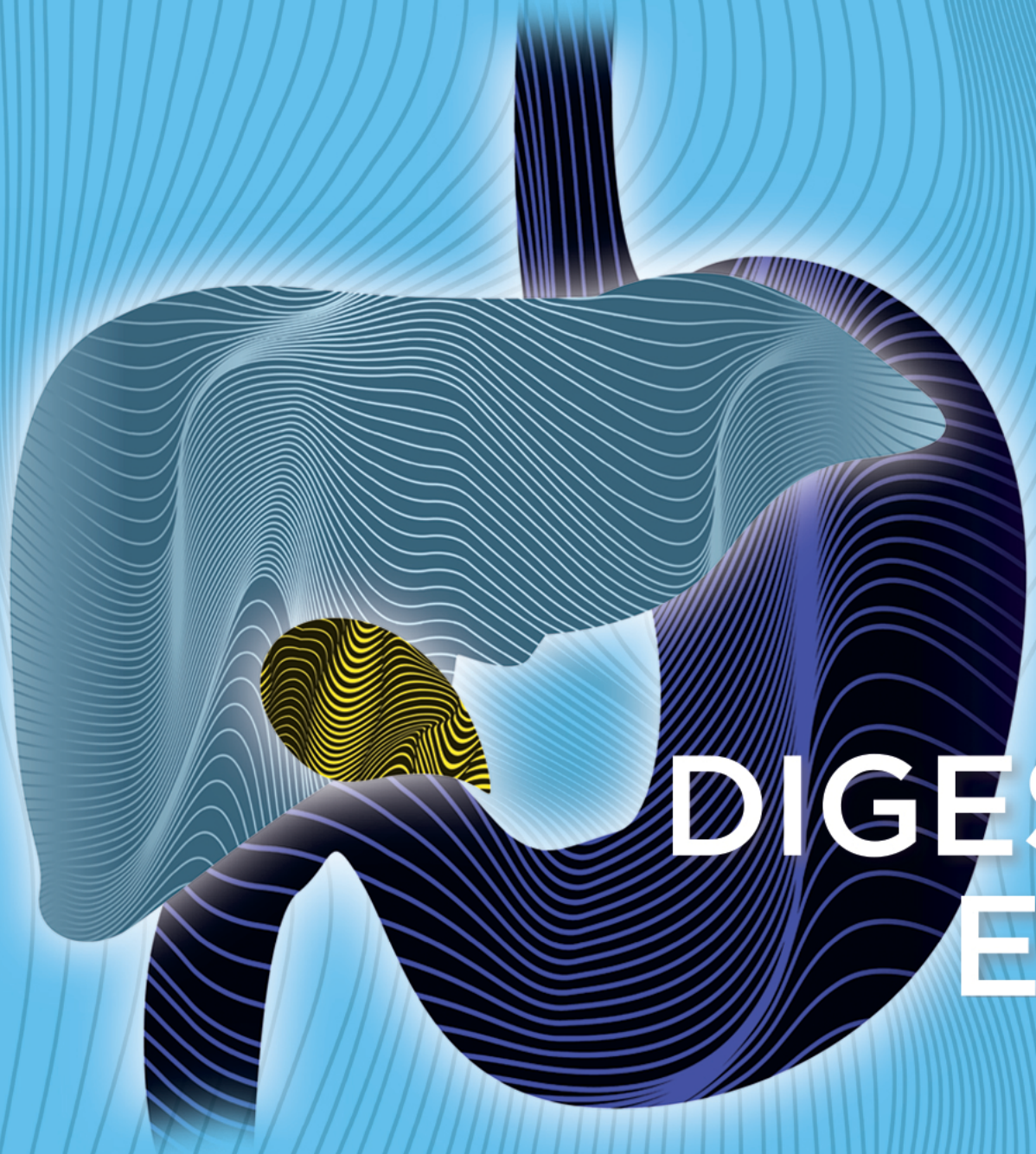


52e CONGRÈS

ASSOCIATION QUÉBÉCOISE
DE CHIRURGIE

19 AU 22 MAI 2022
FAIRMONT LE MANOIR RICHELIEU

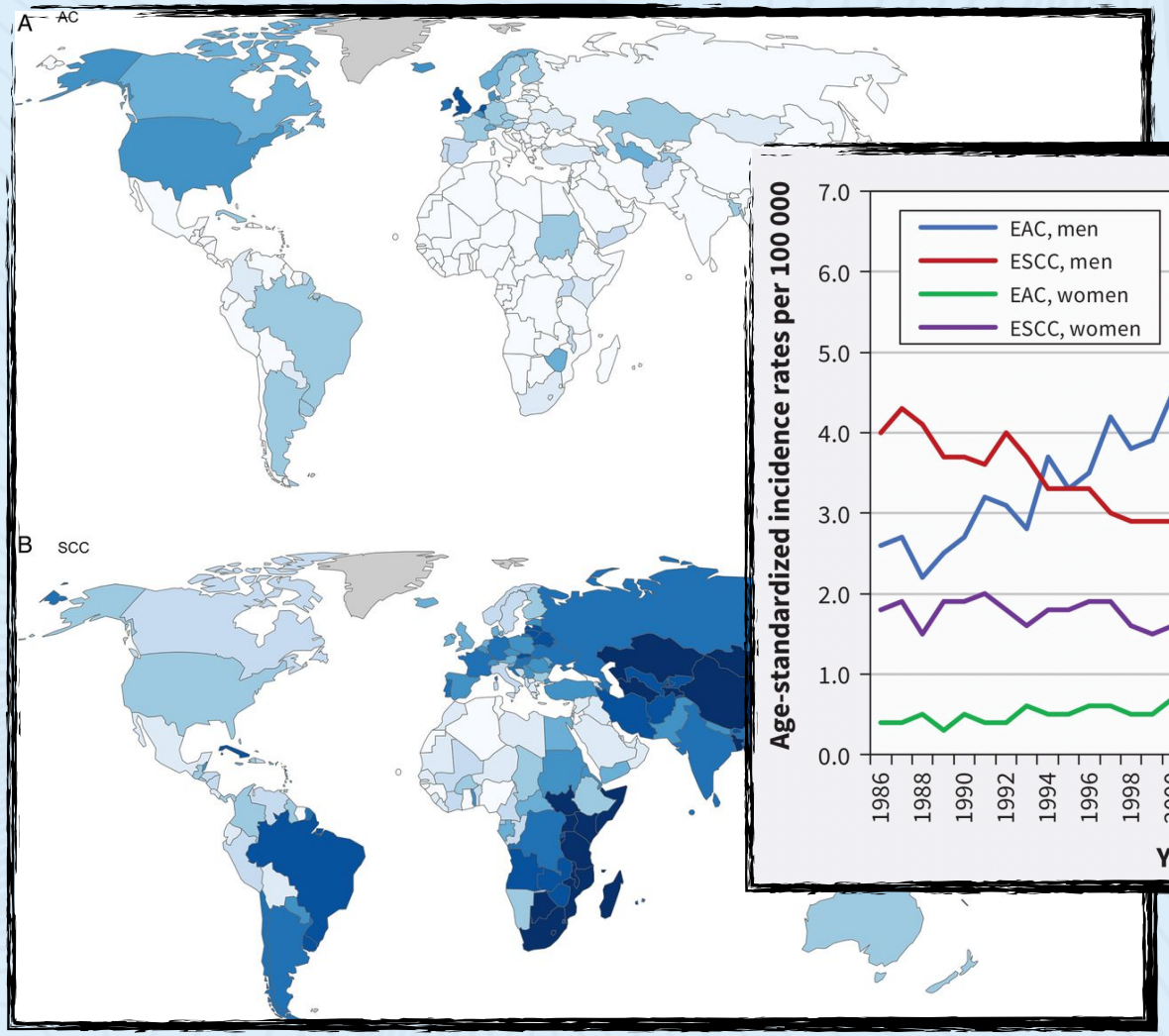
CHIRURGIE DIGESTIVE HAUTE ET INCLUSION

Stratégies néoadjuvantes dans la prise en charge du cancer de l'œsophage

- Jonathan Cools-Lartigue MD PhD
- Professeur adjoint de chirurgie
- Département de chirurgie thoracique, Hôpital Générale de Montreal

DIVULGATION
DES CONFLITS D'INTÉRÊTS POTENTIELS

TYPE D'AFFILIATION	COMPAGNIES	PÉRIODE
Aucune	Aucune	Aucune


A
AC
B
SCC

Age-standardized incidence rates per 100 000
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
EAC, men
ESCC, men
EAC, women
ESCC, women
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
Year

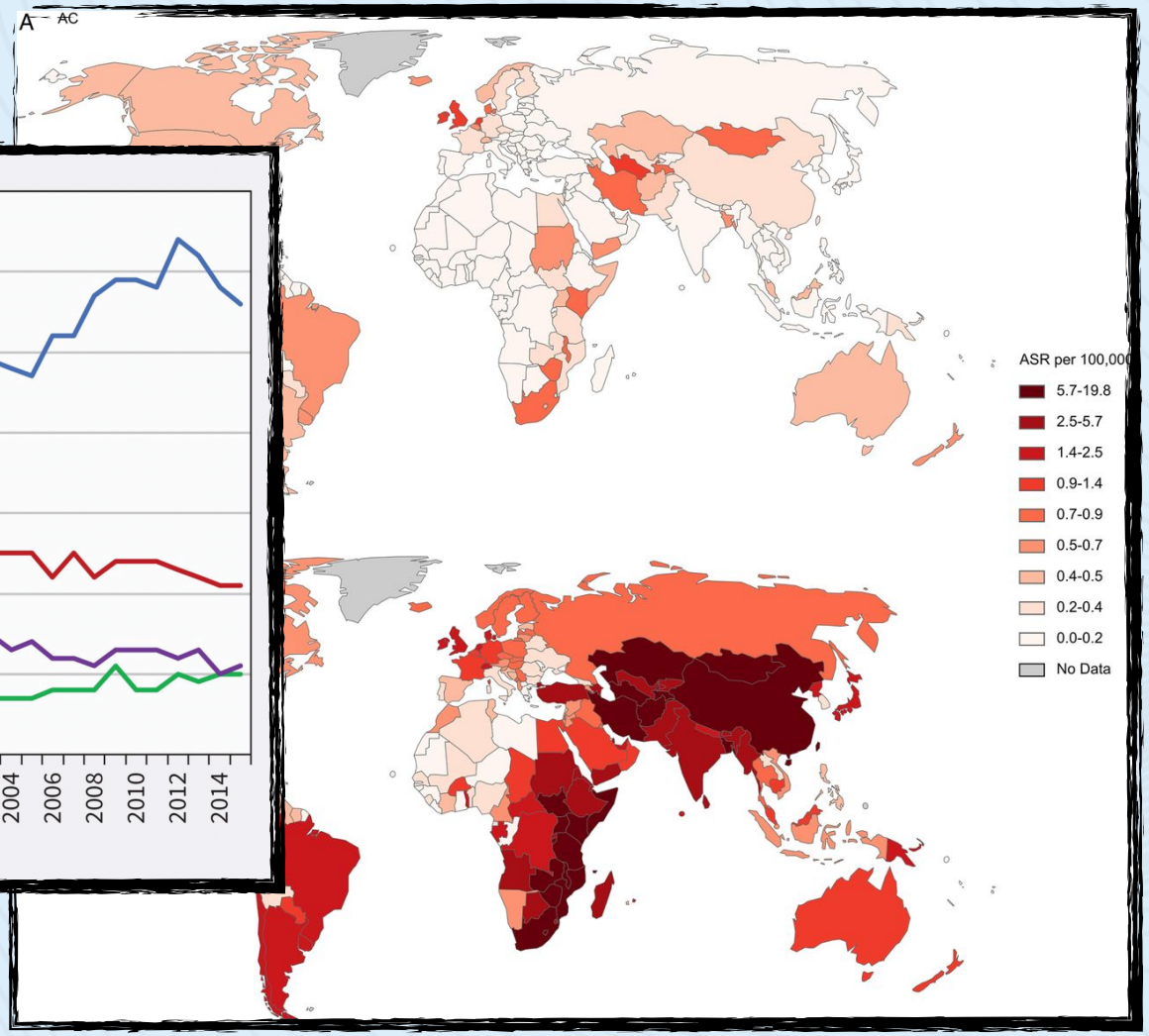

A
AC
ASR per 100,000
5.7-19.8
2.5-5.7
1.4-2.5
0.9-1.4
0.7-0.9
0.5-0.7
0.4-0.5
0.2-0.4
0.0-0.2
No Data

TABLE 2
Clinical and Histopathologic Factors and Patterns of Recurrence

		Pattern of recurrence			
		Local (n = 53)	Regional (n = 90)	Distant (n = 87)	Total (n = 230)
