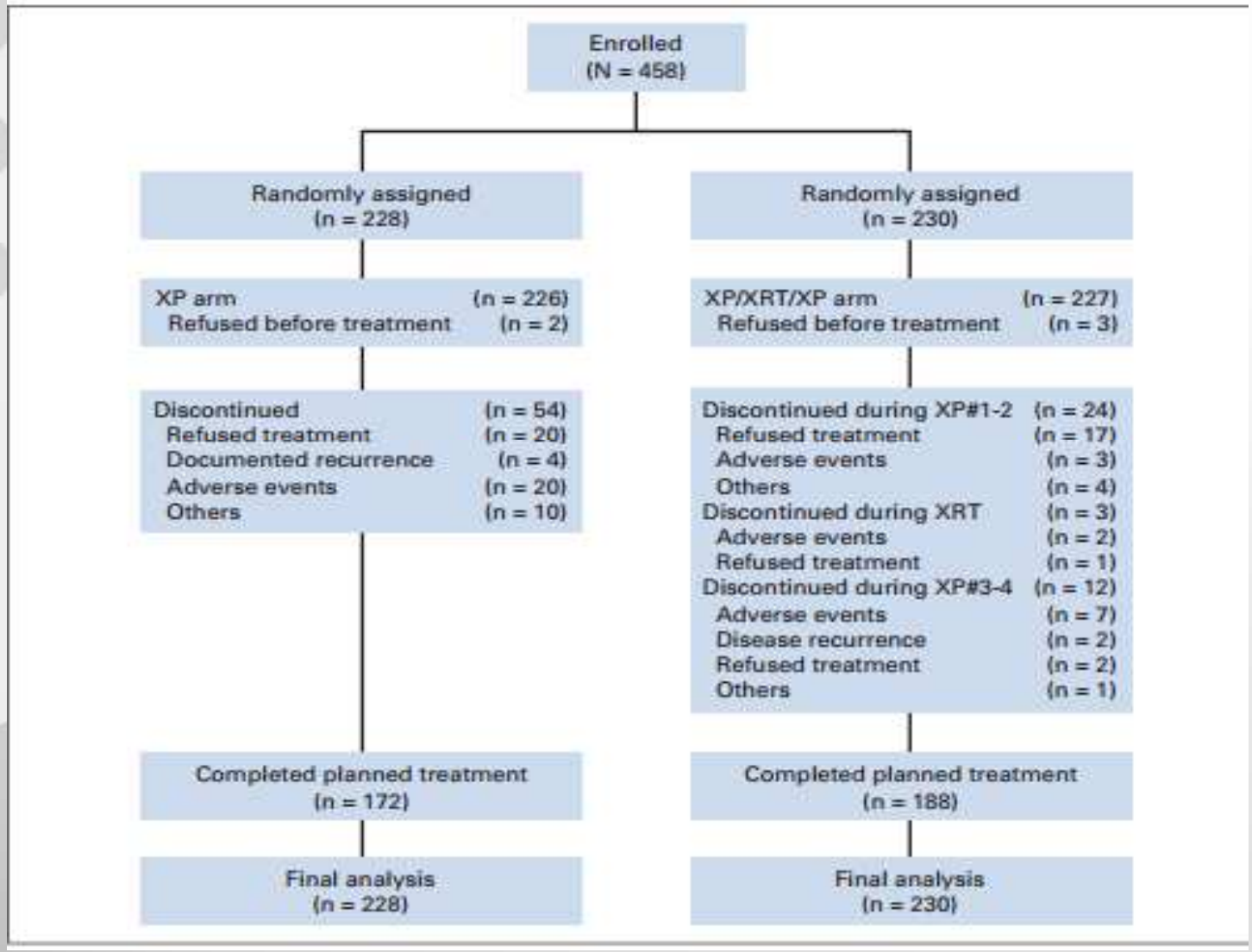
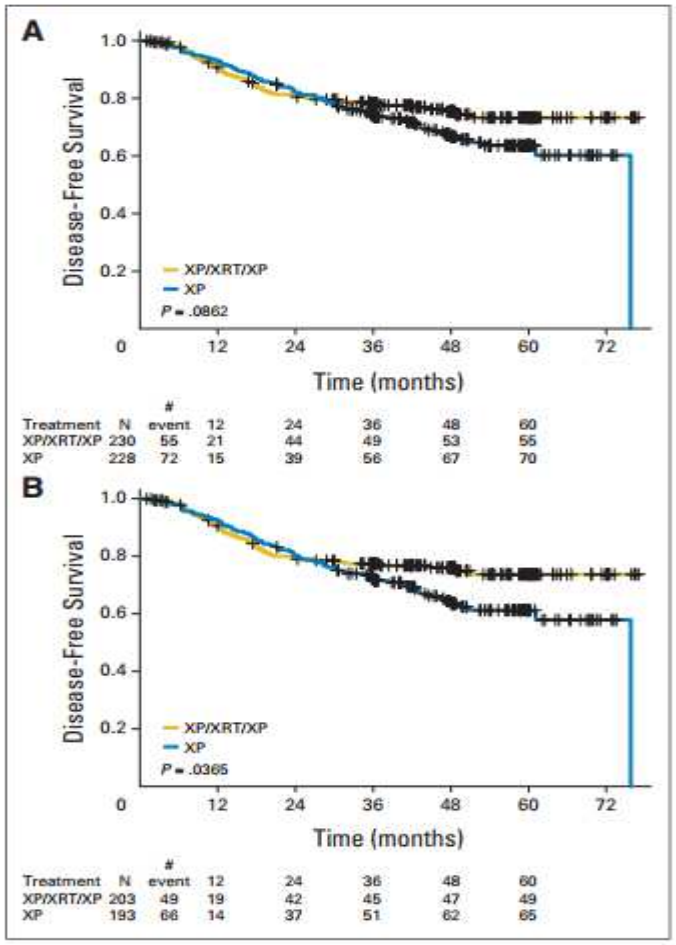
