GASTRIC CANCER:
Should all patients be treated with adjuvant and/or neoadjuvant treatment?

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Introduction

- Operable gastric cancer has a poor prognosis
  - Most studies show that 65 -75% of patients who relapse after localised treatment have systemic disease
  - The majority of patients who relapse die of disease within 2 years

- Neoadjuvant and/or adjuvant treatment can improve outcomes….

  …. how can we select the most appropriate treatment option for an individual patient?

Pre-operative staging

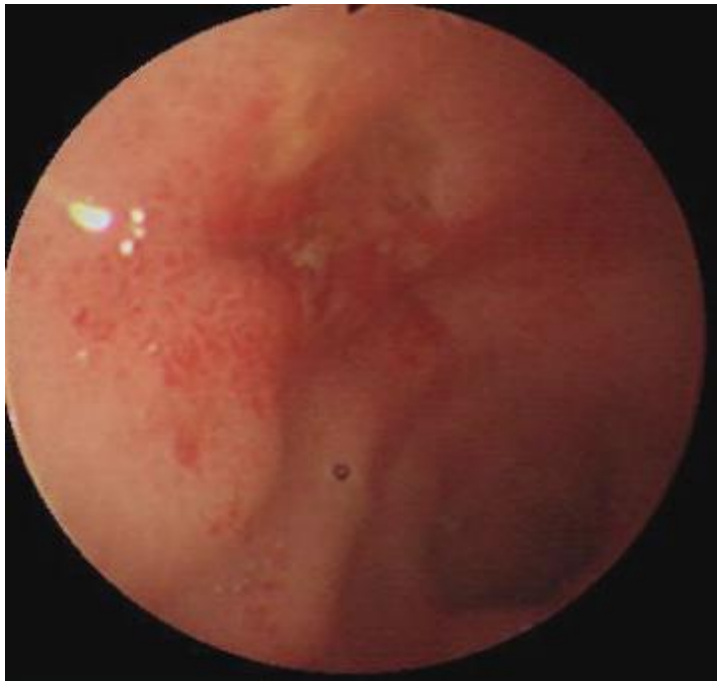
- Accurate staging of gastric cancer is essential but can be challenging

Procedure	Advantages	Disadvantages
CT (thorax, abdomen +/- pelvis)	▪ Detection of local/distant lymphadenopathy & distant metastases	▪ Primary tumour can be difficult to assess
Endoscopic ultrasound (EUS)	▪ Accurate assessment of T & N stages ▪ Determination of proximal & distal tumour extent	▪ Less useful in antral tumours
PET	▪ Improved detection of involved lymph nodes & metastases	▪ May be uninformative in mucinous tumours
Laparoscopy	▪ To exclude metastatic disease involving the diaphragm/peritoneum	▪ Invasive