Mean (SD) age at presentation in years		58.1 (10.5)	56.7 (10.2)	56.4 (7.8)	57.6 (9.4)
Gender ratio	(M:F)	6.6:1	10.3:1	16.4:1	10.5:1
Location of the main tumor	Upper third	6	17	11	34
	Middle third	36	53	47	136
	Lower third	11	20	29	60
Weight loss	<10%	40	74	68	182
	≥10%	13	16	19	48
Dysphagia	Yes	50	72	70	192
	No	3	18	17	38
Neoadjuvant chemoradiotherapy	Yes	28	47	40	115
	No	25	43	47	115
Anastomotic site	Cervical	17	29	23	69
	Intrathoracic	36	61	64	161
Anastomotic leak	Yes	5	8	7	20
	No	48	82	80	210
Respiratory complication	Yes	13	19	15	47
	No	[illegible]	[illegible]	[illegible]	[illegible]
Histologic subtype	SCC	43	80	63	186
	Adenocarcinoma	10	10	24	44
Differentiation	Well	38	69	63	170
	Moderately or poorly	15	21	24	60
Depth of invasion	pT1	10	17	16	43
	pT2	10	15	16	41
	pT3	33	57	55	145
	pT4	0	1	0	1
Lymph node metastasis	pN0	20	40	31	91
	pN1	33	50	56	139
Mean (SD) number of lymph nodes with positive metastasis		2.2 (3.3)	1.7 (2.2)	2.5 (3.4)	2.1 (3.0)
pTNM stage	I	7	13	10	30
	IIa	13	25	21	59
	IIb	9	10	15	34
	III	24	42	41	107

