Role of Chemotherapy in Gastric Adenocarcinoma

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- **Adjuvant treatment-NEED?**
- **What are the options?**
- **Chemoradiation benefit?**
- **Chemotherapy alone?**

The Need

- The five-year survival rate for patients with completely resected stage I gastric cancer is approximately 70 to 75 percent
- 35% or less for Stage II and beyond

Options

- Chemoradiation
- Chemotherapy alone
  - Neoadjuvant/Perioperative
  - Adjuvant

No consensus for best approach

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Adjuvant Chemoradiation

Over 80% patients develop local recurrence

INT0116

- Largest trial
- After complete curative resection
- Observation/ChemoRT

- 556 patients
- T1-T4, N0-1
- 68% were T3/T4
- 85% nodal disease

INT0116 Regimen

One cycle Chemo FU(425mg/m^2) and CaLV (20mg/m^2) D1-D5

One month later RT 45Gy/25#. Concurrent FU(400mg/m^2) and CaLV (20mg/m^2) on D1-D4 and last three days of RT

One month later 2 cycles of FU(425mg/m^2) and CaLV (20mg/m^2) at monthly interval

- Three-year disease free survival- 48 vs 31%
- Overall survival rates -50 vs 41 %
- median survival - 36 vs 27 months

All favoring ChemoRT

Site of relapse

Site	Surgery only (n=177)	Adjuvant ChemoRT(n=120)
Local	51 (29%)	23 (19%)
Regional	127 (72%)	78 (65%)
Distant	32 (18%)	40 (33%)

Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345:725.

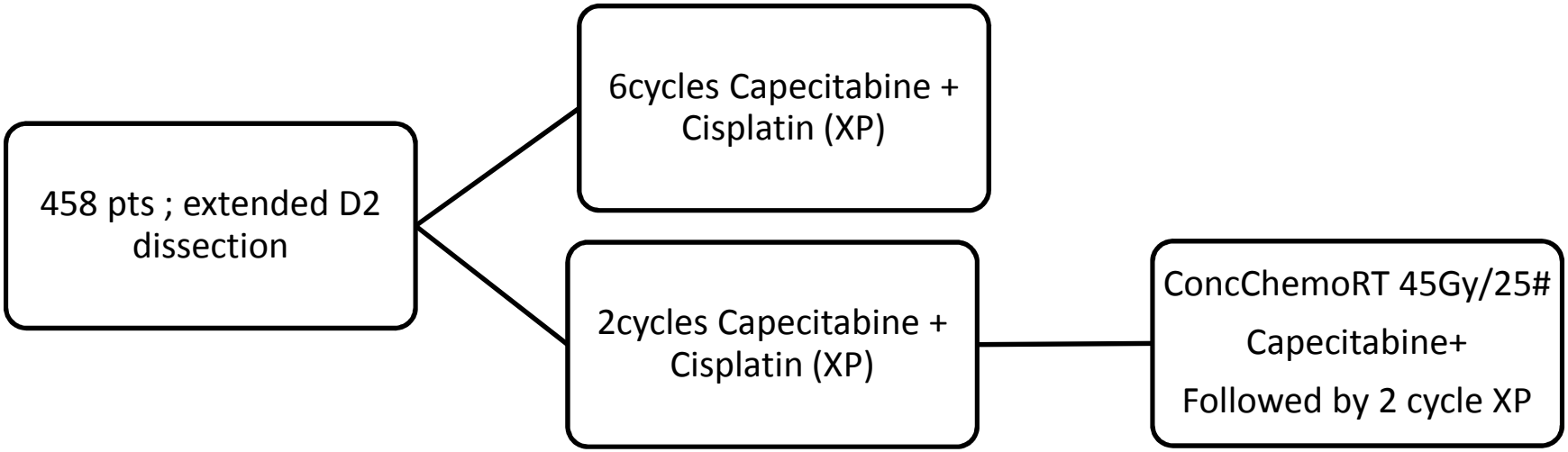
Toxicity

- Chemoradiation toxicity- Grade 3 in 41% and Grade 4 in 32%.
- Hematologic toxicity 54%
- GI toxicity- 33%

CALGB 80101

- Compared the INT0116 protocol regimen versus postoperative ECF before and after FU plus concurrent RT
- 546 patients with completely resected gastric or EGJ tumors
- Beyond T2 and Node positive
- ECF arm had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia.
- Overall survival-not significantly better with ECF
- Not adequately powered

ARTIST trial



- Capecitabine 2000 mg/m2 per day on days 1 to 14
- cisplatin 60 mg/m2 on day 1
- repeated every 3 week

