Peri-operative Treatment for Gastric Cancer

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Disclosures

- I have no financial disclosures or conflicts of interest
- If I did I would be able to afford a house in Vancouver

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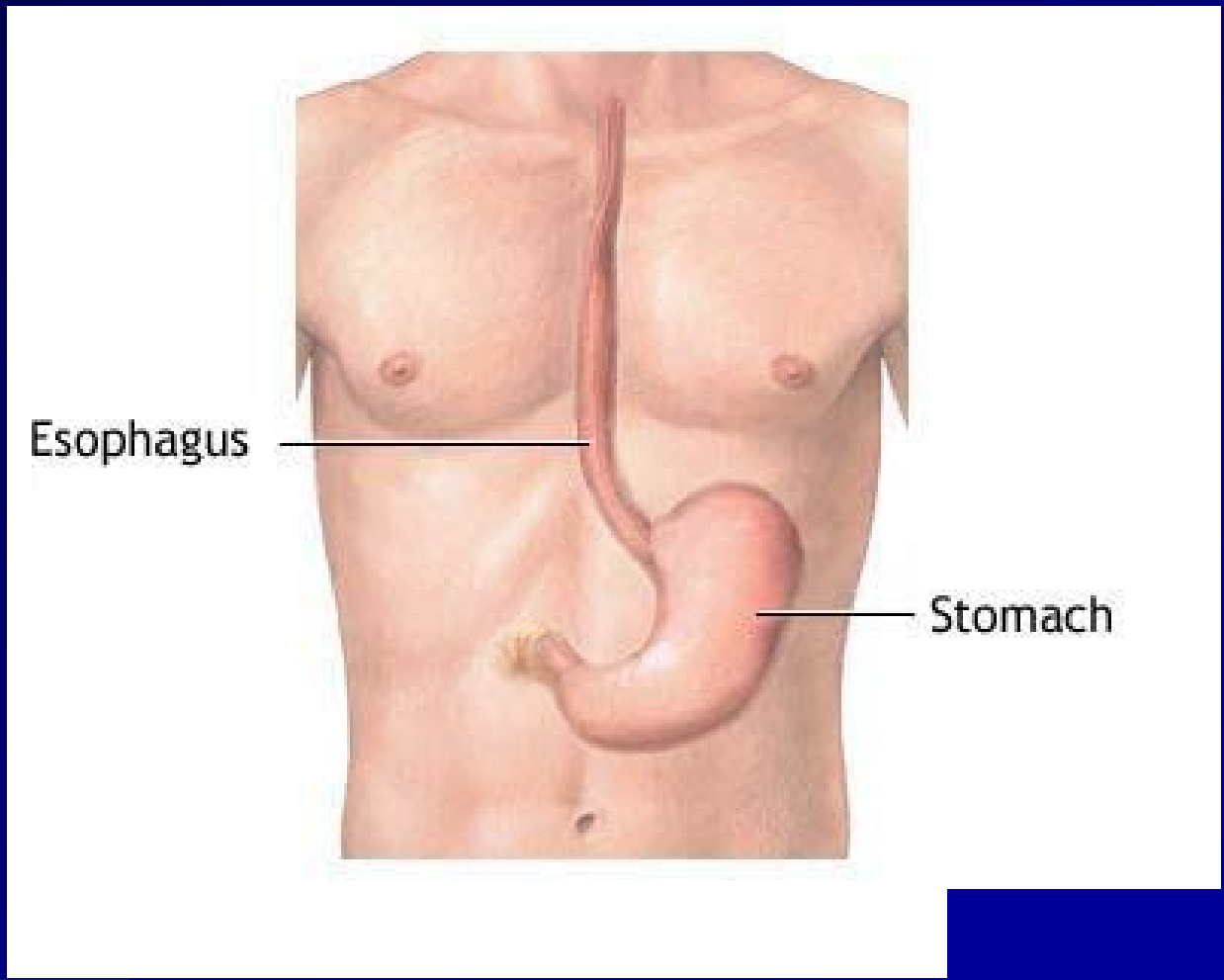
Esophagus and Stomach



Question

- Is there a preferred perioperative treatment for patients with gastric cancer?

Surgery

The Goal – R0 Resection

	Esophageal SCC (%)	Esophageal Adeno-CA (%)	Gastric Adeno-CA (%)
pT1			
Mucosa	100	100	100
Submucosa	91	100	98
pT2	84	84	87
pT3	70	68	60
pT4	48	59	41

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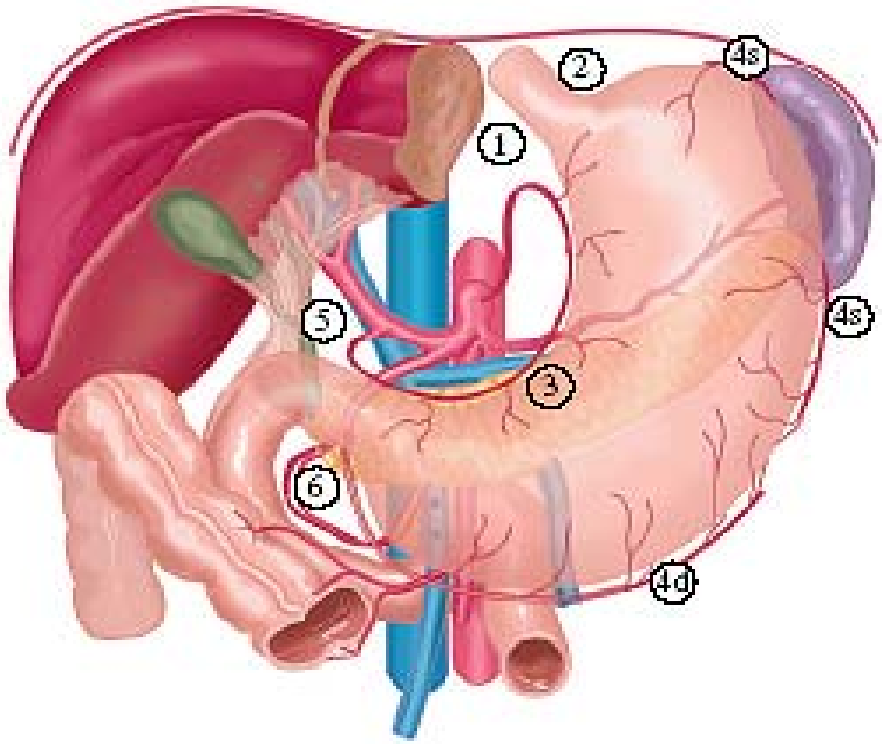
Siewert et al. *Ann Surg* 1998; 228: 449-461
Siewert et al. in Kelsen (Ed.) *GI Oncology* 2002; Table 18-3