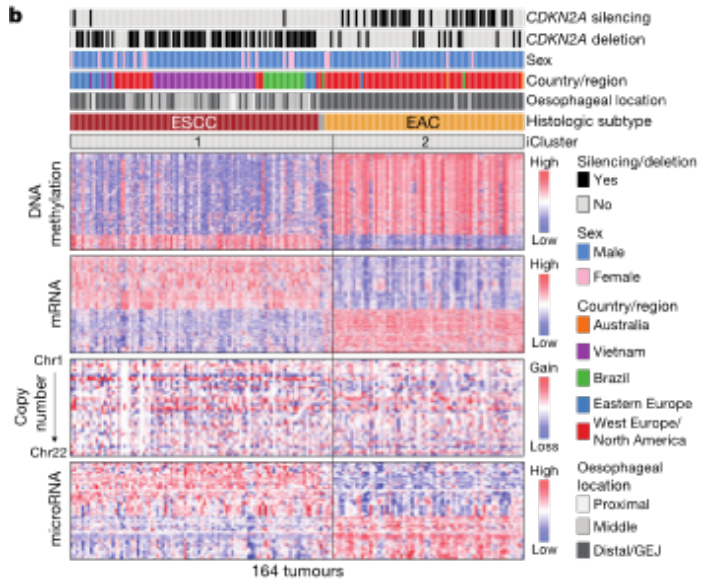
	Locoregional recurrence	Distant Recurrence
ESCC	66 %	34 %
EADC	45 %	55 %

L'adénocarcinome œsophagien et le carcinome épidermoïde sont des maladies DIFFÉRENTES

Integrated genomic characterization of oesophageal carcinoma

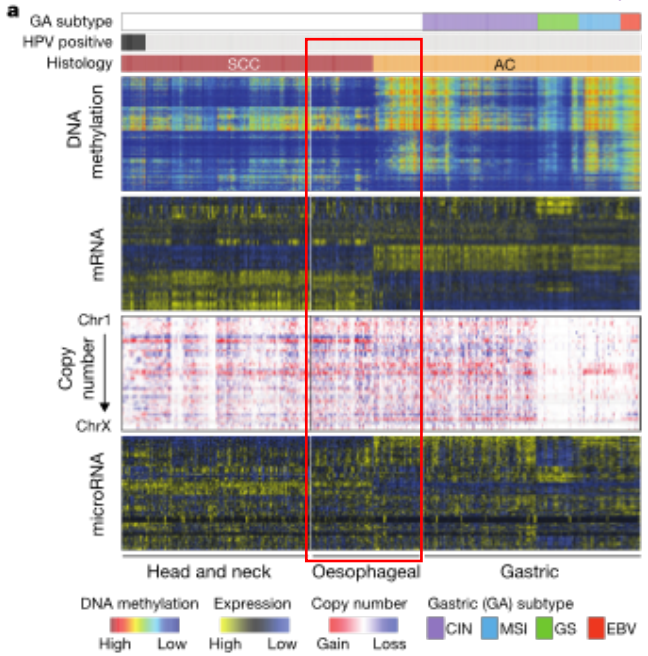
The Cancer Genome Atlas Research Network*

Perfect Separation of EAC and ESCC



ESCC = Head and Neck Cancer

EAC= Gastric Adenocarcinoma(*CIN*)



Oesophageal squamous cell carcinomas resembled squamous carcinomas of other organs more than they did oesophageal adenocarcinomas…….
Oesophageal adenocarcinomas strongly resembled the chromosomally unstable variant of gastric adenocarcinoma, *suggesting that these cancers could be considered a single disease entity [and treated similarly].*

Adam Bass et al, Nature Jan 2017

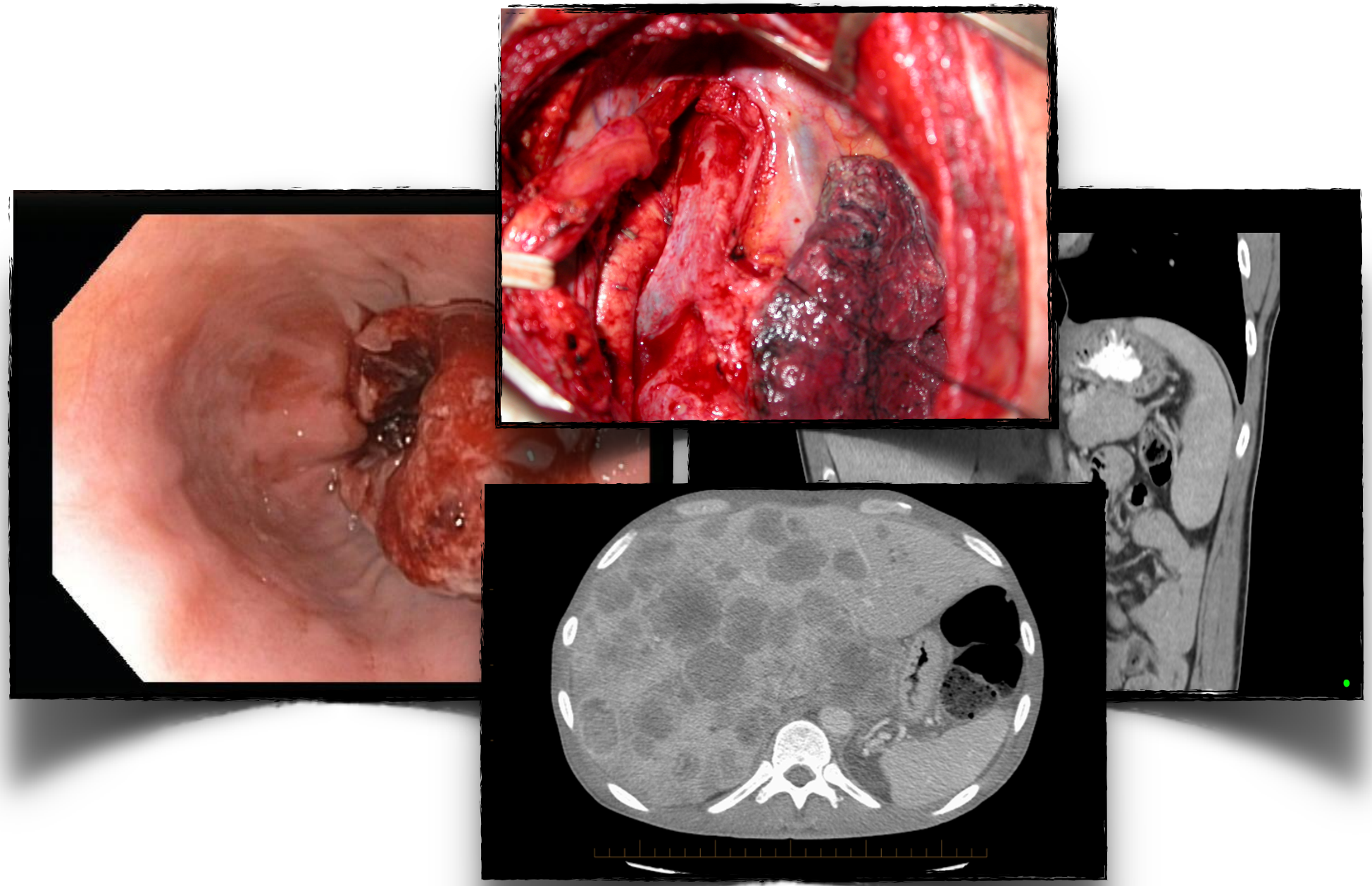


Table 2 Randomized trials comparing chemoradiotherapy and surgery versus surgery alone in the treatment of esophageal cancer patients; $p<0.05$. Adapted from Sjoquist et al.[10]