- XP/XRT/XP arm received two cycles of XP capecitabine 1650 mg/m2/d for 5 weeks
- Followed by 2 cycles XP

- Addition of radiotherapy to XP chemotherapy did not significantly prolong DFS (HR 1.352, 95% CI 0.952 - 1.922; P=0.0922)

- Unplanned subgroup analysis showed benefit in N+ disease

Lee J, Lim DH, Kim S, et al. Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial (abstract). J Clin Oncol 32: 5s, 2014 (suppl; abstr 4008)

Patient selection-Adj ChemoRT

- Any T stage with N+ disease
- T3 N0 and above

- **Adjuvant treatment-NEED?**
- **What are the options?**
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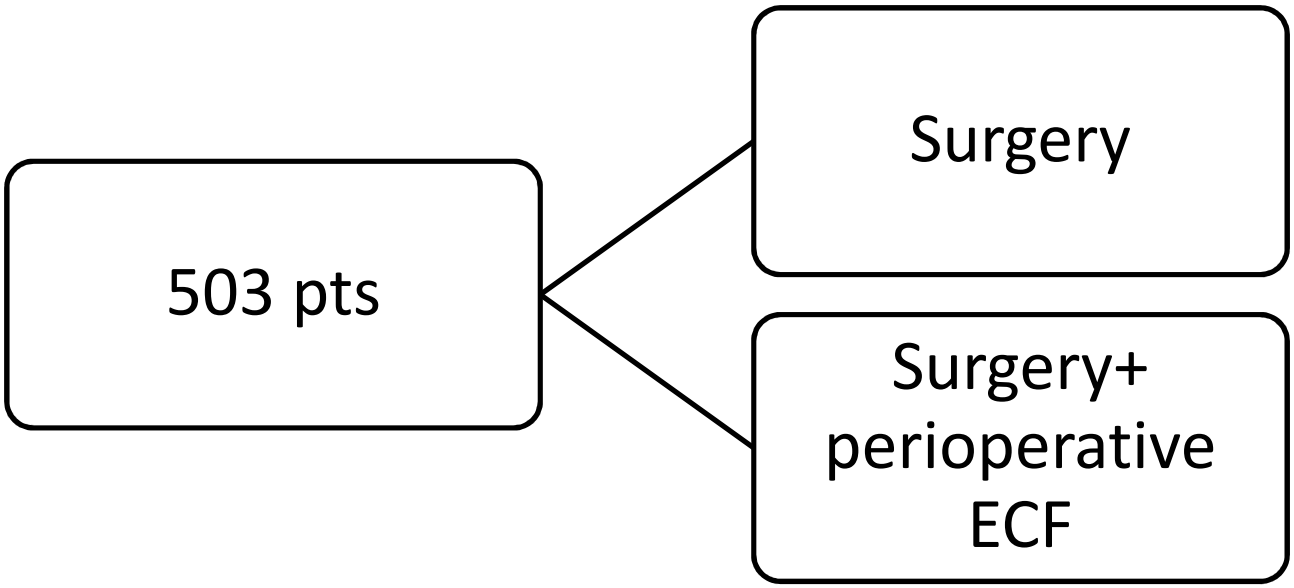
Neo adjuvant/Perioperative Chemotherapy

- Advantage of neoadjuvant
  - Down staging
  - High risk patients developing distant mets not responding to chemo are spared of morbid procedure

MAGIC trial

- 503 patients with potentially resectable
  - gastric (74 %),
  - distal esophageal (11 %),
  - EGJ adenocarcinomas (15%)

MAGIC trial



MAGIC- ECF regimen

Epirubicin	50 mg/m^2 IV	Day 1
Cisplatin	60 mg/m^2 IV	Day 1
Fluorouracil (FU)	200 mg/m^2 per day IV	Continuous infusion upto 6 months

Results

	Surgery+ECF arm	Surgery alone arm
Curative resection	79%	70%
Pathological T1/T2	52%	37%
N0/N1	84%	71%
Local failure	14%	21%
Distant metastases	24%	37%
5yr OS	36%	23%

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355:11.

- Only 42 percent were able to complete protocol treatment, including surgery and all three cycles of the postoperative chemotherapy

French FNLCC/FFCD

- 224 patients with potentially resectable stage II or greater
  - adenocarcinoma of the stomach (n = 55),
  - EGJ (n = 144) or
  - distal esophagus (n = 25)

Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29:1715.

Randomly assigned to

- two to three cycles of preoperative chemotherapy
- surgery alone

Patients in the chemotherapy arm were to receive three to four cycles of postoperative chemotherapy as well.