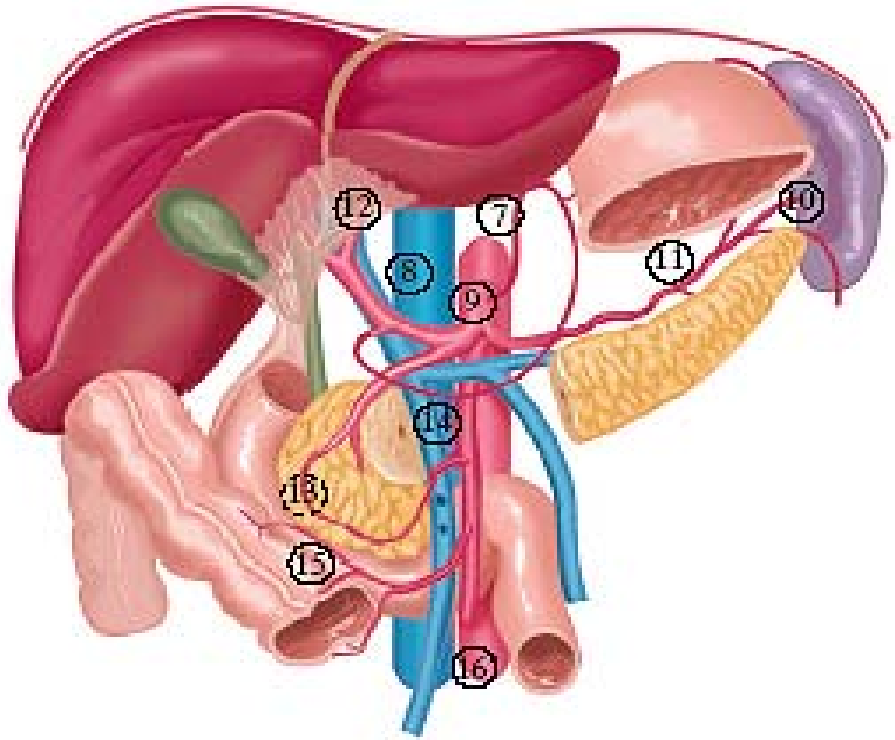
Stomach Surgery - Lymphadenectomy

D1 **nodes adjacent to the stomach**

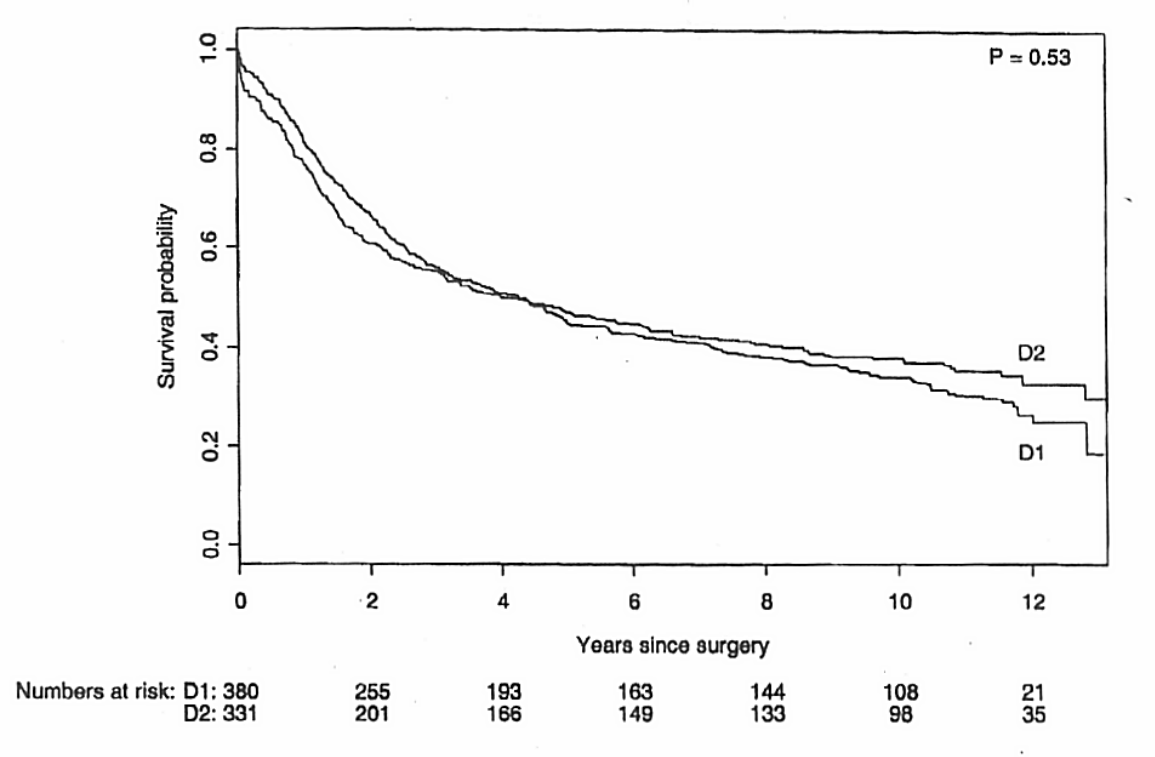
D2 **+ branches celiac axis**

D3 **nodes along the aorta**





D1 versus D2 Lymphadenectomy



Morbidity 25% *v* 43%; *P* = .001

Mortality 4% *v* 10%; *P* = .004

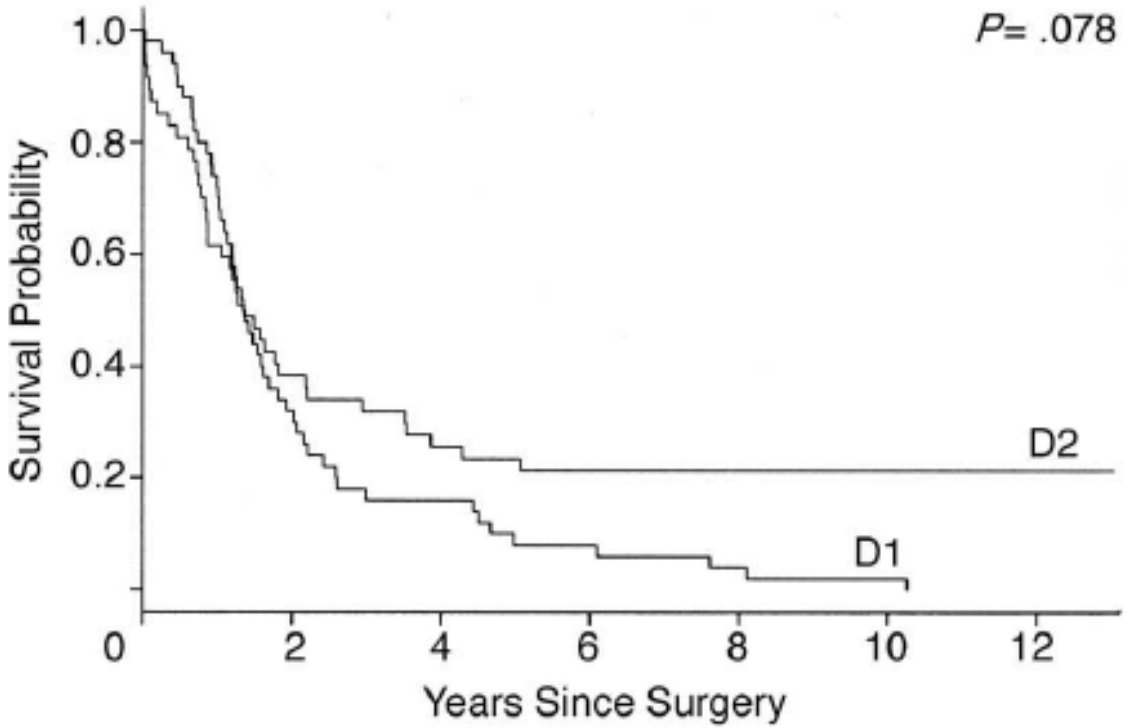
Morbidity and mortality influenced

- pancreatectomy
- splenectomy
- and age

Hartgrink et al., *J Clin Oncol* 2004;22:2069-2077

D1 versus D2 Lymphadenectomy

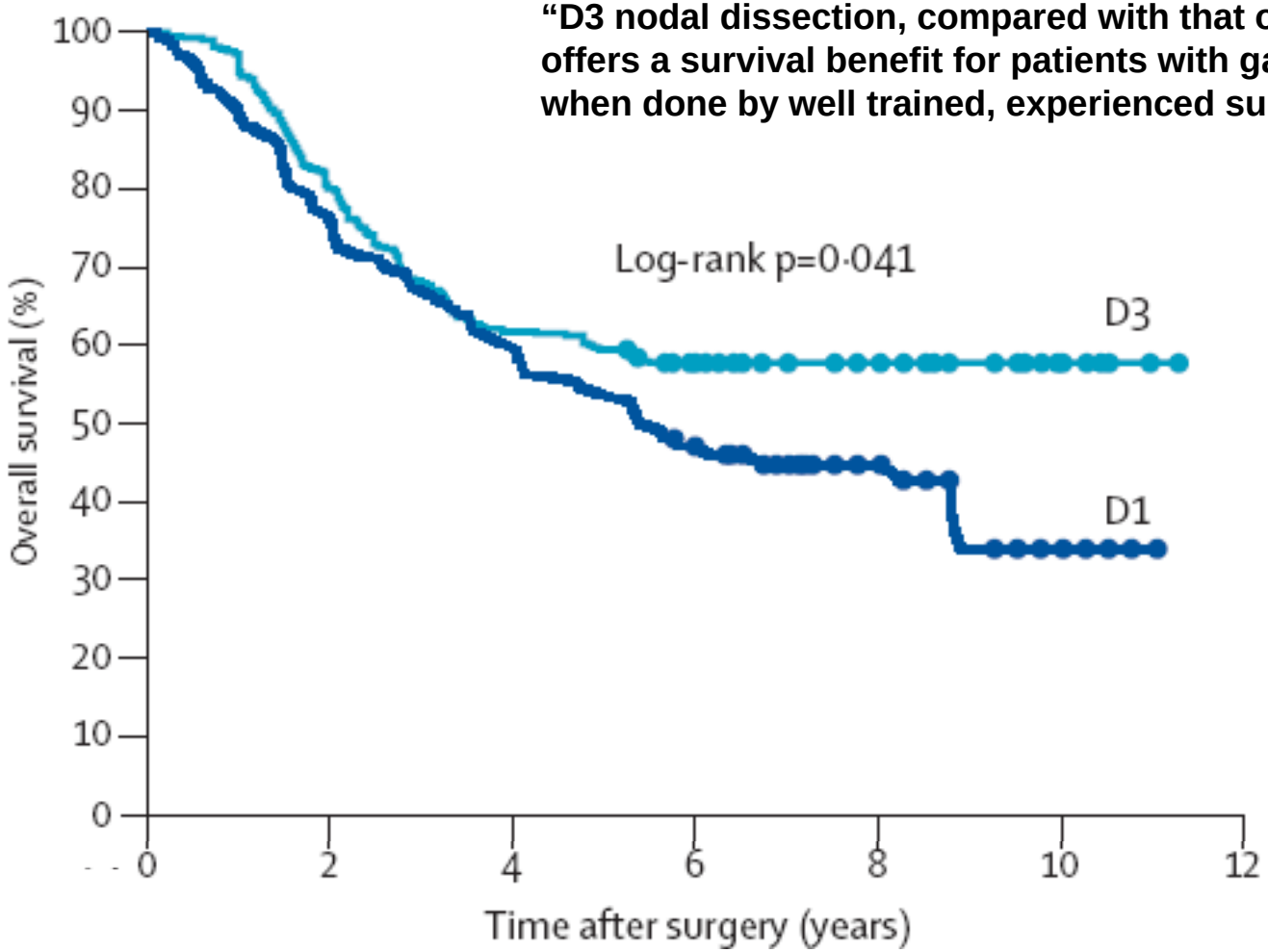
Subgroup with N2 disease



Hartgrink et al., *J Clin Oncol* 2004;22:2069-2077

D1 versus D3 Lymphadenectomy

“D3 nodal dissection, compared with that of D1, offers a survival benefit for patients with gastric cancer when done by well trained, experienced surgeons.”



Wu et al. *Lancet Oncol* 2006;7:309–15

Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial

Ilfet Songun, Hein Putter, Elma Meershoek-Klein Kranenbarg, Mitsuru Sasako, Cornelis J H van de Velde

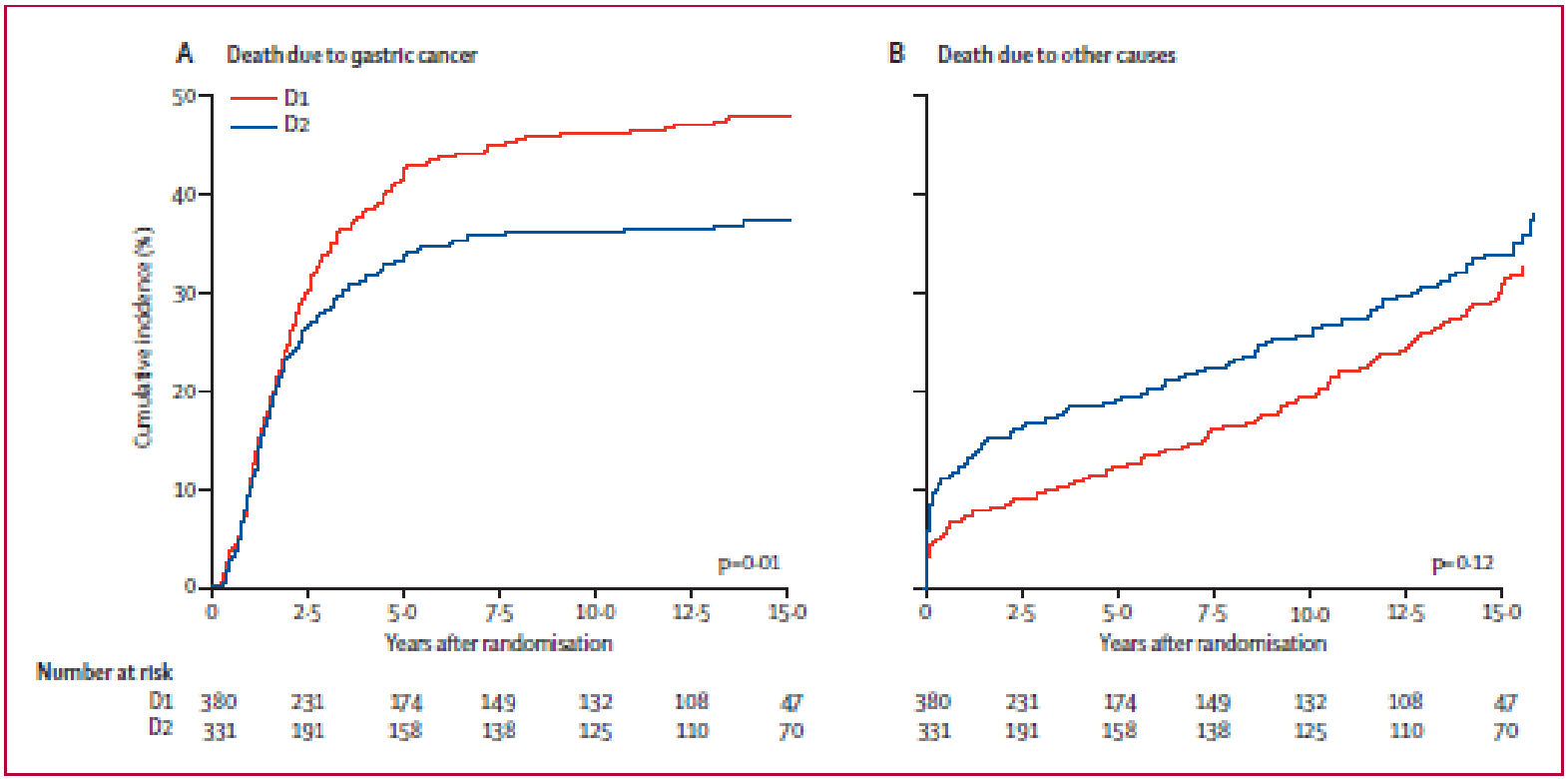


Figure 4: Cumulative risk of death due to gastric cancer and due to other causes in patients treated with curative intent (n=711)
D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy.