Trial	*N*	Histology	Chemotherapy	RT (Gy)	pCR (%)	R0 (%)	Survival
Mariette[33]		SCC, ADC	Cisplatin, 5FU	45	33.3		3 years (%)
CT-RT-Sx	98					93.8	47.5
Sx	97					92.1	53

Table 3 Randomized trials comparing chemotherapy and surgery versus surgery alone in the treatment of esophageal cancer patients. Adapted from Palta et al.[55], *$p<0.05$

Trial	*N*	Histology	Chemotherapy	R0 (%)	Survival
MRC[23]		SCC, ADC	Cisplatin, 5FU		Median (months)
CT	400			60	17
Sx	402			54	13
RTOG 8911[22]		SCC, ADC	Cisplatin, 5FU		Median (months)
CT	213			63	14.9
Sx	227			59	16.1
MAGIC[24]		ADC	Epirubicin, Cisplatin, 5FU	NA	5 years (%)
CT	250				36*
Sx	253				23
FFCD[25]		ADC	Cisplatin, 5FU		5 years (%)
CT	113			84	38*
Sx	111			74	24

CT chemotherapy, *RT* radiotherapy, *Sx* surgery, *SCC* squamous cell carcinoma, *ADC* adenocarcinoma, *5FU* 5 fluorouracil

CROSS trial: Conception de l'étude

Un essai randomisé, multicentrique et contrôlé de phase 3

Key eligibility criteria

- Histologically confirmed, potentially curable squamous cell carcinoma, adenocarcinoma or large-cell undifferentiated carcinoma of the esophagus or GEJ
- Length and width of the tumor could not exceed 8 cm and 5 cm, respectively
- T1N1 or T2–3N0–1 and M0[a]
- WHO PS ≤2
- Loss of ≤10% body weight
- Adequate hematologic, renal, hepatic and pulmonary function, as well as no history of other cancer or previous radiotherapy or chemotherapy

R
1:1
N=368

n=180

CRT
Carboplatin + paclitaxel
on Days 1, 8, 15, 22 and 29 for 5 weeks +
41.4 Gy (1.8 Gy/23fx with
5 fx/week on Day 1)[b]

Surgery[c]

n=188

Surgery[d]

Stratification factors

- Histologic tumor type
- Treatment center
- Lymph-node stage
- WHO PS

Endpoints

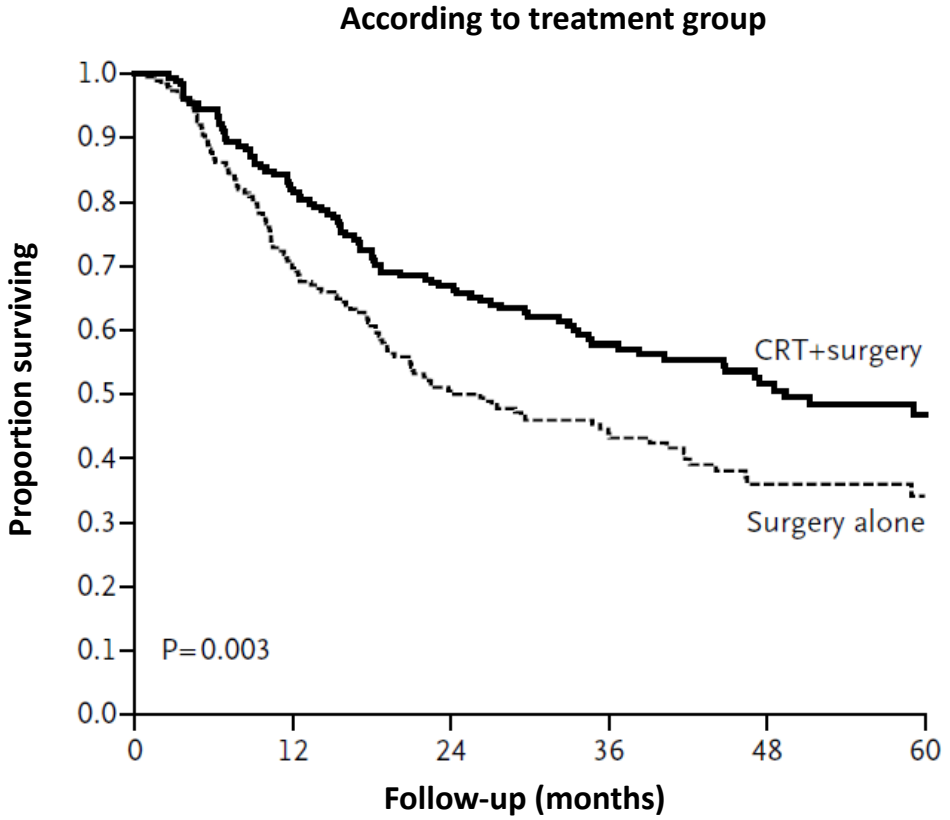
- **Primary:** OS
- **Secondary:** Safety in CRT arm, assessment of perioperation, pathological assessment, DFS