Infusional FU 800 mg/m^2 daily for five days plus cisplatin 100 mg/m^2 on day 1 or 2, every four weeks

Results

- Neoadjuvant chemotherapy were significantly more likely to undergo R0 resection (84 versus 73 percent)
- 35 percent reduction in the risk of disease recurrence at 5.7 yr median follow up
- five-year survival 38 versus 24 percent

META ANALYSIS

- Twelve RCTs with a total of 1,820 patients were included
- neoadjuvant chemotherapy
  - overall survival (OR 1.32, 95% CI 1.07-1.64)
  - progression-free survival (OR 1.85, 95% CI 1.39-2.46)
  - Higher R0 resection rate (OR 1.38, 95% CI 1.08-1.78)
  - no significantly worsen rates of complications

Xiong BH, Cheng Y, Ma L, Zhang CQ. An updated meta-analysis of randomized controlled trial assessing the effect of neoadjuvant chemotherapy in advanced gastric cancer. Cancer Invest 2014; 32:272.

Patient Selection for NACT

- Patients of any age with a performance status of 0 or 1
- Histologically proven adenocarcinoma of the stomach
- stage T2 or higher
- locally advanced inoperable disease

Adjuvant Chemotherapy

- Many trials have evaluated adjuvant chemotherapy
- Different regimen
- Mostly negative results when overall survival was end point

JAPANESE S-1 trial

- Japanese ACTS-GC trial
- 1059 patients with stage II or III gastric cancer -curative surgery with D2 lymphadenectomy
- randomly assigned to
  - Post op six months of S1 (80 to 120 mg daily for four weeks, repeated every six weeks for one year)
  - surgery alone

Result

- Five-year overall survival better with S-1 (72 versus 61 percent)

Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387–4393

CLASSIC Trial

- Capecitabine in combination with oxaliplatin
- 1035 patients with stage II, IIIA, or IIIB gastric
  - Randomly assigned to eight 21-day cycles of capecitabine (1000 mg/m^2 twice daily in days 1 to 14) plus oxaliplatin (130 mg/m^2 on day 1)
  - surgery alone after D2 gastrectomy

Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, et al. (2012) Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 379: 315–321

- Only 67 percent of the patients assigned to chemotherapy received all eight cycles
- Adverse events led to chemotherapy dose modifications in 90 percent of patients.
- Median follow-up of 34 months,
  - improvement in three-year disease-free survival (74 versus 59 percent, HR for death 0.56, 95% CI 0.44-0.72)
  - five-year overall survival 78 versus 69 percent, HR for death 0.66 percent, 95% CI 0.51-0.85

Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: Final results of the CLASSIC trial (abstract)

Cochrane Meta analysis

Outcomes	Relative effect (95% CI)	No of Participants (studies)
Overall Survival (OS)	HR 0.85 (0.80 to 0.90)	7523 (34 studies)
Disease Free Survival	HR 0.79 (0.72 to 0.87)	4133 (15 studies)

Diaz-Nieto R, Orti-Rodríguez R, Winslet M. Post-surgical chemotherapy versus surgery alone for resectable gastric cancer. Cochrane Database Syst Rev. 2013;9:CD008415.

Cochrane Meta analysis

	Relative Effect	No of participants
Chemobased OS - 5-FU based chemotherapy OS	HR 0.88 (0.83 to 0.94)	5694 (28 studies)
Chemobased OS - Platinum-based chemotherapy OS	HR 0.9 (0.81 to 1)	1504 (9 studies)
Chemobased OS - Platinum-based chemotherapy OS	HR 0.9 (0.81 to 1)	1504 (9 studies)
Chemobased DFS - Platinum-based chemotherapy DFS	HR 0.89 (0.75 to 1.06)	969 (4 studies)