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Lancet Oncol 2010; 11: 439–49

BC Experience

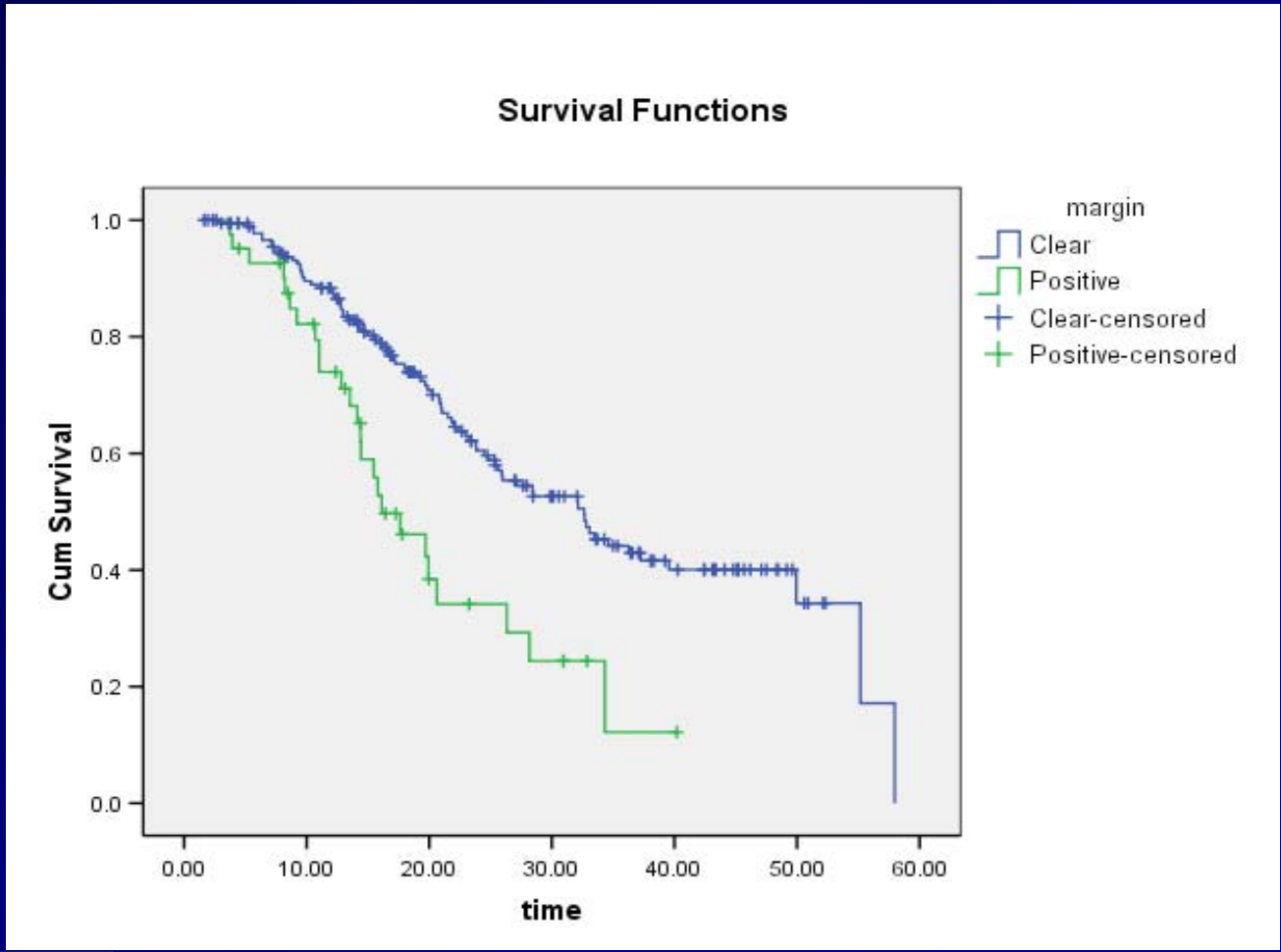


Figure 5 – Kaplan-Meier survival curves comparing margins

BC Experience

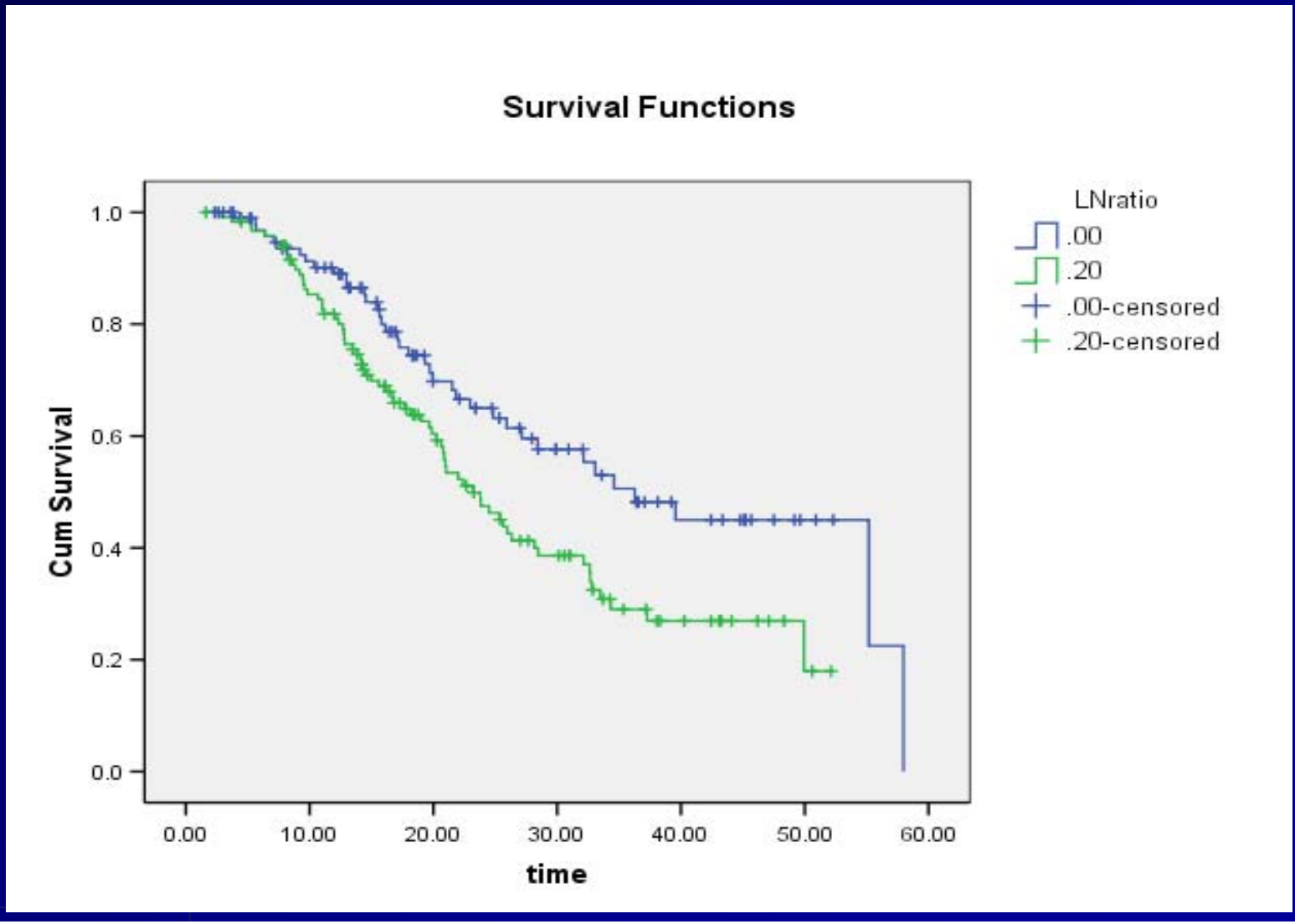


Figure 3 – Kaplan-Meier survival curves comparing lymph node ratio. ≤ 0.2 vs > 0.2