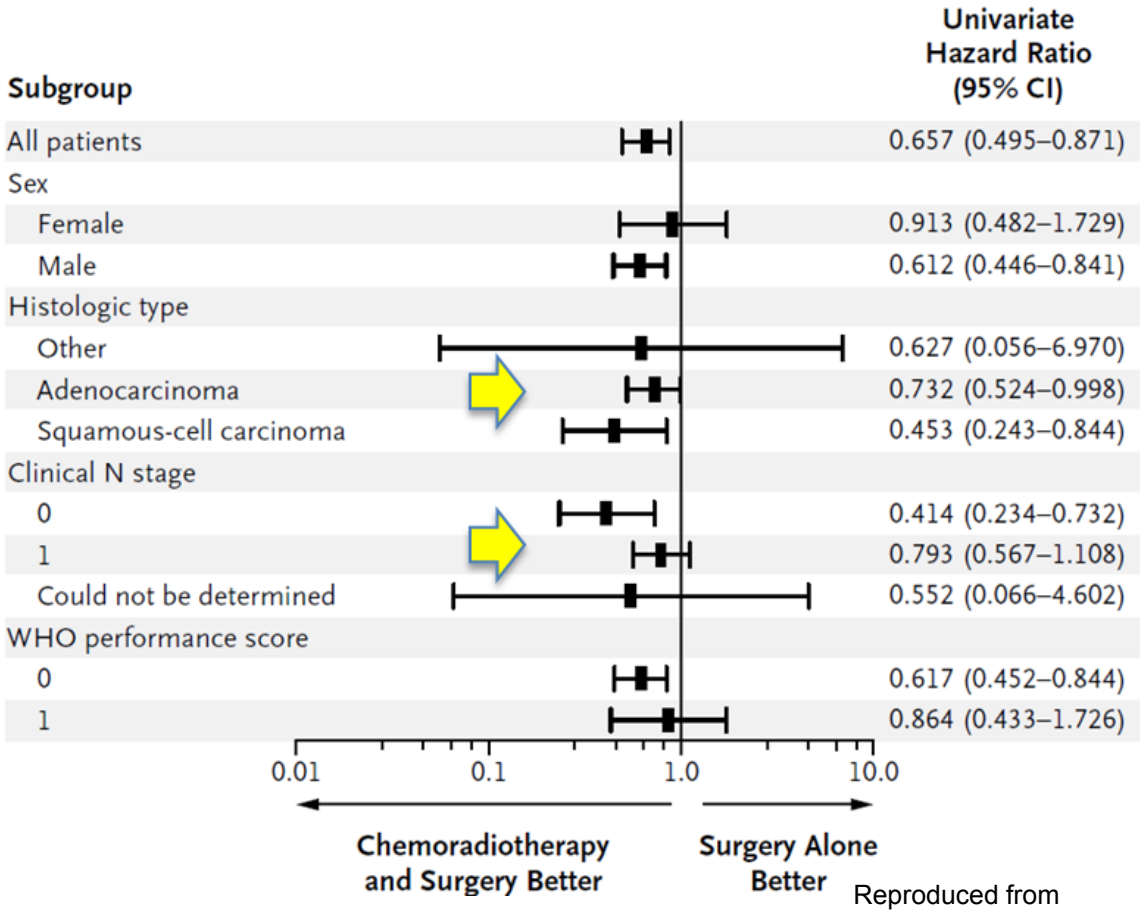
[a]According to UICC; [b]All patients were treated by means of external-beam radiation; [c]Patients underwent surgery as soon as possible after completion of CRT (preferably within 4–6 weeks); [d]Patients were treated as soon as possible after randomization.
CRT, chemoradiotherapy; DFS, disease-free survival; fx, fractions; GEJ, gastroesophageal junction; Gy, Gray; M, metastasis; N, node; OS, overall survival; R, randomization; T, tumor; UICC, International Union against Cancer tumor–node–metastasis classification; WHO PS, World Health Organization performance score.

1. van Hagen P et al. *N Engl J Med* 2012;366:2074–2084.

CROSS trial: OS

Patient demographic:
SCC, 23%; AC, 75%
ES tumor, 73%; GEJ, 24%; cN1, 64%





Reproduced from
van Hagen P et al. 2012.

cN1, clinical Node stage 1; CI, confidence interval; CRT, chemoradiotherapy; ES, esophagus tumor; GEJ, gastroesophageal junction; OS, overall survival; WHO, World Health Organization.
van Hagen P et al. *N Engl J Med* 2012;366:2074–2084.

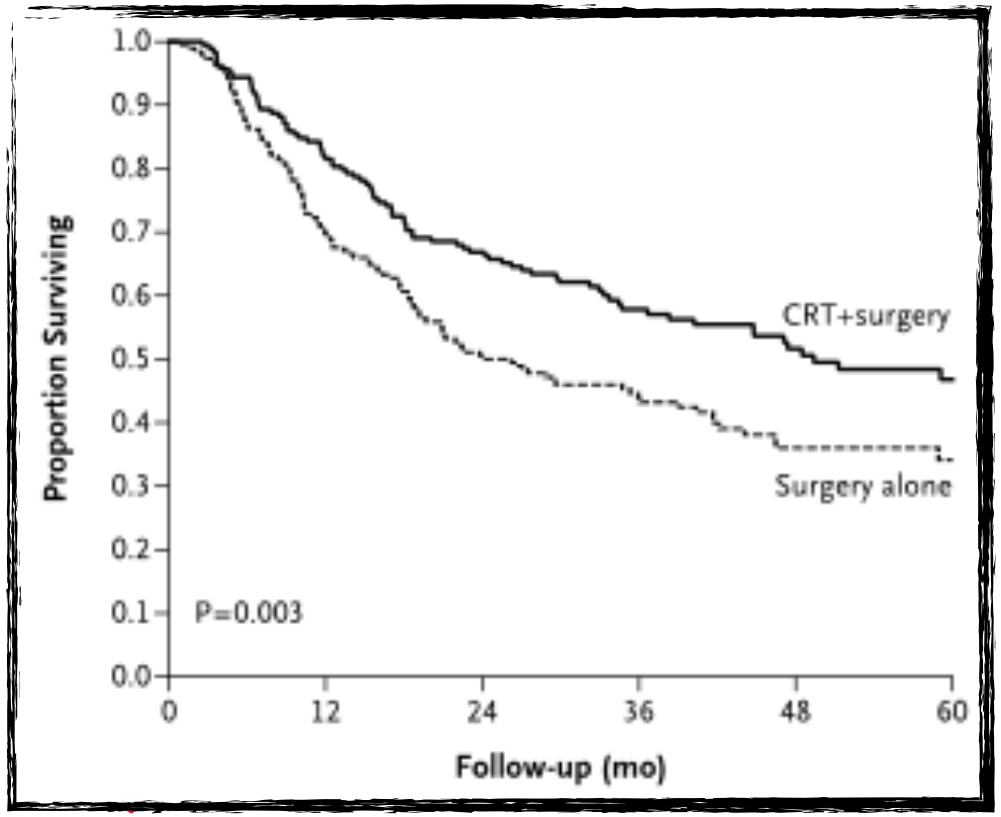
Esophageal Adenocarcinoma and Squamous Cell Carcinoma are DIFFERENT Diseases