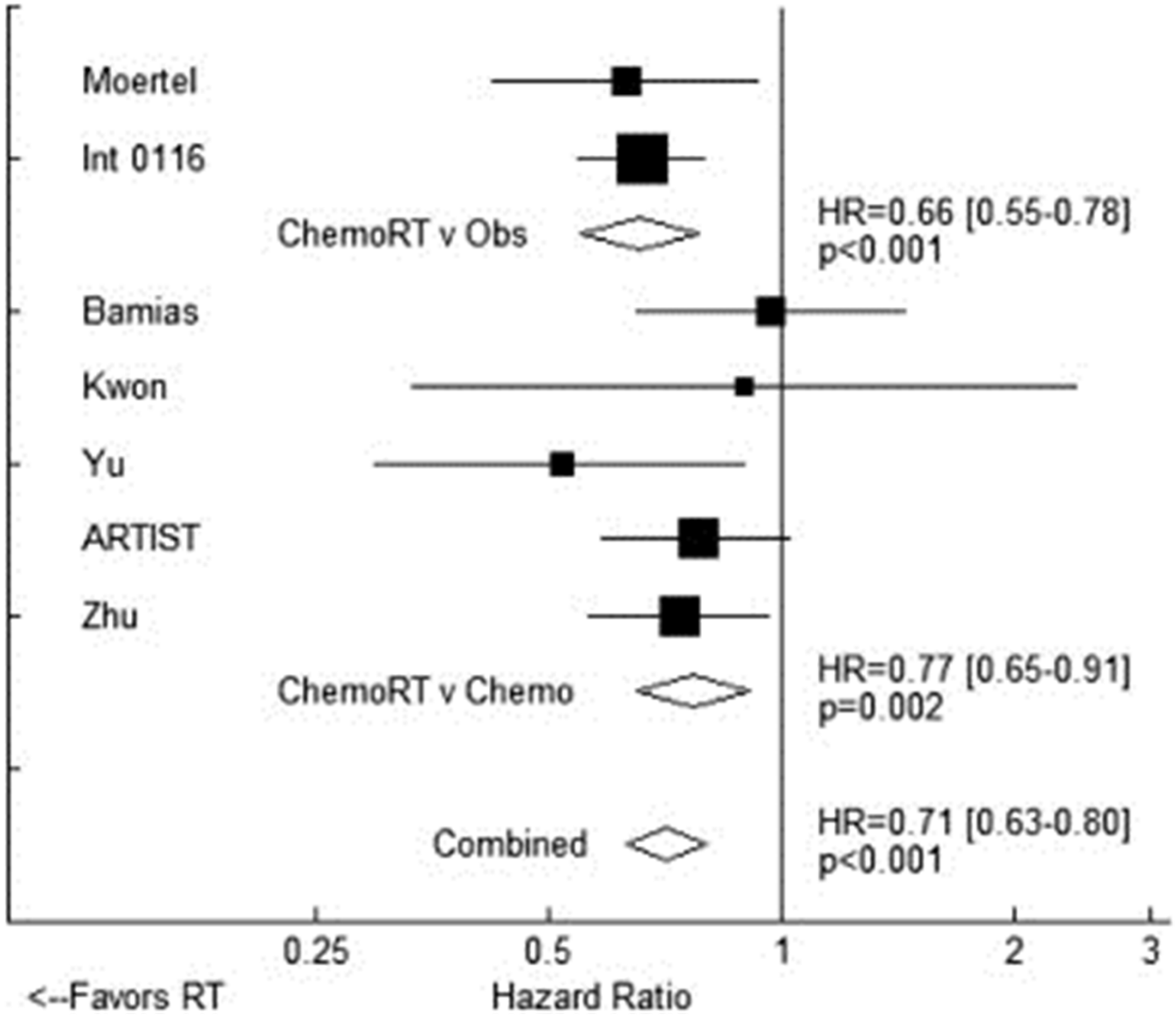
Optimal Chemo regimen not established

Comparison between Chemotherapy vs. Chemoradiation

Chemotherapy vs. ChemoRT – Meta analysis

Author/Study	Number	Nodal dissection	End points reported
Bamias et al	143	56% D0 44% D1-2	OS, DFS
Kwon et al	61	D2	OS, DFS
Yu et al	68	31% D1 69% D2	OS, DFS
ARTIST	458	D2	DFS
Zhu et al	351	D2	OS, DFS

N. Ohri, M.K. Garg, S. Aparo, A. Kaubisch, W. Tome, T.J. Kennedy, S. Kalnicki, C. Guha
Who benefits from adjuvant radiation therapy for gastric cancer? A meta-analysis.
Int J Radiat Oncol Biol Phys, 86 (2013), pp. 330–335


Moertel
Int 0116
ChemoRT v Obs
HR=0.66 [0.55-0.78]
p<0.001
Bamias
Kwon
Yu
ARTIST
Zhu
ChemoRT v Chemo
HR=0.77 [0.65-0.91]
p=0.002
Combined
HR=0.71 [0.63-0.80]
p<0.001
0.25
0.5
1
2
3
<--Favors RT
Hazard Ratio

Patient selection-Adj. Chemotherapy

- Any T stage with N+ disease
- T3 N0 and above

Conclusion

- Optimal way to integrate combined modality is yet to be defined.
- Institutional /Patient preference
- Upfront curative resection- INT0116 as treatment protocol
- Prior to surgery- MAGIC trial protocol

THANK YOU