BC Experience

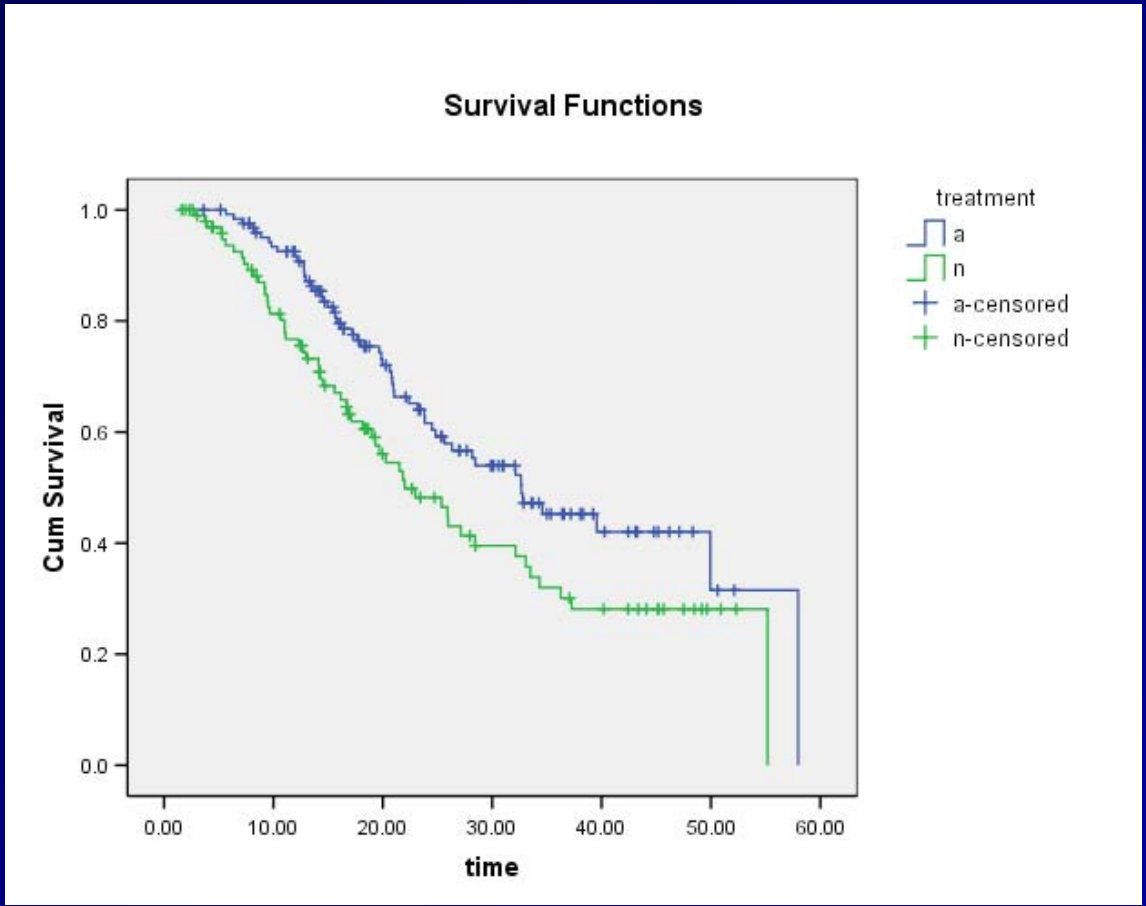


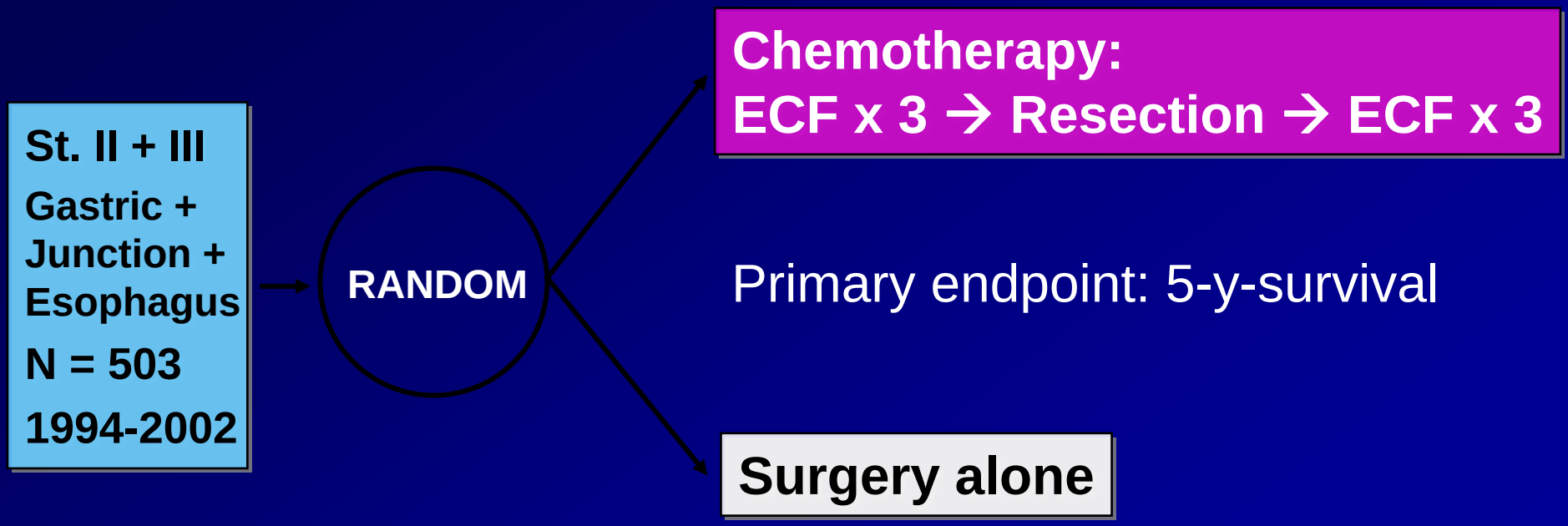
Figure 4 – Kaplan-Meier survival curves comparing use of perioperative treatment. a indicates chemotherapy +/- radiation, n indicates no treatment

Key to Gastric Cancer

- Surgery is the key for curative intent treatment
- Chemotherapy and Radiation do not make up for inadequate surgery
- Peri-operative treatment still confers a survival benefit

Peri-operative chemotherapy

UK MAGIC Trial



Primary endpoint: 5-y-survival

*ECF: Epirubicin 50mg/m2 d1, Cisplatin 60mg/m2 d1, 5-FU 200mg/m2/d cont iv, qd 22

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Cunningham D et al. *N Engl J Med* 2006;355:11-20

Table 1. Pretreatment Characteristics of the Patients.*

Characteristic	Perioperative-Chemotherapy Group (N=250)	Surgery-Only Group (N=253)
Age		
<60 yr — no. (%)	108 (43.2)	104 (41.1)
60–69 yr — no. (%)	91 (36.4)	95 (37.5)
≥70 yr — no. (%)	51 (20.4)	54 (21.3)
Median — yr	62	62
Range — yr	29–85	23–81
Sex — no. (%)		
Male	205 (82.0)	191 (75.5)
Female	45 (18.0)	62 (24.5)
WHO performance status — no. (%)†		
0	169 (67.6)	173 (68.4)
1	81 (32.4)	80 (31.6)
Site of tumor — no. (%)		
Stomach	185 (74.0)	187 (73.9)
Lower esophagus	37 (14.8)	36 (14.2)
Esophagogastric junction	28 (11.2)	30 (11.9)
Maximum tumor diameter		
0.0–3.9 cm — no. (%)‡	50 (30.9)	61 (33.3)
4.0–7.9 cm — no. (%)‡	79 (48.8)	87 (47.5)
8.0–11.9 cm — no. (%)‡	29 (17.9)	24 (13.1)
12.0–15.9 cm — no. (%)‡	2 (1.2)	8 (4.4)
>16.0 cm — no. (%)‡	2 (1.2)	3 (1.6)
Unknown — no. (%)	88 (35.2)	70 (27.7)
Median — cm	5.0	5.0
Interquartile range — cm	3.0–7.0	3.0–7.0

Table 3. Surgical and Pathological Results.

Variable	Perioperative-Chemotherapy Group (N=250)	Surgery Group (N=253)
	number of patients/total number (percent)	
Extent of resection according to surgeon		
Curative	169/244 (69.3)	166/250 (66.4)
Palliative	44/244 (18.0)	70/250 (28.0)
Opinion not specified	16/244 (6.6)	8/250 (3.2)
No surgery	15/244 (6.1)	6/250 (2.4)
Surgical status unknown	6/250 (2.4)	3/253 (1.2)
Operation performed*		
Esophagogastrectomy	58/219 (26.5)	52/238 (21.8)
D1 distal resection	19/219 (8.7)	30/238 (12.6)
D1 total resection	20/219 (9.1)	20/238 (8.4)
D2 distal resection	32/219 (14.6)	24/238 (10.1)
D2 total resection	61/219 (27.9)	72/238 (30.3)
Nonresectional surgery	29/219 (13.2)	40/238 (16.8)
Unknown	10/229 (4.4)	6/244 (2.5)
Pathology reports		
Tumor stage (all patients)		
T1	27/172 (15.7)	16/193 (8.3)
T2	62/172 (36.0)	55/193 (28.5)
T3	75/172 (43.6)	106/193 (54.9)
T4	8/172 (4.7)	16/193 (8.3)
Nodal status (patients with gastric cancer)		
N0	42/135 (31.1)	42/156 (26.9)
N1 (<7 nodes involved)	72/135 (53.3)	68/156 (43.6)
N2 (7–14 nodes involved)	19/135 (14.1)	34/156 (21.8)
N3 (>14 nodes involved)	2/135 (1.5)	12/156 (7.7)

* D1 denotes limited lymph-node dissection, and D2 extended lymph-node dissection.

UK MAGIC Trial

	CTX	SURG	P-value
Maximal Diameter	3 cm	5 cm	< 0.001
(y)pT1/2	51.7%	36.8%	0.002
(y)pN0/1	84.4%	70.5%	0.01

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Cunningham D et al. *N Engl J Med* 2006;355:11-20

Chemotherapy

250 pts assigned to chemotherapy (86% completed all 3 cycles)

↓

209 pts underwent surgery

↓ → 37 pts disease progression
→ 10 post-op complications
→ 11 pt choice
→ 2 lack of response
→ 9 Other

↓

137 pts proceeded to post-op chemotherapy

↓

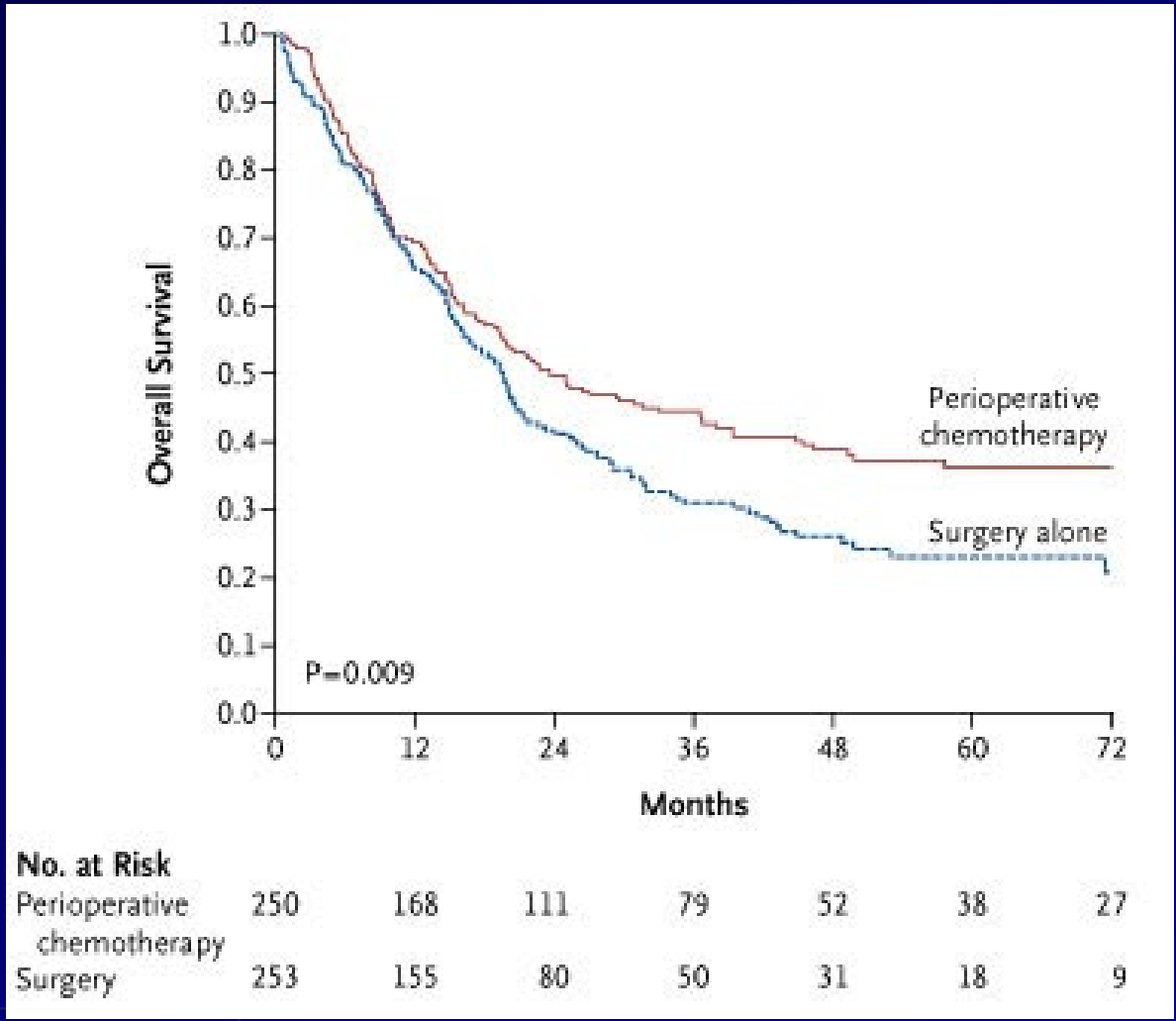
104 pts completed post-op chemotherapy (41.6% of 250 pts initially assigned)

- After surgery – no increase in grade 3/4 toxicity

Surgery Details

- Chemotherapy group – 229 (91.6%) pts went for surgery
- Surgery within 3-6 weeks of completion of chemotherapy
- Post-operative complications were similar (45.7% vs 45.3%; chemo vs. no chemo), number of deaths at 30 days (5.6% vs 5.9%) and median stay in hospital 13 days both groups.