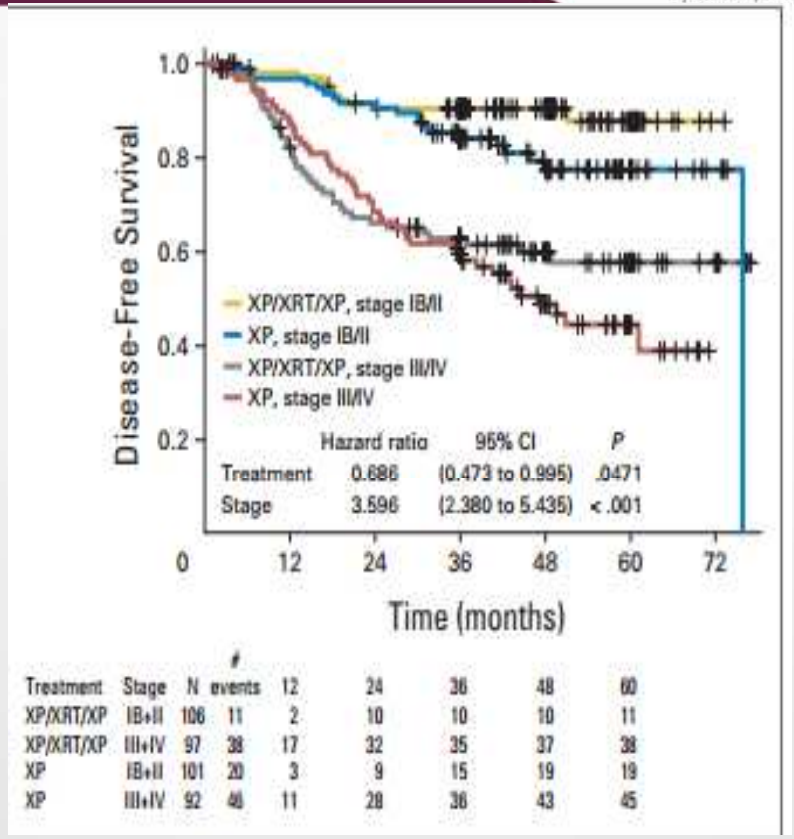