Accurate staging requires a combination of these investigations

Waddell et al, 2013, Annals Oncol, 24 (supp 6) vi 57-63

Early stage disease



Depressed gastric lesion confirmed on biopsy as an early gastric cancer

- T1 N0 tumours (stage IA) have an excellent prognosis

  → these patients do not require adjuvant and/or neoadjuvant treatment

- However, only 1 in 100 western patients present with stage I disease

  → therefore very few patients are suitable for surgery alone

Image from: www.gastrohep.com, statistics: www.cancerresearchuk.org

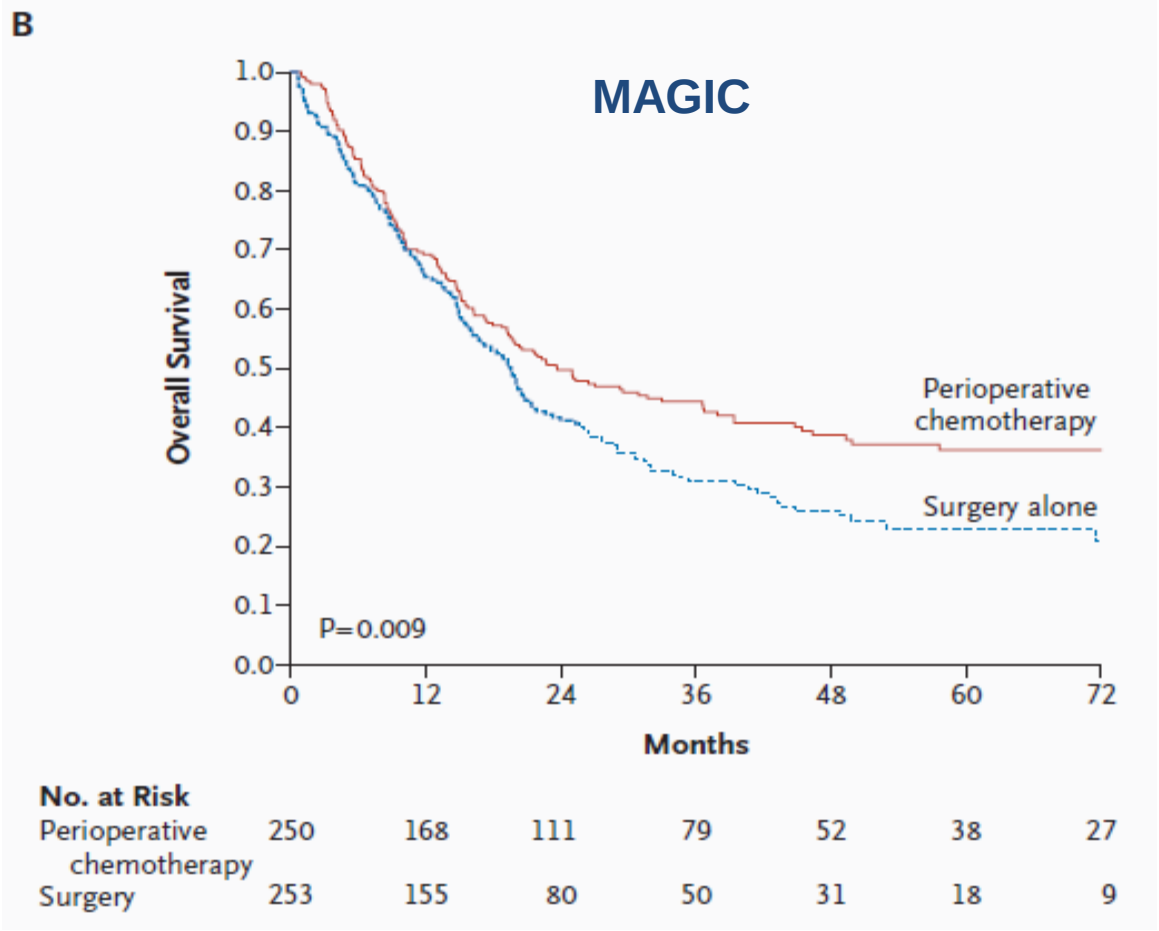
What is the optimal treatment approach?

Peri-operative chemotherapy?

Adjuvant chemotherapy?

Adjuvant chemoradiotherapy?

Peri-operative chemotherapy



- MAGIC & FFCD trials established peri-operative chemotherapy as an international standard in OG cancer
- Improves OS / PFS & decreases risk of death by 25%

Cunningham et al, 2006, NEJM, 355(1): 11-20. Ychou et al, 2011, JCO, 29(13): 1715-1721

What are the benefits of peri-operative chemotherapy?

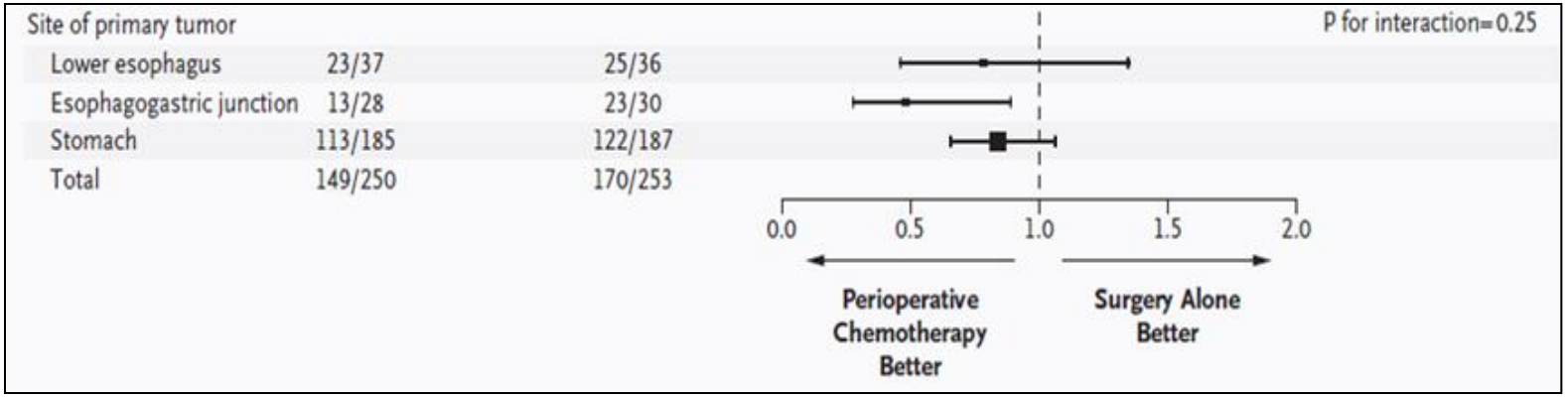
1. Systemic chemotherapy decreases risk of distant metastases