UK MAGIC Trial



No. at Risk							
Perioperative chemotherapy	250	168	111	79	52	38	27
Surgery	253	155	80	50	31	18	9

5-y-OS

36%

23%

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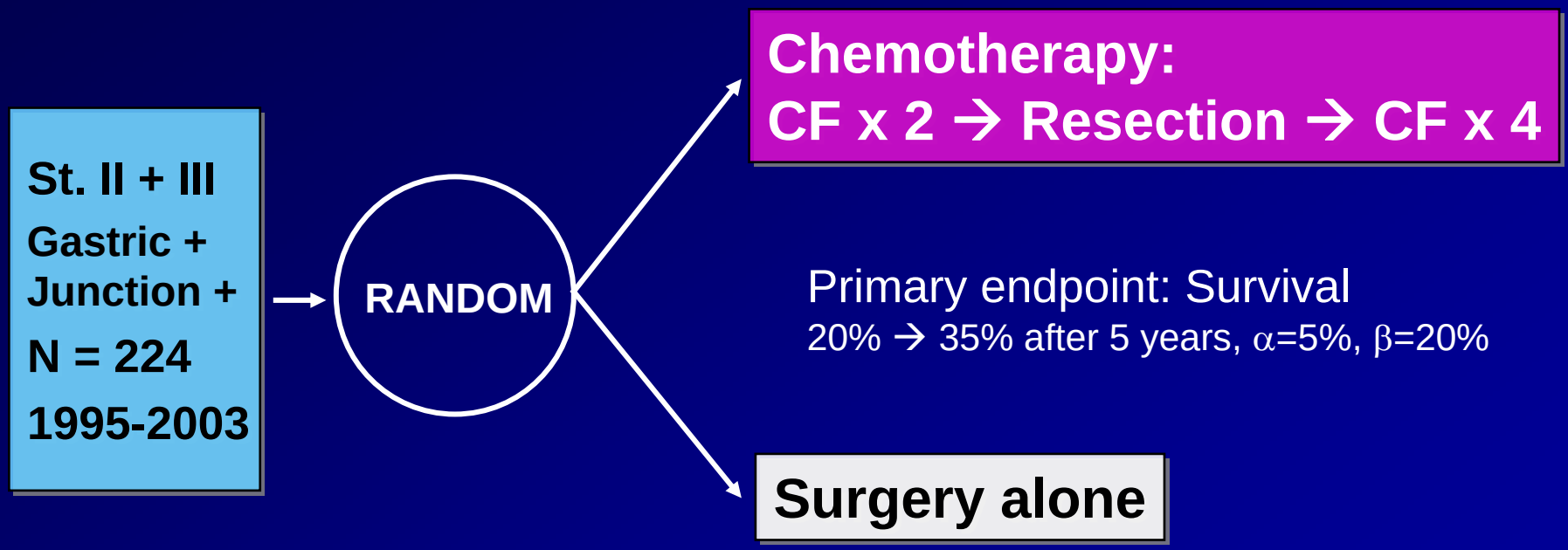
Cunningham D et al. *N Engl J Med* 2006;355:11-20

France FNCC 94012 - FFCD 9703



Primary endpoint: Survival
20% → 35% after 5 years, α=5%, β=20%

*CF: Cisplatin 100mg/m2 d1, 5-FU 800mg/m2/d d1-5, qd 28

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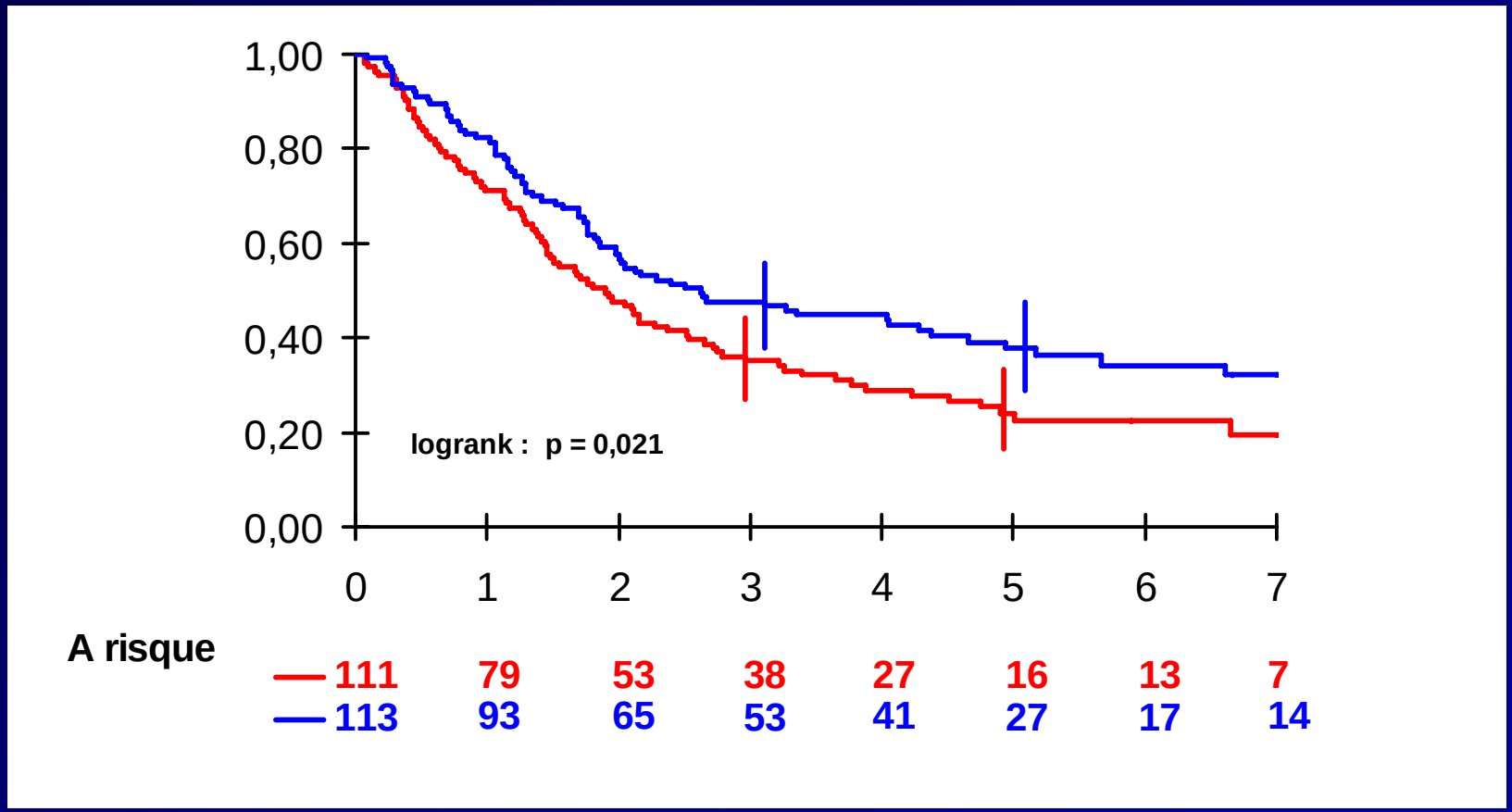
Boige, V. et al. ASCO 2007 #4510

France FNCC 94012 - FFCD 9703



5-year-survival: 24% (16-33%) vs 38% (28-47%)

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Boige, V. et al. ASCO 2007 #4510

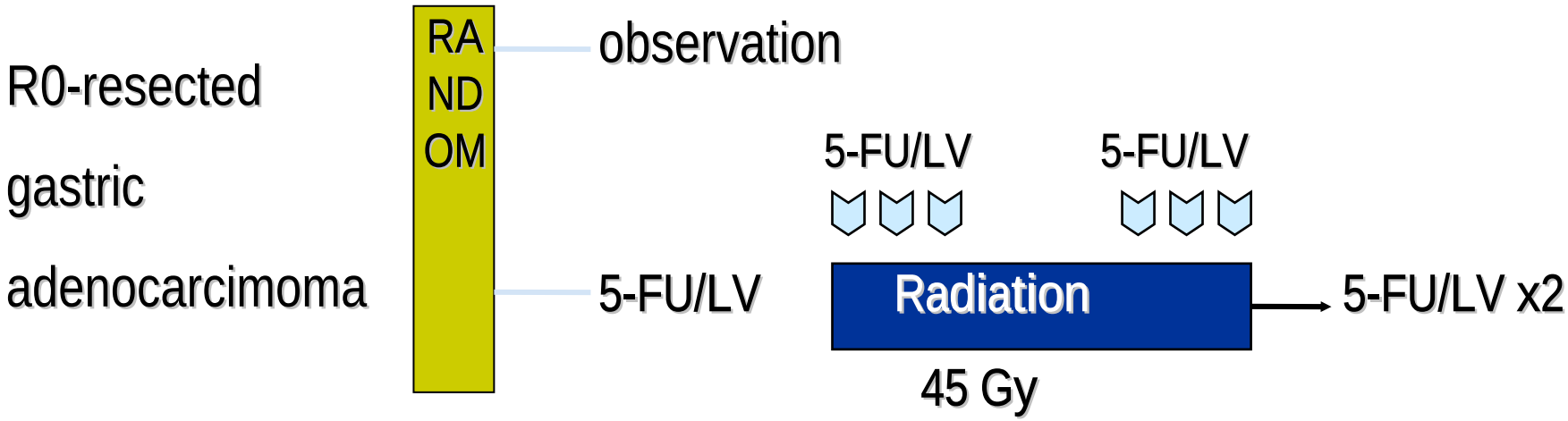
Adjuvant Treatment

Adjuvant Radiotherapy

- Two early trials using radiation alone
- Post-operative XRT vs. surgery alone 3 yr OS 23 % vs 27 %
- Intra-operative radiation vs surgery - Mean survival 26.9 months vs. 30.8 month

Adjuvant chemoradiation

SWOG 9008 / INT 0116



Chemotherapy

Leucovorin 20mg/m^2 d1-5, 5-FU 425mg/m^2 d1-5, qd28

Modification cycle 2: leucovorin 20mg/m^2 d1-4, 5-FU 400mg/m^2 d1-4

Modification cycle 3: leucovorin 20mg/m^2 d1-3, 5-FU 400mg/m^2 d1-3

Macdonald et al., *NEJM* 2001; 345: 725-730

TABLE 1. CHARACTERISTICS OF THE PATIENTS AND THE TUMORS.*

CHARACTERISTIC	SURGERY-ONLY GROUP (N=275)	CHEMORADIOTHERAPY GROUP (N=281)
Age (yr)		
Median	59	60
Range	23–80	25–87
Performance status of 0 or 1 (%)	94	94
Male sex (%)	71	72
Race (%)		
White	73	75
Black	16	16
Asian	7	5
Other	4	4
T stage (%)		
T1 or T2	31	31
T3	61	62
T4	8	6
No. of positive nodes (%)		
0	16	14
1–3	41	42
⩾4	43	43
Location of primary tumor (%)		
Antrum	56	53
Corpus	25	24
Cardia	18	21
Multicentric	<1	2

*Because of rounding, not all percentages total 100.

Surgical Details

- Eligibility:
  - Curative intent en bloc resection of the tumor
  - Negative Margins
  - Recommended D2 – perigastric, celiac, splenic, hepaticoartery and cardial lymph nodes

Surgical Details

- Of the 552 patients whose records were reviewed
- D2 lymphadecotomy – 10% (52 pts)
- D1 lymphadecotomy – 36% (199 pts)
- D0 lymphadecotomy – 54%

TABLE 2. REASONS FOR THE CESSATION OF CHEMORADIOTHERAPY AMONG THE 281 PATIENTS IN THE CHEMORADIOTHERAPY GROUP.