ARTIST : Results



DFS in (A) all patients
(B) lymph node positive patients



DFS survival according to stage

XP: Capecitabine + Cisplatin
XRT: Capecitabine + RT

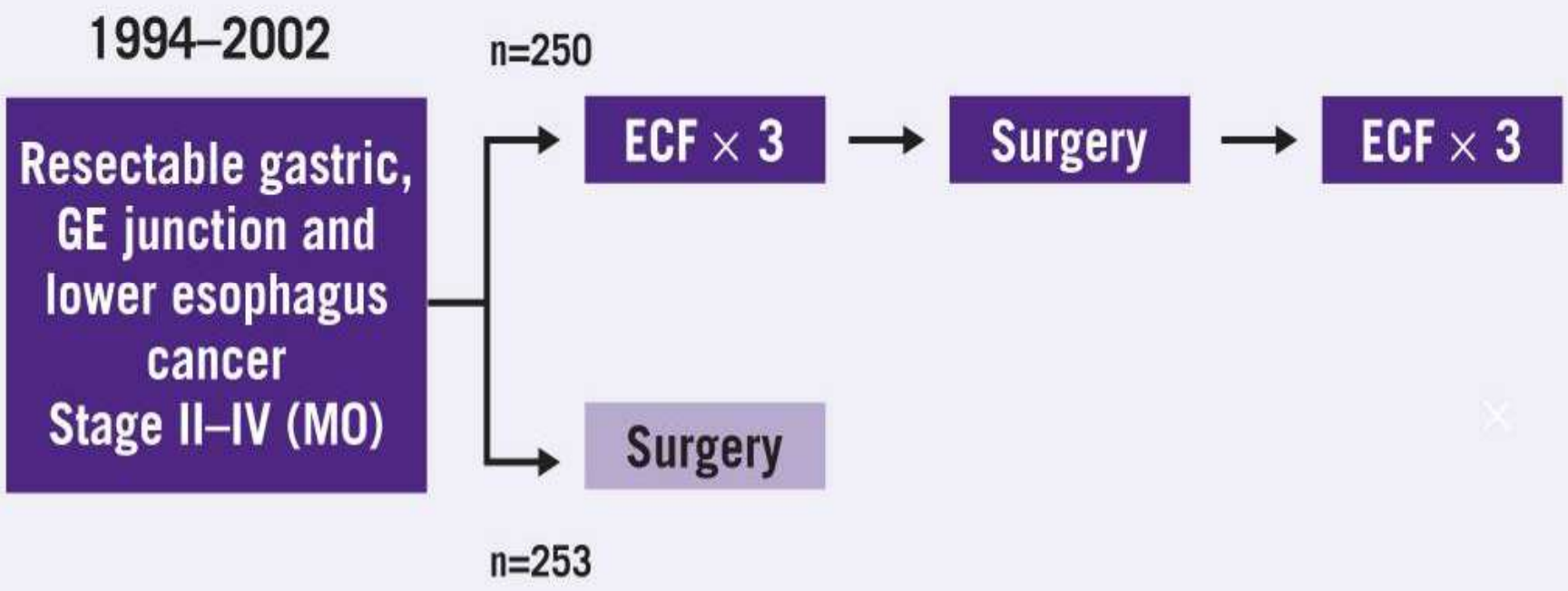
Conclusion

- The addition of XRT to XP chemotherapy did not significantly prolong disease-free survival (DFS; P = .0862).

- In the subgroup of patients with pathologic lymph node metastasis, patients in XP/XRT/XP arm experienced superior DFS when compared with those who received XP alone (P = .0365)
- The addition of XRT to XP chemotherapy did not significantly reduce recurrence after curative resection and D2 lymph node dissection in gastric cancer.
- A subsequent trial (ARTIST-II) in patients with lymph node-positive gastric cancer is planned.

Lee at al:J Clin Oncol. 2012 Jan 20;30(3):268-73.