Study	N	% distant metastases	Median OS (months)	HR	5yr Survival Rate
MAGIC	253 (S) 250 (CS)	37% 24% ↓	20 24	0.75 P=0.009	23% 36% ↑
FFCD	111 (S) 113 (CS)	38% 30% ↓	22 32	0.69 P=0.02	24% 38% ↑

Cunningham et al, 2006, NEJM, 355(1): 11-20. Ychou et al, 2011, JCO, 29(13): 1715-1721

What are the benefits of peri-operative chemotherapy?

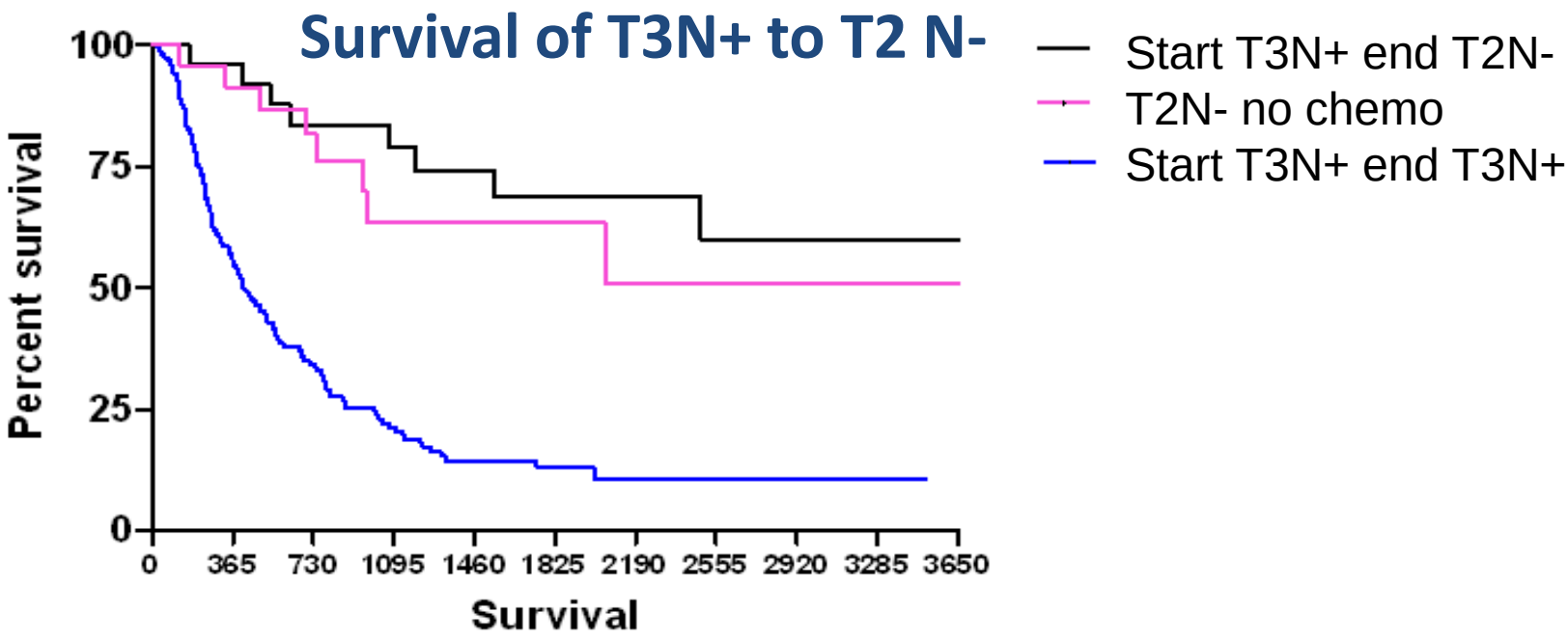
2. Pre-operative chemotherapy leads to tumour downstaging and increases R0 resection rate:
   - MAGIC: 79.3% vs 70.3% (p = 0.03)
   - FFCD: 84% vs 73% (p = 0.04)
- Greatest benefit seen in GOJ tumours (HR ~ 0.5)



Cunningham et al, 2006, NEJM, 355(1): 11-20. Ychou et al, 2011, JCO, 29(13): 1715-1721

Does tumour downstaging improve outcomes?