REASON FOR CESSATION	NO. OF PATIENTS (%)
Protocol treatment completed	181 (64)
Toxic effects	49 (17)
Patient declined further treatment	23 (8)
Progression of disease	13 (5)
Death	3 (1)
Other	12 (4)

Adjuvant chemoradiation

SWOG 9008 / INT 0116

SITES OF RELAPSE *

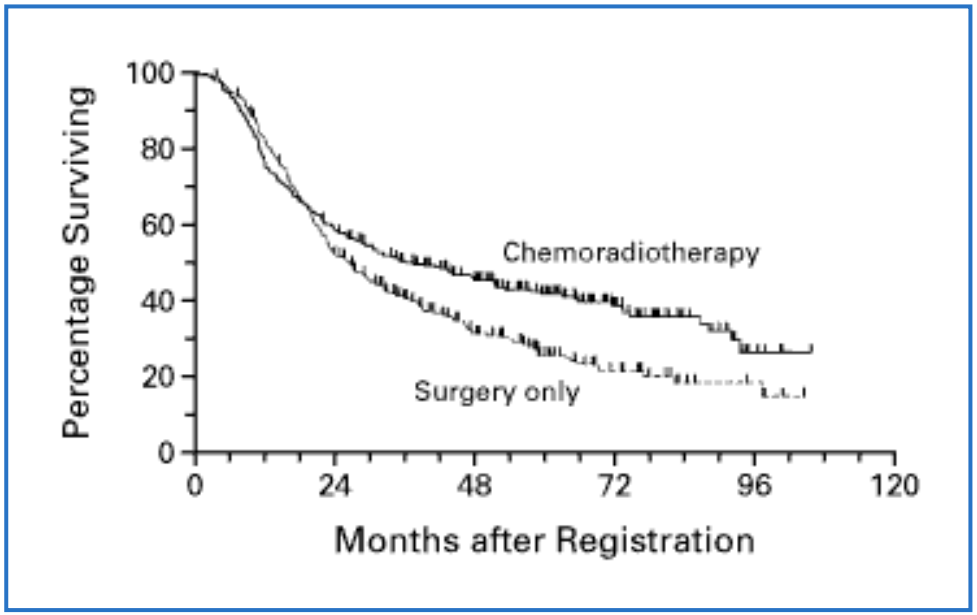
SITE	PATIENTS WITH RELAPSES	
	SURGERY-ONLY GROUP (N=177)	CHEMORADIOTHERAPY GROUP (N=120)
	no. (%)	
Local	51 (29)	23 (19)
Regional	127 (72)	78 (65)
Distant	32 (18)	40 (33)

*Because patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients in each group who had relapses.

Macdonald et al., *NEJM* 2001; 345: 725-730

Adjuvant chemoradiation

SWOG 9008 / INT 0116



Median OS:	
Chemo XRT	36 mos
Surgery	27 mos
HR for death	1.35 p=0.005

Macdonald et al., *NEJM* 2001; 345: 725-730

Subset Analysis

- At 10 ys f/u – HR 1.32 for OS and 1.51 for DFS
- Sex, race, T and N stage, D-level of resection, tumor location, histology and Maruyama index
- Chemoradiation benefitted all subsets except women (HR 1.0) and diffuse histology (HR 0.97)

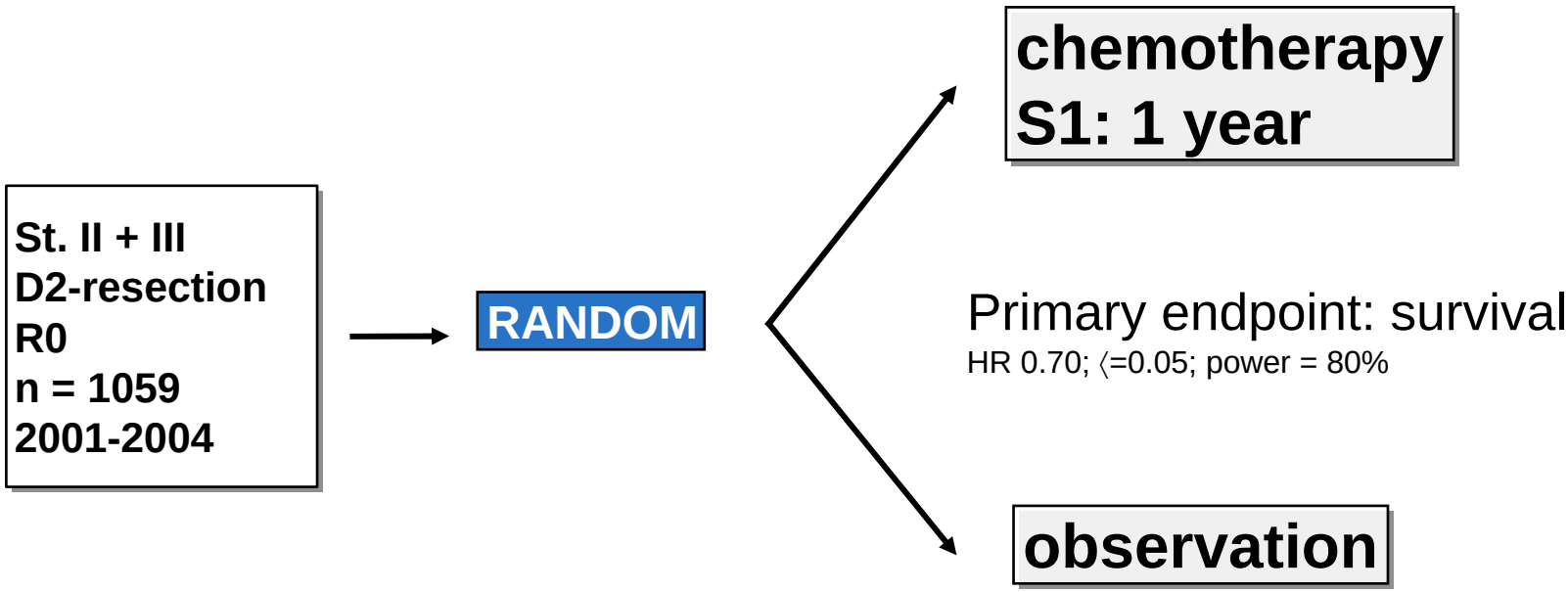
ASCO 2009, Abstract 4515

Conclusions

- ChemoXRT is recommended for resected gastric cancer
- Majority of patients - D0/D1 surgery
- Reflection of current practice
- Sub group analysis did not reflect a difference between D0/D1/D2 resection
- Small numbers

Adjuvant S-1

ATCS-GC study

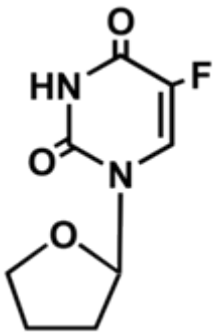


*S1 (Tegafur, Gimeracil, Oteracil): 80mg/m² d1-28, qd 43

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820

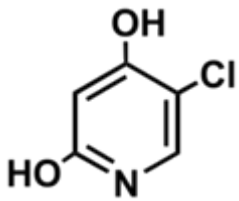
The role of oral fluoropyrimidines: S-1

New oral DPD-inhibiting fluoropyrimidin,
developed by Taiho (Japan), consisting of
Tegafur (FT), **Gimeracil (CDHP)** und **Oteracil-Kalium (Oxo)**
in a molar ratio of 1 : 0.4 : 1



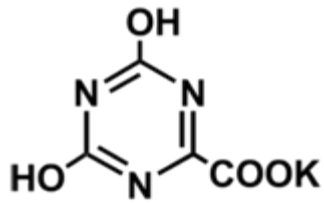
Tegafur (FT)

+



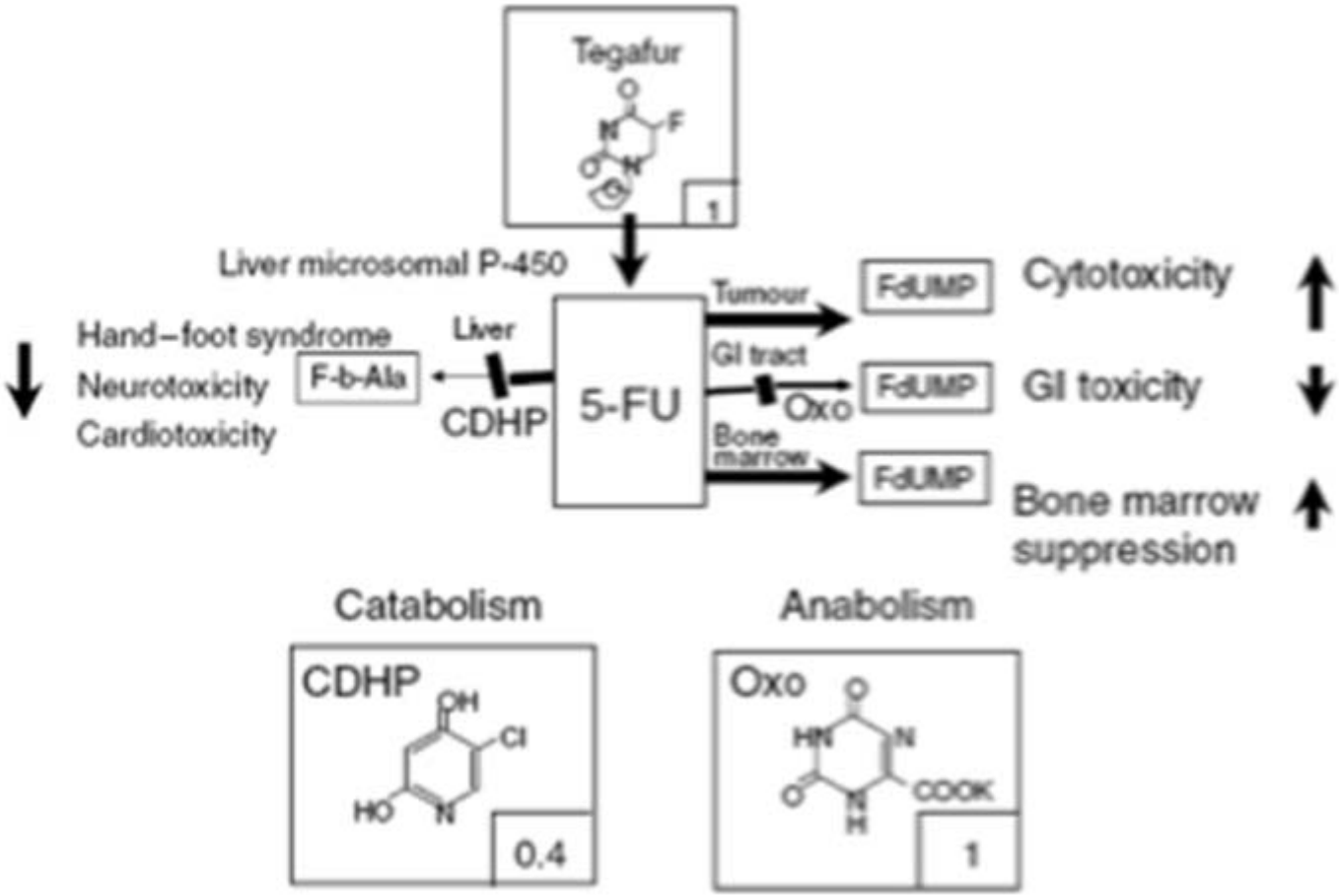
Gimeracil (CDHP)

+



Oteracil-K (Oxo)

The role of oral fluoropyrimidines: S-1



Kubota T. *Br J Cancer* 2008; 98:1301.1304

Table 1. Baseline Characteristics of the Patients.