MAGIC Trial

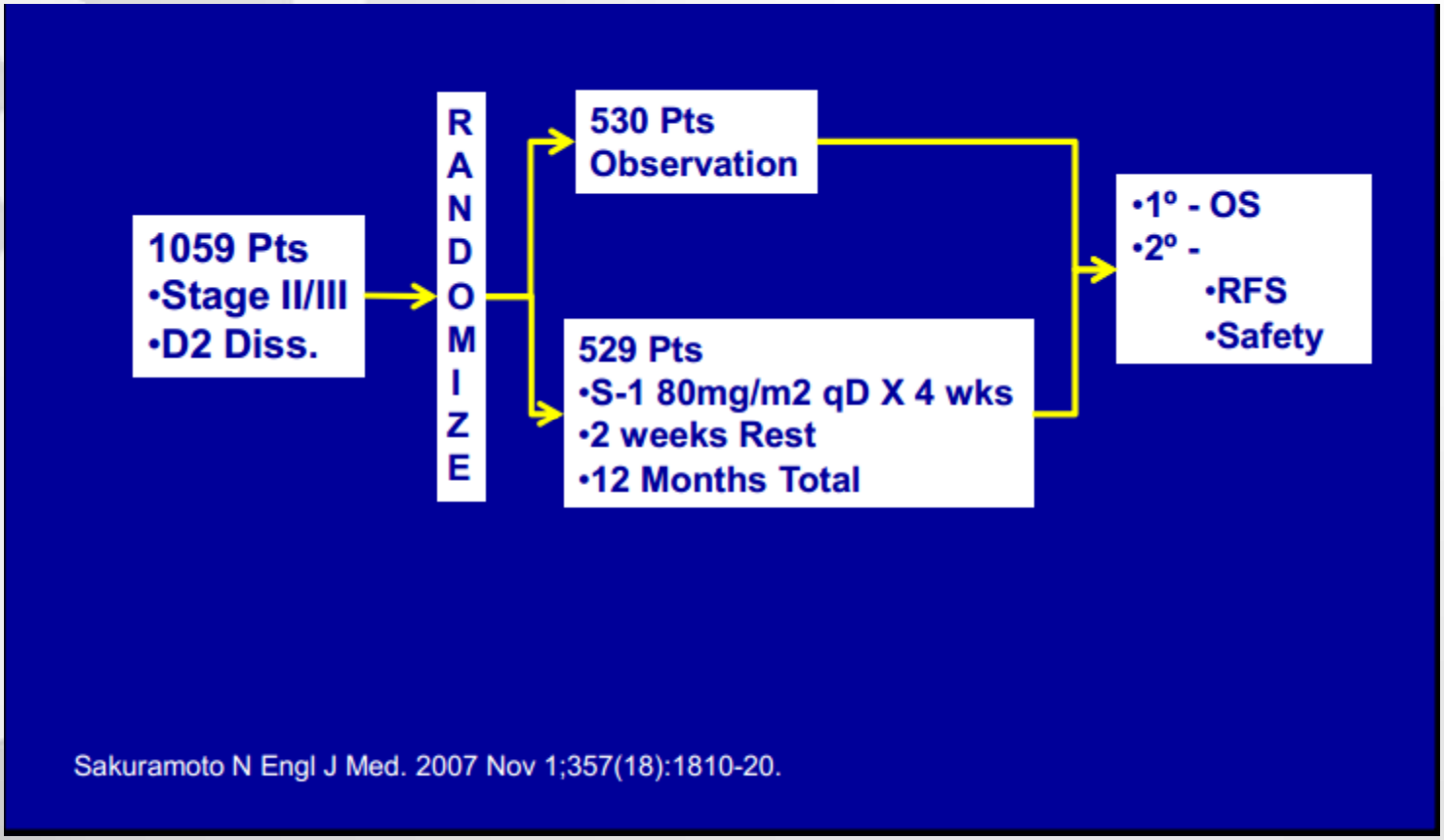

1994–2002
Resectable gastric, GE junction and lower esophagus cancer Stage II–IV (MO)
n=250
ECF × 3
Surgery
ECF × 3
Surgery
n=253

Results

- Five years after the initial publication of INT-0116, the British MAGIC (MRC Adjuvant Gastric Infusional Chemotherapy Trial) trial demonstrated the superiority of epirubicin, cisplatin, and fluorouracil (ECF) administered before and after surgical resection when compared with surgery alone