CROSS Trial

Response to Radiotherapy

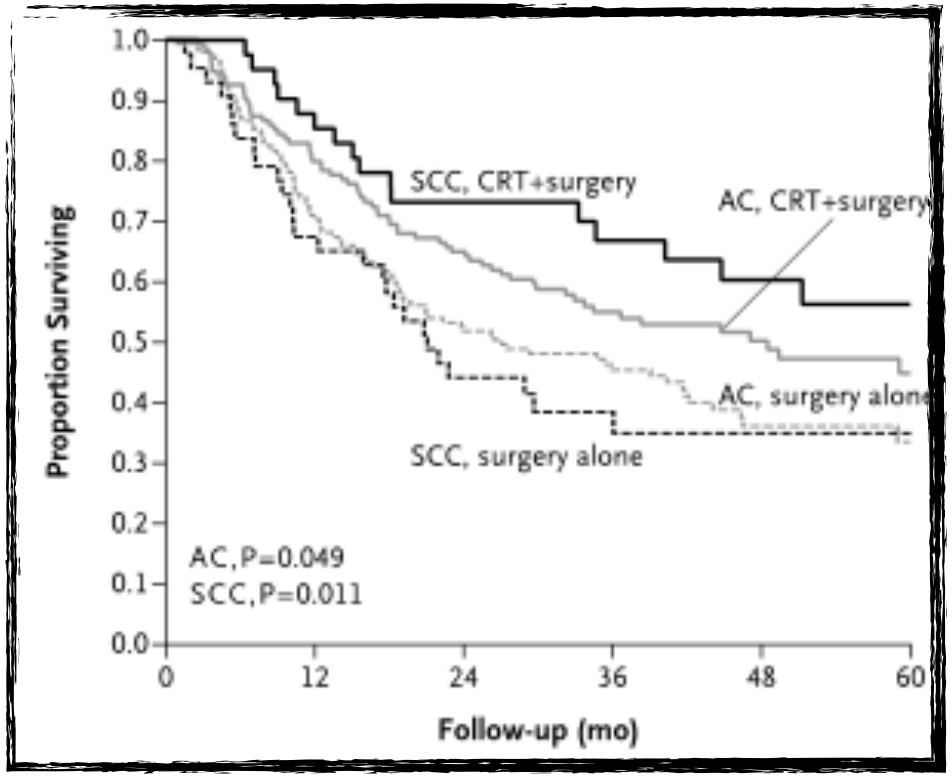
van Hagen, NEJM 2012

- SCC – HR 0.42 (95%CI 0.22-0.78) P=0.007
- ADC – HR 0.74 (95%CI 0.53-1.02) p=0.07



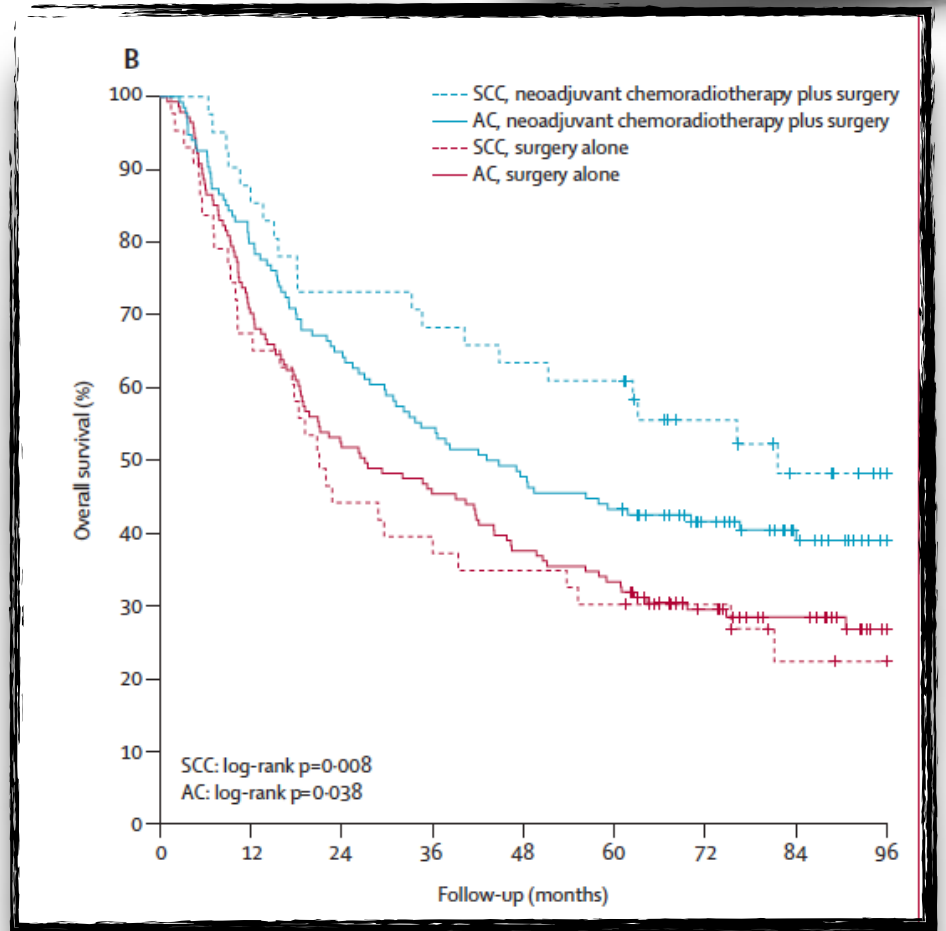
Pathologic Complete Response

- Overall = 29%
- SCC = 49%
- ADC = 23%



Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

Joel Shapiro, J Jan B van Lanschot, Maarten C C M Hulshof, Pieter van Hagen, Mark I van Berge Henegouwen, Bas P L Wijnhoven, Hanneke W M van Laarhoven, Grard A P Nieuwenhuijzen, Geke A P Hospers, Johannes J Bonenkamp, Miguel A Cuesta, Reinoud J B Blaisse, Olivier R C Busch, Fiebo J W ten Kate, Geert-Jan M Creemers, Cornelis J A Punt, John Th M Plukker, Henk M W Verheul, Ernst J Spillenaar Bilgen, Herman van Dekken, Maurice J C van der Sangen, Tom Rozema, Katharina Biermann, Jannet C Beukema, Anna H M Piet, Caroline M van Rij, Janny G Reinders, Hugo W Tilanus, Ewout W Steyerberg, Ate van der Gaast, for the CROSS study group



- SCC – aHR 0.46 (95%CI 0.26-0.79) P=0.005
- ADC – aHR 0.75 (95%CI 0.56-1.01) p=0.059

	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)	HR (95% CI)	p value
Locoregional progression	39 (22%)	72 (38%)	0·45 (0·30–0·66)	<0·0001
Distant progression	70 (39%)	90 (48%)	0·63 (0·46–0·87)	0·0040
Overall progression	87 (49%)	124 (66%)	0·58 (0·44–0·76)	<0·0001

Data are n (%), unless otherwise indicated. Comparison between treatment groups was based on univariable cause-specific Cox regression modelling of progression-free intervals. Deaths from non-disease-related causes were censored. Overall progression was defined as either locoregional progression or distant progression. Patients with both locoregional disease progression and distant disease progression (22 patients in the neoadjuvant chemoradiotherapy plus surgery group and 38 in the surgery alone group) were counted in both locoregional progression and distant progression categories. HR=hazard ratio.