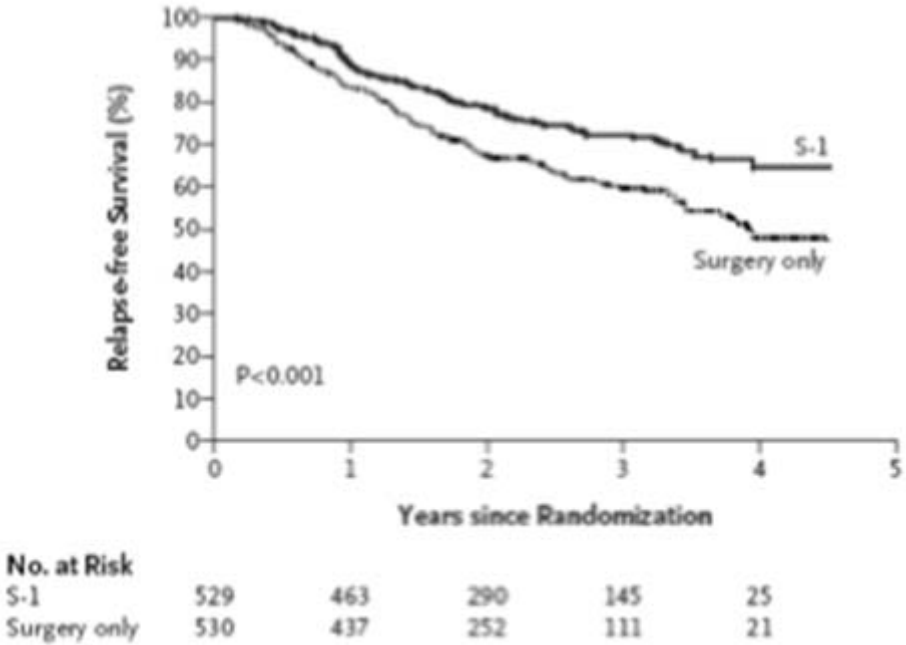
Characteristic	S-1 (N=529)	Surgery Only (N=530)	P Value*
Sex — no. (%)			0.98
Male	367 (69.4)	369 (69.6)	
Female	162 (30.6)	161 (30.4)	
Age			0.86
<60 yr — no. (%)	199 (37.6)	195 (36.8)	
60–69 yr — no. (%)	193 (36.5)	215 (40.6)	
70–80 yr — no. (%)	137 (25.9)	120 (22.6)	
Median — yr	63	63	
Range — yr	27–80	33–80	
Tumor stage — no. (%)			0.81
T1	1 (0.2)	0	
T2	289 (54.6)	286 (54.0)	
T3	225 (42.5)	232 (43.8)	
T4	14 (2.6)	12 (2.3)	
Nodal stage, Japanese classification — no. (%)†			0.72
N0	51 (9.6)	64 (12.1)	
N1	296 (56.0)	281 (53.0)	
N2	182 (34.4)	185 (34.9)	
N3	0	0	
No. of lymph-node metastases — no. (%)			0.37
0	51 (9.6)	64 (12.1)	
1–6	331 (62.6)	325 (61.3)	
7–15	117 (22.1)	113 (21.3)	
≥16	30 (5.7)	28 (5.3)	

Table 1. (Continued.)

Characteristic	S-1 (N=529)	Surgery Only (N=530)	P Value*
Cancer stage, Japanese classification — no. (%)‡			0.78
II	236 (44.6)	238 (44.9)	
IIIA	202 (38.2)	207 (39.1)	
IIIB	90 (17.0)	85 (16.0)	
IV	1 (0.2)	0	
Cancer stage, TNM classification — no. (%)			0.37
IB	1 (0.2)	0	
II	264 (49.9)	282 (53.2)	
IIIA	170 (32.1)	157 (29.6)	
IIIB	54 (10.2)	56 (10.6)	
IV	40 (7.6)	35 (6.6)	
Type of lymph-node dissection — no. (%)			0.69
D1	0	1 (0.2)	
D2	501 (94.7)	497 (93.8)	
D3	28 (5.3)	32 (6.0)	
Type of gastrectomy — no. (%)			0.26
Total	220 (41.6)	201 (37.9)	
Distal	301 (56.9)	316 (59.6)	
Proximal	4 (0.8)	11 (2.1)	
Other	4 (0.8)	2 (0.4)	

Adjuvant S-1

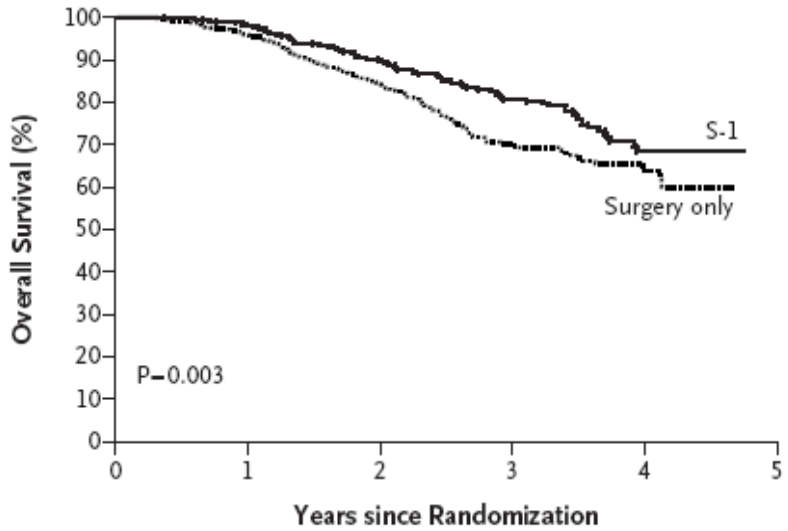
Relapse-free survival



No. at Risk					
S-1	529	463	290	145	25
Surgery only	530	437	252	111	21

HR = 0.62 (95% CI, 0.50 to 0.77)
P<0.001
3 yr RFS 72.2% vs. 59.6%

Overall survival



No. at Risk					
S-1	529	515	270	196	46
Surgery only	530	504	352	163	40

HR = 0.68 (95% CI, 0.52 to 0.87)
P = 0.003
3 yr OS 80.1% vs. 70.1%

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820

Adjuvant S-1

Pattern of relapse

Table 3. Site of First Relapse, According to Treatment Group.*

Site	S-1 (N=529)	Surgery Only (N=530)	Hazard Ratio for Relapse in the S1 Group (95% CI)	P Value
	no. of patients (%)			
Total no. of relapses	133 (25.1)	188 (35.5)		
Local	7 (1.3)	15 (2.8)	0.42 (0.16–1.00)	0.05
Lymph nodes	27 (5.1)	46 (8.7)	0.54 (0.33–0.87)	0.01
Peritoneum	59 (11.2)	84 (15.8)	0.64 (0.46–0.89)	0.009
Hematogenous	54 (10.2)	60 (11.3)	0.84 (0.58–1.21)	0.35

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820

Conclusions

- Adjuvant S1 improves OS by approx. 10%
- Majority of patients had D2 resection
- May not be valid in D0/D1 resection
- Asian vs. Western patients? - Several studies showing that there does not appear to be a genetic difference
- When equivalent surgery performed - treatment outcomes similar
- S1 not approved in Canada

Adjuvant Chemotherapy

- Meta-analyses: only borderline significance for adjuvant chemotherapy.
- Single studies: virtually all negative.
- Subgroup analyses: stronger trend towards better survival with chemotherapy in lymph node + disease.

Meta-analyses	Studies (n)	Patients (n)	Odds ratio (CI)
Hermans 1993	11	2096	0.88 (0.78-1.08)
Earle 1999	13	1990	0.80 (0.66-0.97)
Mari 2000	21	3658	0.82 (0.75-0.89)
Janunger 2002	21	3962	0.84 (0.74-0.96)

Lordick F & Siewert JR. *Gastric Cancer* 2005; 8: 78-85

Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

- Individual patient-level meta-analysis
- 17 trials – 3838 patients representing 60% of targeted data
- Median f/u 7 years

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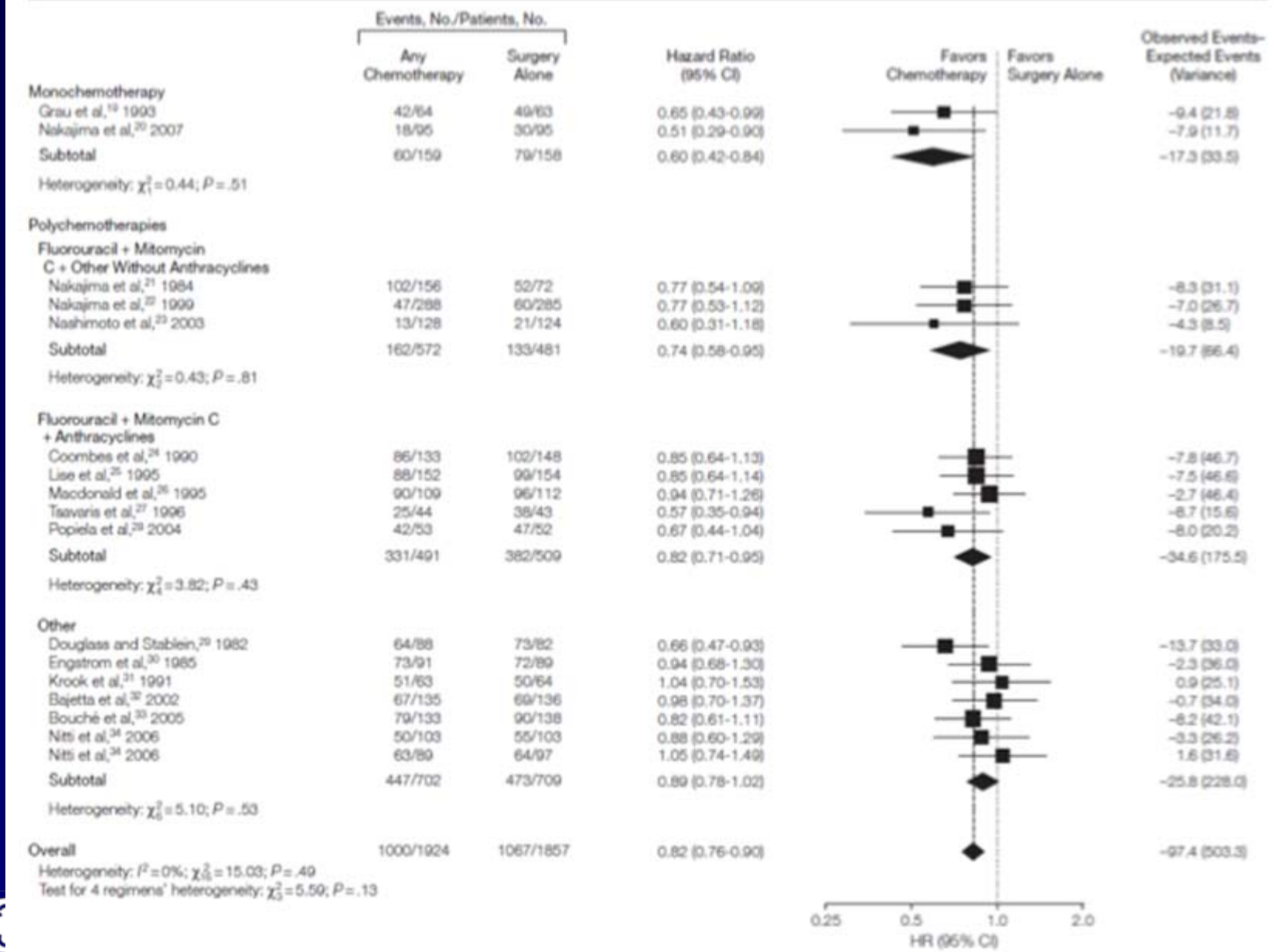
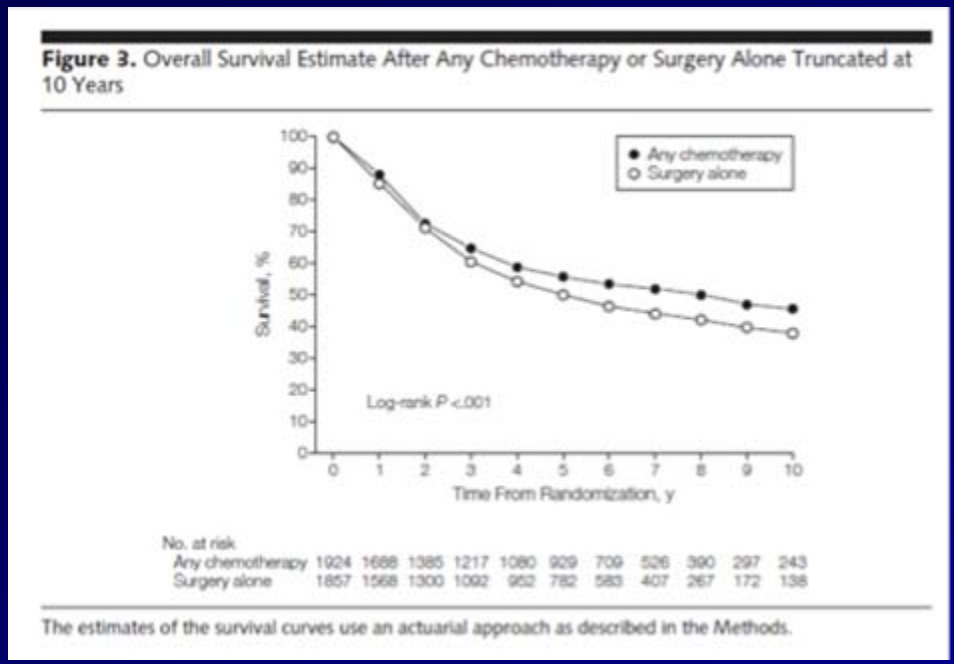
JAMA, May 5, 2010—Vol 303, No. 17