- In oesophageal/junctional adenocarcinoma:
  - Survival is determined by tumour stage after neoadjuvant chemotherapy



Davies et al, JCO in press

Can peri-operative treatment be improved?

- Trastuzumab has improved survival in HER2 positive metastatic gastric cancer….

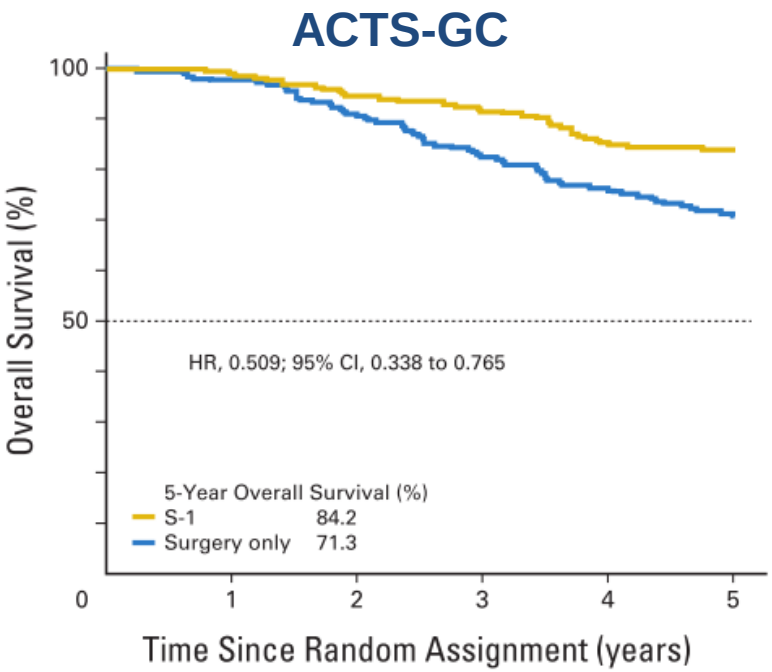
  …. is there also a benefit in the neoadjuvant/perioperative setting?

- The phase II HER-FLOT study:
  - Peri-operative 5-FU, oxaliplatin, docetaxel + trastuzumab
  - Interim results of 45 patients:
    - 93.3% R0 resection rate
    - Pathological response:
      - 22.2% pCR rate
      - 24.4% near complete response

Hofheinz et al, 2014, ASCO abstract 4073

Adjuvant chemotherapy

- In Asian patients:
  - Adjuvant S1 or XELOX improves survival in Asian patients following D2 resection
  - S-1 was better tolerated



- In western patients:
  - S1 is poorly tolerated due to CYP2A6 polymorphisms
  - Pre-operative chemotherapy is better tolerated:
    - In the MAGIC trial – 91% completed pre-op chemo but only 50% completed post-op chemo

Bang et al, 2012, Lancet, 379 (9813): 315-321,
Sasako et al, 2011, JCO, 29 (33): 4387-93, Cunningham et al, 2006, NEJM, 355(1): 11-20.

Adjuvant chemoradiotherapy

- INT-0116 trial: adjuvant chemoradiotherapy improved relapse-free survival and OS

  But… 90% of patients had D0 or D1 resections…

  ….did chemoradiotherapy merely compensate for insufficient lymph node resection?