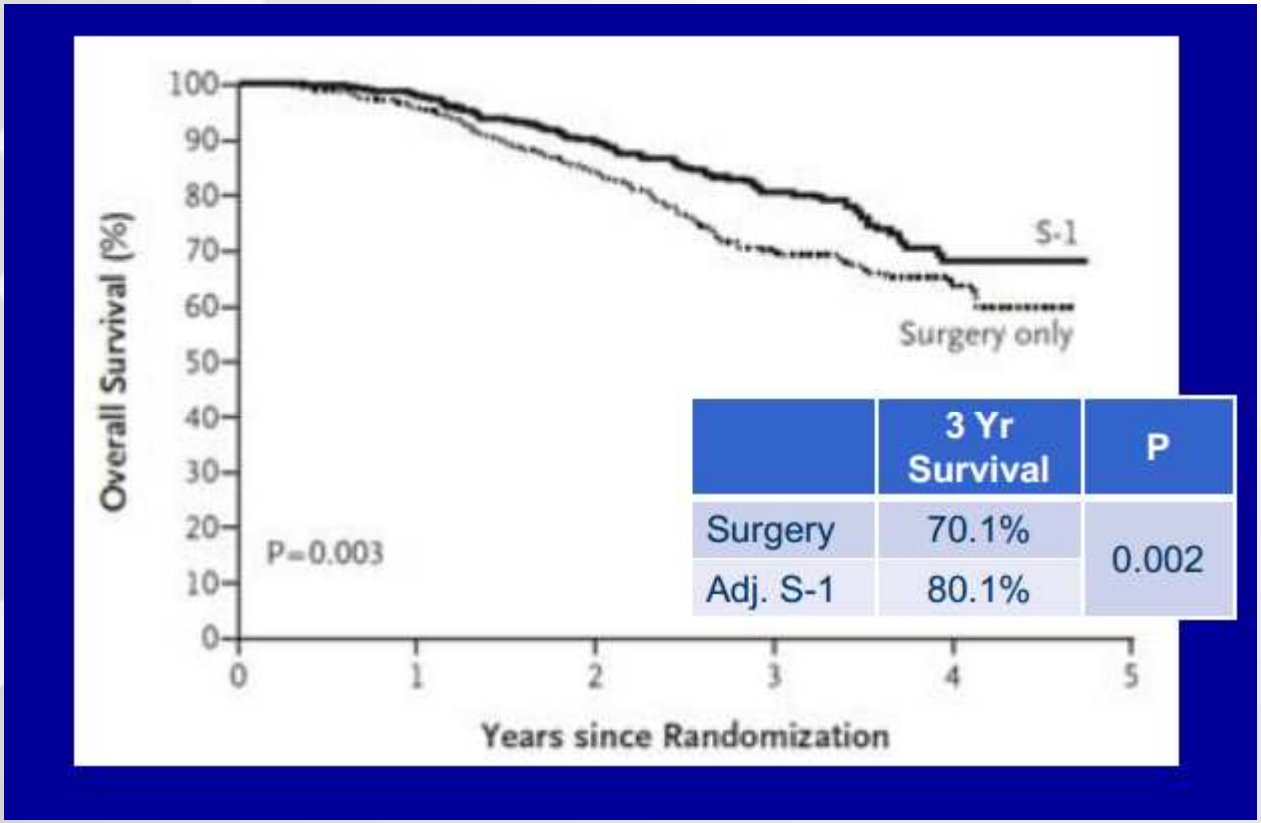
- Despite the omission of radiotherapy, perioperative ECF conferred a statistically and clinically significant reduction in death and cancer recurrence, establishing perioperative chemotherapy, without radiation therapy, as an alternative, reasonable standard in the adjuvant treatment of gastric cancer.

ACTS GC Trial



S-1 is a novel oral fluorouracil anticancer product that combines 3 pharmacological agents: tegafur which is a pro-drug of 5 fluoro-uracil; gimeracil (5-chloro-2,4 dihydropyridine (CDHP)) which inhibits dihydropyrimidine dehydrogenase (DPD) enzyme activity; and oteracil (potassium oxonate (Oxo)) a gastrointestinal side effects corrector.