***Table* 3: Patients with locoregional or distant progression in the two treatment groups**

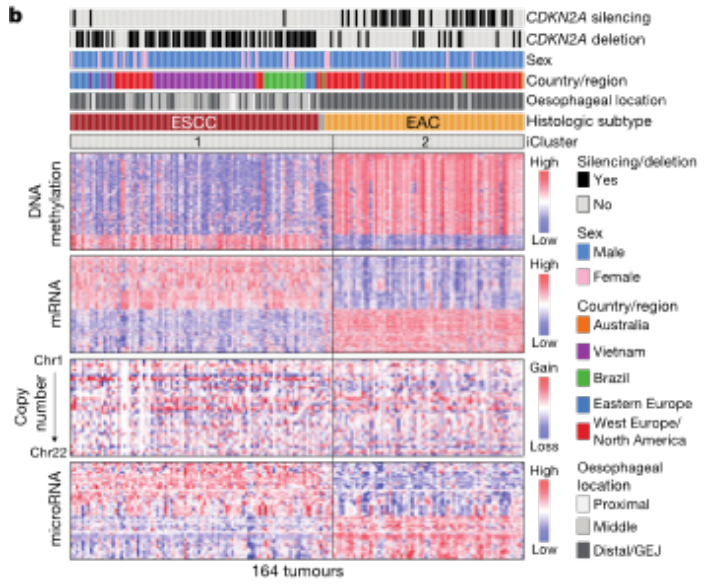
Lancet Oncology 2016

L'adénocarcinome œsophagien et le carcinome épidermoïde sont des maladies DIFFÉRENTES

Integrated genomic characterization of oesophageal carcinoma

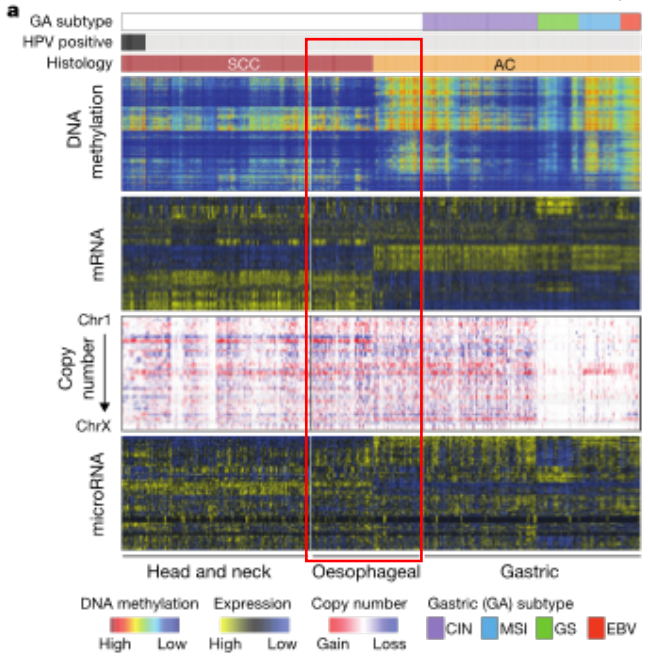
The Cancer Genome Atlas Research Network*

Perfect Separation of EAC and ESCC



ESCC = Head and Neck Cancer

EAC= Gastric Adenocarcinoma(*CIN*)



Oesophageal squamous cell carcinomas resembled squamous carcinomas of other organs more than they did oesophageal adenocarcinomas…….
Oesophageal adenocarcinomas strongly resembled the chromosomally unstable variant of gastric adenocarcinoma, *suggesting that these cancers could be considered a single disease entity [and treated similarly].*

Adam Bass et al, Nature Jan 2017

Perioperative chemotherapy for gastric and GEJ adenocarcinoma

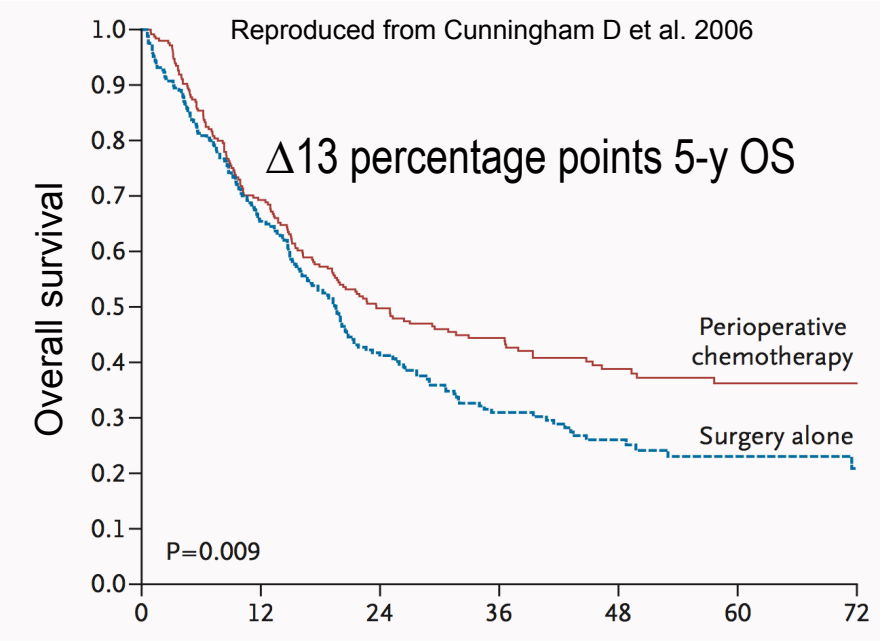
Trial	Comparison	N	Survival rate, %	HR for death (95% CI)	P value
MAGIC[1]	ECF vs surgery alone	503	5y: 36 vs 23	0.75 (0.60–0.93)	p=0.009
FFCD[2]	CF vs surgery alone	224	5y: 38 vs 24	0.69 (0.50–0.95)	p=0.02
FLOT4-AIO[3]	FLOT vs ECF/ECX	716	5y: 45 vs 36	0.77 (0.63–0.94)	p=0.012

CF, cisplatin fluorouracil; CI, confidence interval; ECF, epirubicin, cisplatin and fluorouracil; ECX, epirubicin, cisplatin and capecitabine; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; y, years.

1. Cunningham D et al. *N Engl J Med* 2006;355:11–20; 2. Ychou M et al. *J Clin Oncol* 2011;29:1715–1721; 3. Al-Batran SE et al. *Lancet* 2019;393:1948–1957.

Perioperative chemotherapy highly effective in GEJ adenocarcinoma

MAGIC[1], N=503

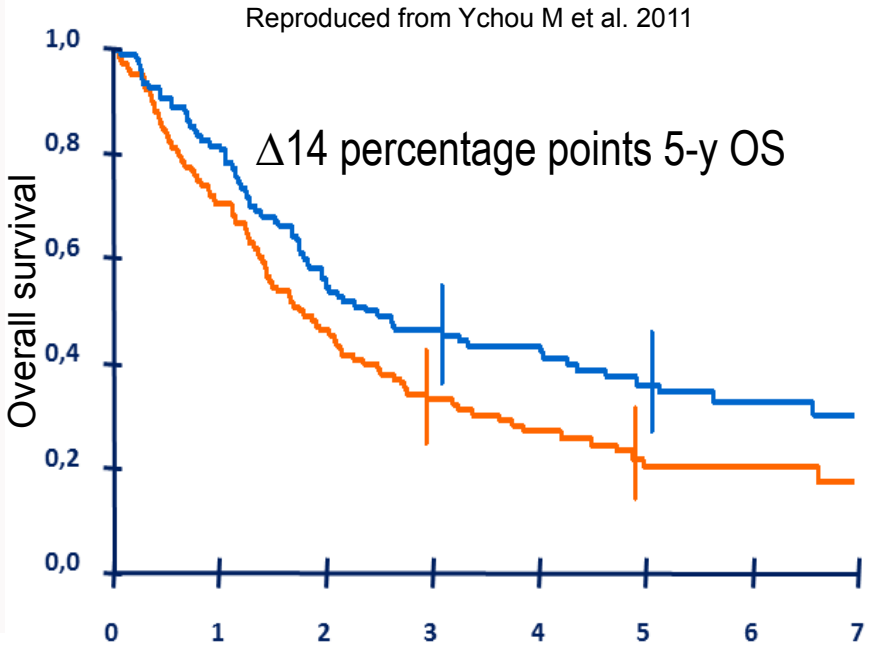


ECF vs surgery alone

HR (overall population) = 0.75

HR (GEJ subgroup) ~0.49[1]