Figure 2. Individual Trial and Overall Hazard Ratio for Overall Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone





- Median OS 4.9 years surgery only vs 7.8 years in the adjuvant chemotherapy 5FU based chemotherapy
- HR for OS 0.82 p< 0.001 and DFS 0.82 p< 0.001
- 49.6% to 55.3% (5.8%) benefit at 5 years and 37.5% to 44.9% (7.4%) benefit at 10 years

Peri-operative treatment Outcomes

	Time period	Surgery only			Multimodality treatment		
		N	RFS	OS	N	RFS	OS
MacDonald et al (2001)*	1990-1998	275	31% (3-year)	43% (3-year)	281 CRT	48% (3-year)	50% (3-year)
Cunningham et al (2006)†	1994-2002	253	NA	23% (5-year)	250 ECF	NA	36% (5-year)
Sakuramoto et al (2007)‡	2001-2004	530	60% (3-year)	70% (3-year)	529 S-1	72% (3-year)	80% (3-year)
Boige et al (2007)§	1995-2003	111	21% (5-year)	26% (5-year)	113 FP	36% (5-year)	38% (5-year)

RFS=relapse-free survival. OS=overall survival. NA=not available. CRT=postoperative chemoradiotherapy (fluorouracil plus leucovorin followed by 45 Gy radiotherapy). ECF=Three preoperative and three postoperative cycles of epirubicin, cisplatin, and fluorouracil. S-1=cycles of S-1 (orally active combination of tegafur, gimeracil, and oteracil) for 1 year postoperatively. FP=2–3 cycles of preoperative fluorouracil and cisplatin, postoperative FP was recommended for patients with a response or stable disease with pN+.

Table 7: Randomised trials of surgery only versus surgery combined with chemotherapy or chemoradiotherapy

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BC Experience

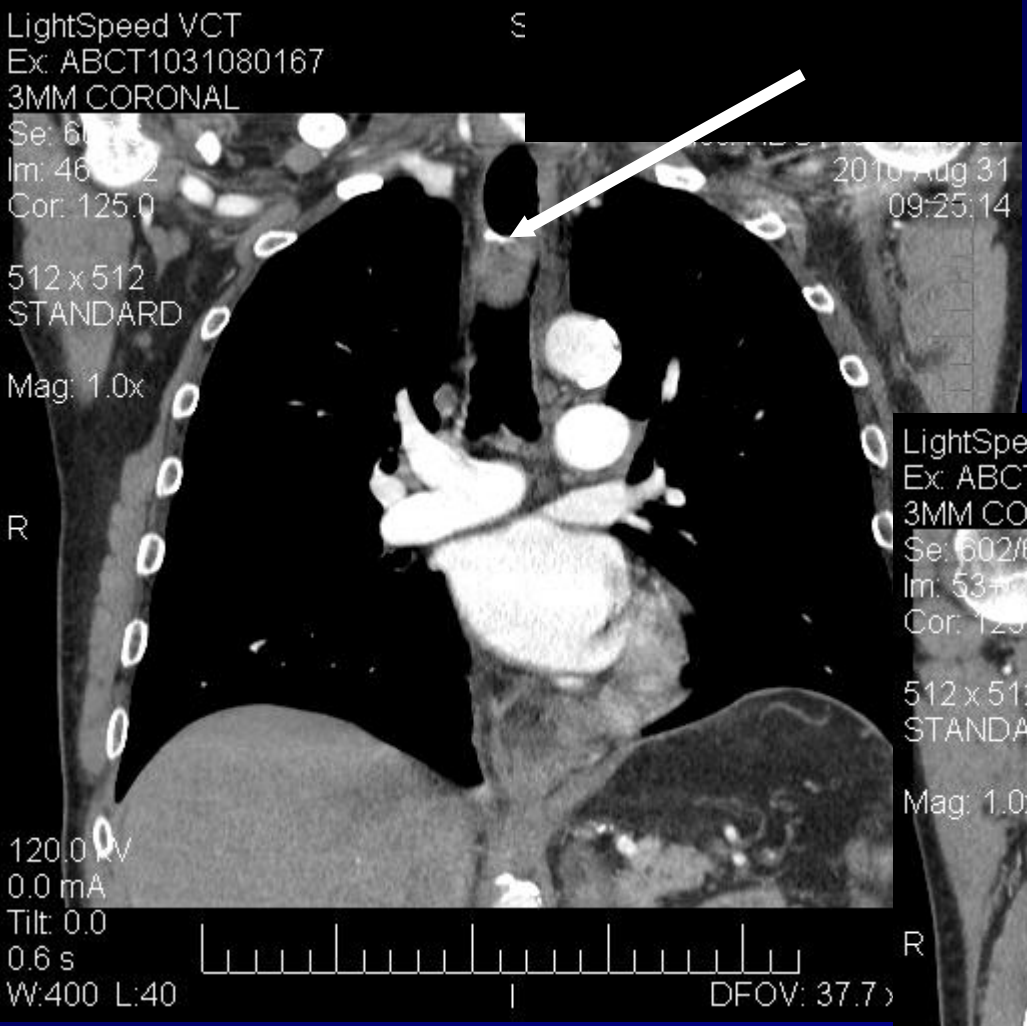
- Gastric/GE junction patients should be evaluated for consideration of peri-operative treatment
- If not deemed to be a candidate for pre-operative treatment – consider post-operative treatment

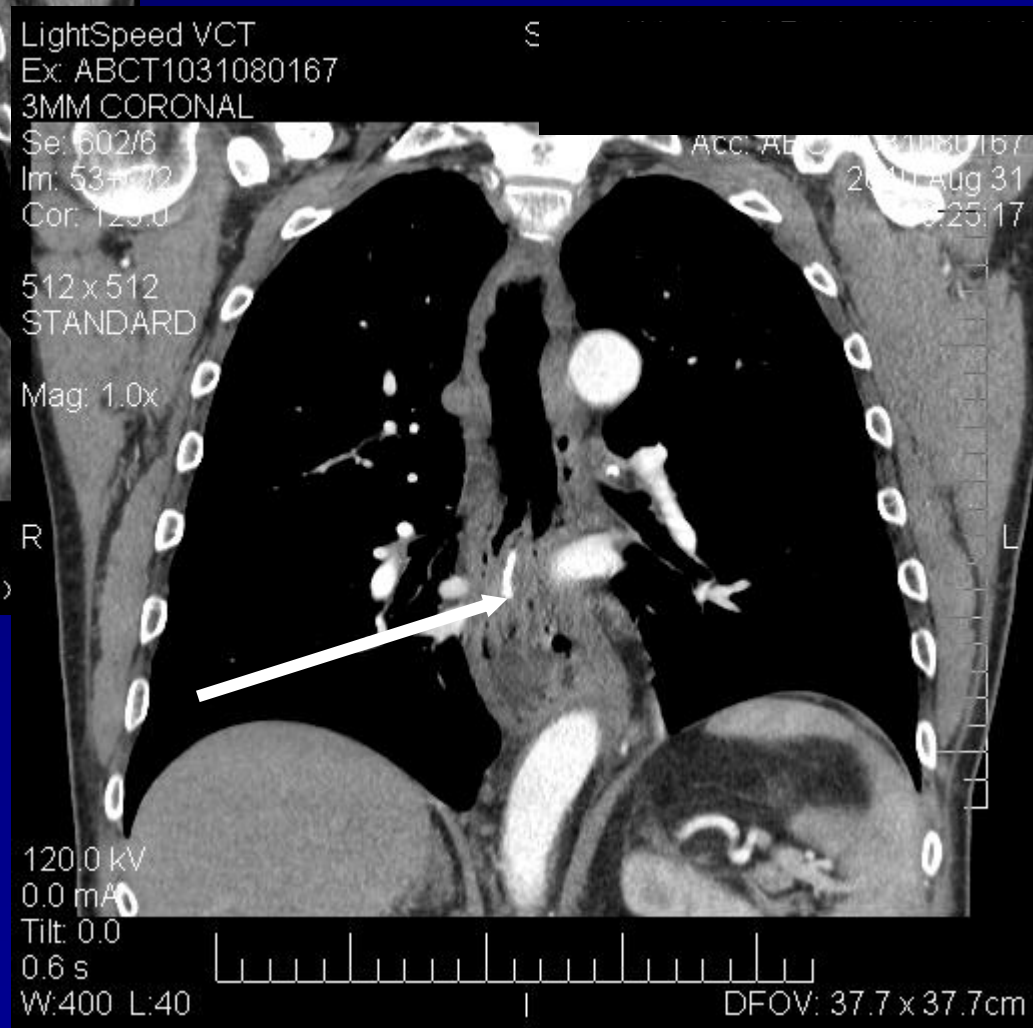
Reasons for peri-operative

- Significant benefit with 3 cycles of pre-operative chemotherapy
- Post-operative patients may not be candidates for adjuvant treatment
- Neo-adjuvant therapy can downstage disease – aid with achieving R0 resection
- May weed out the poor performing patients (patients who progress on neo-adjuvant treatment – will surgery really salvage them?)

BC Experience

- Post-operative options:
  - ChemoXRT preferred – if poorly tolerated – try to complete the ChemoXRT portion
  - If anastomosis high, may not be suitable for XRT as field too large
  - Consider for adjuvant chemotherapy





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Gastric Cancer Treatment Scheme

ECC → Surgery → ECC

Surgery - D1 or D2 resection or > 15 lymph nodes

If upfront surgery - bleeding, not eligible for chemotherapy

Surgery → ChemoXRT - currently 5FU
Future - ECC/CP with XRT or ECC/CP alone

→ Not eligible for XRT - consider 5FU based chemotherapy - ECC?

Conclusions

- All patients with localized/resectable gastric cancer should be referred pre-operatively for consideration of peri-operative treatment
- Surgical management should include a minimum of 15 lymph nodes or D1 lymph node dissection

Thank You!

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