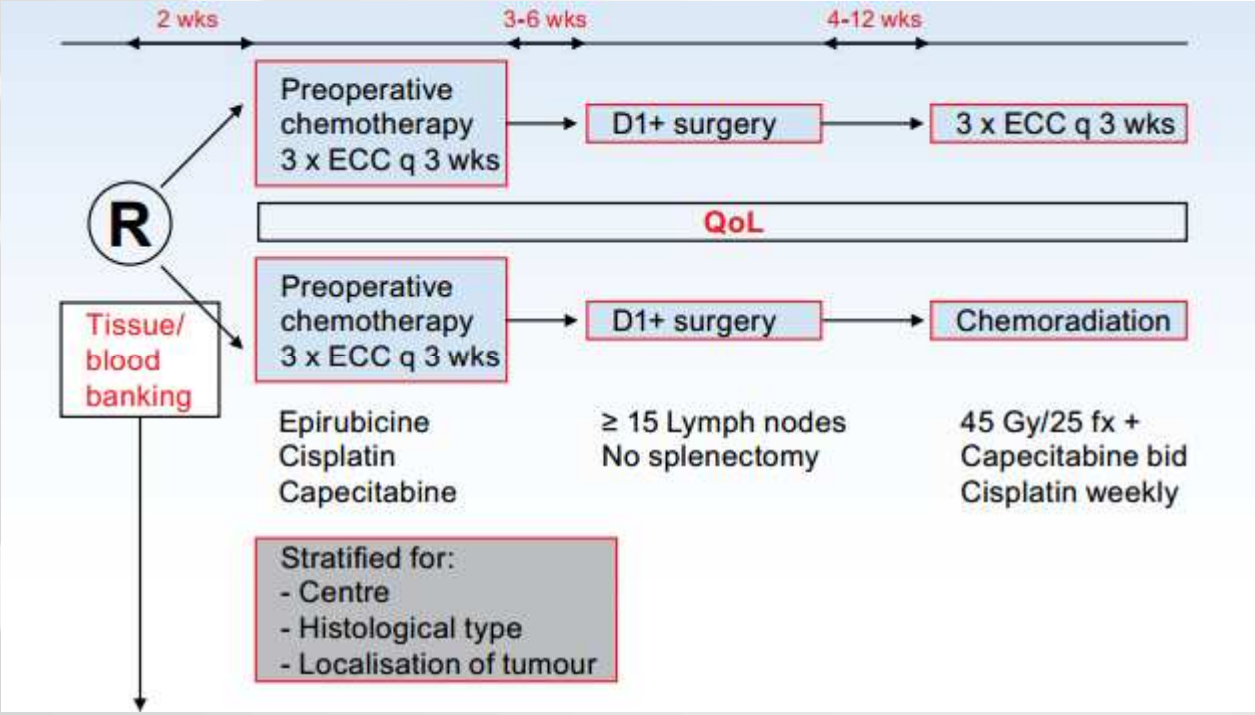
ACTS GC : Results



	3 Yr Survival	P
Surgery	70.1%	0.002
Adj. S-1	80.1%	

CT vs CTRT

CRITICS TRIAL



CLASSIC Trial

Phase 3, randomised controlled trial undertaken in 37 centres in South Korea, China, and Taiwan.
Stage II—IIIB (1035 patients (520 to receive CT and surgery, 515 surgery only)
Curative D2 gastrectomy
Randomly assigned to receive

Adjuvant chemotherapy of eight 3-week cycles of oral capecitabine (1000 mg/m2 twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m2 on day 1 of each cycle) for 6 months

or

Surgery only

This study reports a prespecified interim efficacy analysis, after which the trial was stopped after a recommendation by the data monitoring committee.
Median follow-up was 34·2
3 year disease-free survival was

74% (95% CI 69—79) in the chemotherapy and surgery group and 59% (53—64) in the surgery only group (hazard ratio 0·56, 95% CI 0·44—0·72; p<0·0001).