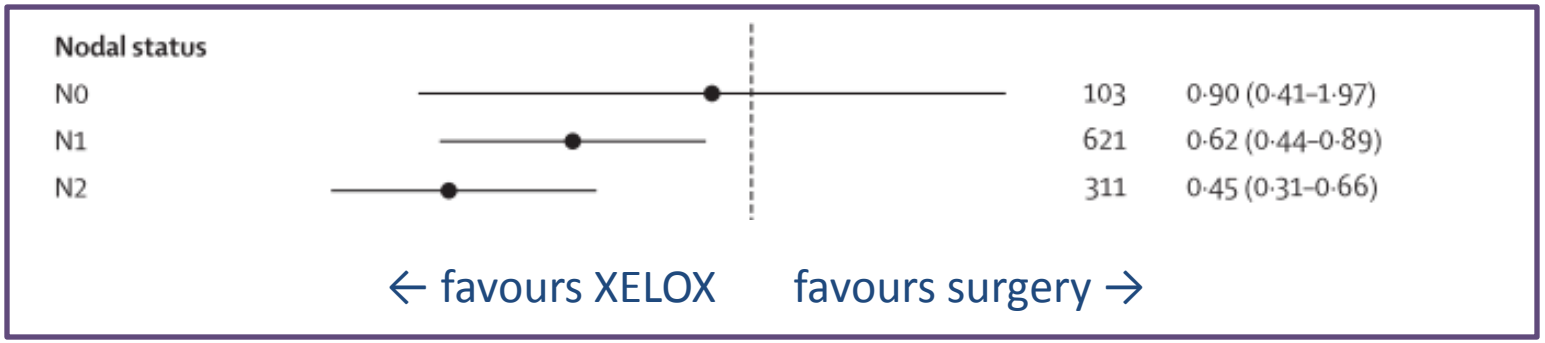
- ARTIST trial (n = 458):
  - 6 cycles of adjuvant XP versus 2 cycles of XP followed by chemoradiotherapy and a further 2 cycles of XP
  - All patients had a D2 resection

  …. no improvement in disease-free survival with the addition of chemoradiotherapy

Lee et al. 2012, JCO, 3: 268-273
MacDonald et al. NEJM, 2001, 345(10): 725-730

Are there subgroups of patients who gain particular benefit?

- Adjuvant XELOX improved DFS in N1/2 but not N0 disease



- But…. no interaction was found between adjuvant S-1 and any characteristic

- Adjuvant chemoradiotherapy:
  - Marginally improves 3-year DFS in node-positive patients (77.5% vs 72.3%, p = 0.0365)

Bang et al, 2012, Lancet, 379 (9813): 315-321,
Sasako et al, 2011, JCO, 29 (33): 4387-93, Lee et al. 2012, JCO, 3: 268-273

Factors to consider when selecting a treatment approach

- Geographical variations in biology and prognosis
  - 5 year overall survival after surgery alone:
    - 23 – 24% in Western patients
    - 61 – 69% in Asian patients

- Tumour site and size:
  - ↑ risk of positive margins in:
    - Proximal gastric tumours
    - Locally advanced, bulky tumours
  - Faster recovery time for distal subtotal gastrectomy

Sasako et al, 2011, JCO, 29 (33): 4387-93, Bang et al, 2012, Lancet, 379 (9813): 315-21
Ychou et al, 2011, JCO, 29(13): 1715-1721, Cunningham et al, 2006, NEJM, 355(1): 11-20

Suggested approach for operable gastric cancer

Setting	Treatment	Rationale
Early-stage disease	Surgery alone	Low risk of metastatic disease
Western patients	Peri-operative chemotherapy	↑R0 resection rate & improved OS Treatment of micrometastatic disease
	Post-operative chemoradiotherapy	*Limited indications:* - Patients understaged prior to resection - No neoadjuvant chemo received - Local control at risk (R1 resection, < D2 resection)
East Asian patients	Adjuvant chemotherapy	Improved OS for optimally resected patients

Selected ongoing clinical trials

Trial	Planned accrual	Treatment	Research question
ST03 (phase II/III)	1140	Peri-operative chemo +/- bevacizumab	Does bevacizumab improve the efficacy of peri-operative chemo?
CRITICS (phase III)	788	Peri-operative chemo vs neoadjuvant chemo + post-op CRT	Does the addition of post-op CRT improve outcomes for patients treated with neoadjuvant chemo?
ITACA-S2 (phase III)	1180	Peri-op chemo (+/- post-op CRT) vs post-op chemo (+/- post-op CRT)	To evaluate the benefit of the addition of post-op CRT and to compare peri-op with post-op chemo
TOXAG (phase II)	40	Adjuvant CRT with capecitabine, oxaliplatin + trastuzumab	Is the addition of trastuzumab to adjuvant CRT safe?
POTENT (phase III)	724	Adjuvant S-1 vs S-1 + oxaliplatin	Does the addition of oxaliplatin improve the efficacy of adjuvant chemo?

Conclusions

- The benefit of peri-operative chemotherapy for GOJ/gastric cancer has been clearly established by RCTs
- Adjuvant chemotherapy has been shown to benefit Asian patients
- Chemotherapy and chemoradiotherapy have significant toxicities – further research is needed to identify the patients most likely to benefit and the optimal treatment schedule