Grade 3 or 4 adverse events were reported in 279 of 496 patients (56%) in the chemotherapy and surgery group and in 30 of 478 patients (6%) in the surgery only group.

INT 0116 vs MAGIC vs ACTS GC

	MAGIC	ACTS-GC	INT 0116
No. Pts	503	1059	554
T3/T4	64%*	46%	68%
Node Negative	28%*	11%	15%
Node Positive	72%*	89%	85%

*Surgery Only Arm

5 Year Survival Rates

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Study	Surgery (%)	CTRT/CT (%)
INT 0116	28	43
MAGIC	23	36
ACTS-GC	61	72

ACTS-GC results are strikingly better both for treatment and for the surgery-only controls than the MAGIC perioperative chemotherapy results and INT0116

Radiation Therapy Planning

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- Preoperative CT scans/GI series/operative findings/clips placement define the tumor bed and nodal areas
- Target Volume:Tumor bed, primary lymph nodes, and a margin of 1.5-2.0 cm
- Tumor bed includes the maximum preoperative stomach volume. In T3-T4 tumors, it
- Should include areas of local tumor extension and medial two thirds to three fourths of Left hemi diaphragm
- Half to two thirds of left kidney should be blocked. Porta hepatis and retroduodenal
- Nodes can be treated while including a small portion of right kidney
- Nodes at risk: celiac, porta hepatis, subpyloric,gastroduodenal,splenic-suprapancreatic, retropancraticodudenal

Radiation Therapy Planning

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AP-PA Field	
Superior Border	**Bottom of T8-T9**
Inferior Border	**Bottom of L3**
Left Border	**2/3rd to 3/4th of left hemidiaphragm**
Right Border	**3-4 cm lateral to vertebral bodies**
Lat Field (if used)	
Superior Border/ Inferior Border	**Same as AP-PA**
Anterior Border	**Anterior abdominal wall**
Posterior Border	**Include ½ to 2/3rd of the verteb bodies**
Dose	45 Gy (1.8 Gy/Fraction)
Dose to crtical organs	
Liver	**No > 60% of liver to receive >30 Gy**
Heart	**No >30% should receive >40 Gy**
Kidneys	**Spare as much as possible**
Spinal Cord	**Limited to 45 Gy**

Techniques to decrease RT Toxicity

- High Energy (>10 MV)
- Treatment 5 days a week and all fields every day
- Port films at least once a week
- Minimize hot spots and increase homogeneity in target volume
- 3 D planning to generate DVH's for liver, kidneys, and small intestine
- Ideal field arrangement (AP-PA vs multiple fields) is the one that a) delivers the most homogeneous dose distribution with in the target volume while b) limiting the dose to critical organs
- AP-PA fields are preferred as addition of lateral field increases the dose to kidneys.
- Some cases where the fundus of stomach is sufficiently anterior a lateral field can be used

CTRT vs CT

- Among the principal concerns regarding INT-0116 has been the quality of surgical resections performed on the study population as majority of patients received less than a D1 lymph node dissection at surgery (<10% had D2 resection)
- No clear survival benefit from D2 lymphadenectomy
- High rate of <D1 resections in INT-0116 gave way to speculation that postoperative chemoradiotherapy simply compensated for inadequate surgery.
- Updated report of INT-0016 finds no evidence that the survival benefit associated with chemoradiotherapy differs according the extent of lymph node dissection, allaying some concerns that chemoradiotherapy only benefits those patients who undergo substandard resection
- The durable benefit associated with postoperative chemoradiotherapy in INT-0116 and the apparent trends reported in the ARTIST trial uphold postoperative chemoradiotherapy as a standard adjuvant approach

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Take Home Message

- Two ongoing trials should refine our understanding
- The ARTIST-II trial will include patients with lymph node–positive gastric cancer
- The ongoing phase III CRITICS trial will evaluate the benefits of adding postoperative chemoradiotherapy to perioperative combination epirubicin, cisplatin, and capecitabine (ECX)
- **Until those trials are mature, adjuvant chemoradiotherapy remains one of the available strategies**