FFCD/ACCORD[2], N=224

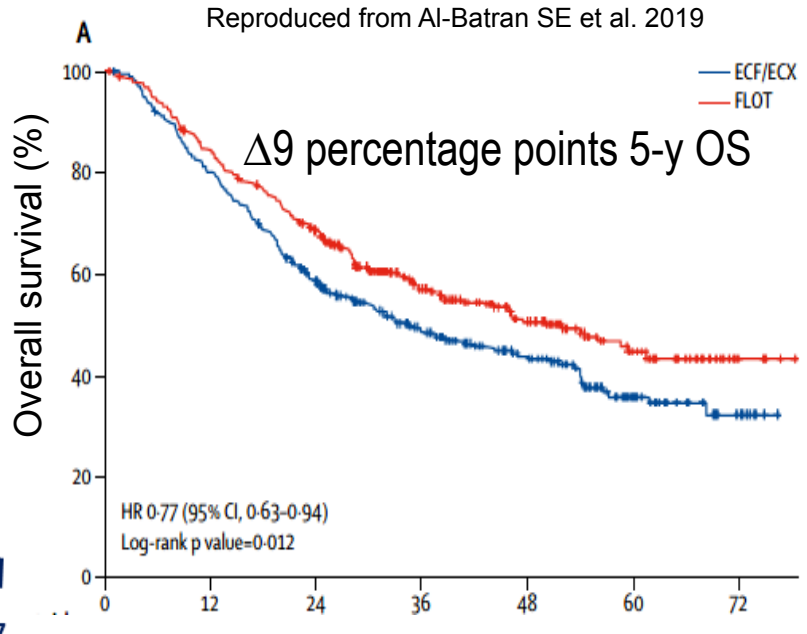


CF vs surgery alone

HR (overall population) = 0.69

HR GEJ subgroup = 0.57[4]

FLOT4-AIO[3], N=716



FLOT vs periop. ECF

HR (overall population) =0.77

HR GEJ subgroup = 0.76[3]

HR Barrett subgroup = 0.62[5]

CF, cisplatin and fluorouracil; ECF, epirubicin, cisplatin, and fluorouracil; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; periop., perioperative; y, years.

1.Cunningham D et al. *N Engl J Med* 2006;355:11–20; 2. Ychou M et al. *J Clin Oncol* 2011;29:1715–1721; 3. Al-Batran SE et al. *Lancet* 2019;393:1948–1957;
4. Sehdev A and Catenacci DVT. *J Hematol Oncol* 2013;6:66;
5. ESMO. 2017. Available at: https://www.esmo.org/meetings/past-meetings/esmo-2017-congress/Press-Media/Press-Releases/Flot4-AIO-Esophagogastric-Cancer-Al-Batran-Ducreux Accessed 25 March 2022;

FLOT4-AIO: Conception de l'étude

Un essai randomisé, multicentrique et contrôlé de phase 2/3

Key eligibility criteria

Gastric cancer or adenocarcinoma of the GEJ type I–III
Medically and technically operable
cT2-4 and/or N+,M0

R
1:1
N=716

n=360

Docetaxel 50 mg/m², D1; oxaliplatin 85 mg/m², D1; leucovorin 200 mg/m², D1; 5-fluorouracil 2600 mg/m², D1; IV every 2 weeks[a,b]

n=356

Epirubicin 50 mg/m², D1; cisplatin 60 mg/m², D1; 5-fluorouracil 200 mg/m² (or capecitabine 1250 mg/m² PO divided into two doses D1–D21), IV every 3 weeks[b,c]

Patient demographic

- 55% GEJ
- 44% gastric
- 81% of patients cT3/4
- 80% of patients cN+

Endpoints

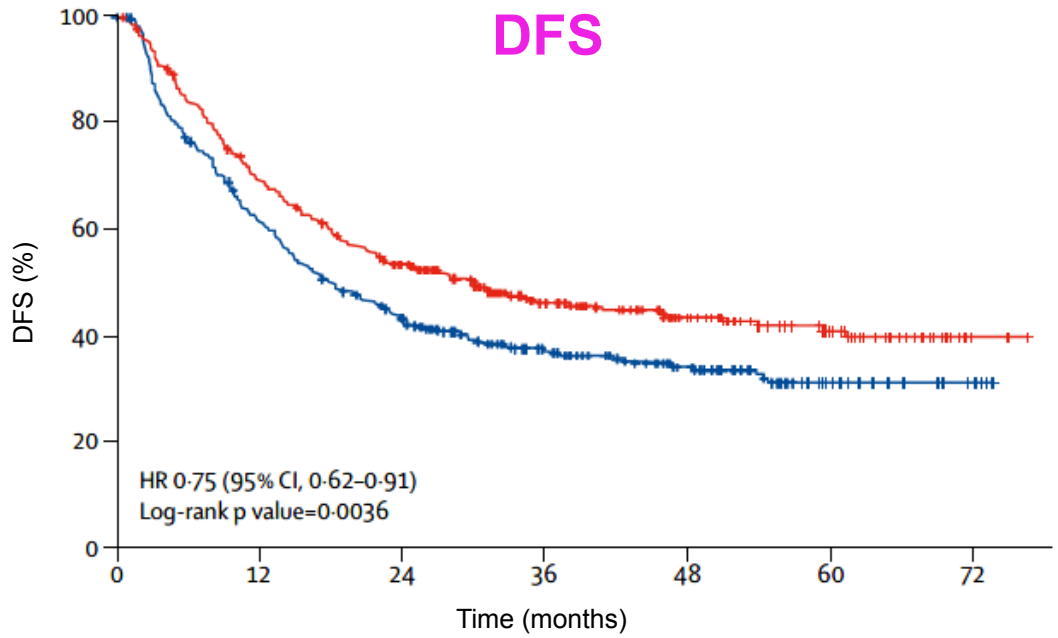
- **Primary:** mOS (HR 0.76; 2-sided log rank test a 5% significance)
- **Secondary:** Histopathological regression rate, DFS, correlation of pCR and DFS, perioperative morbidity and mortality, resection rate

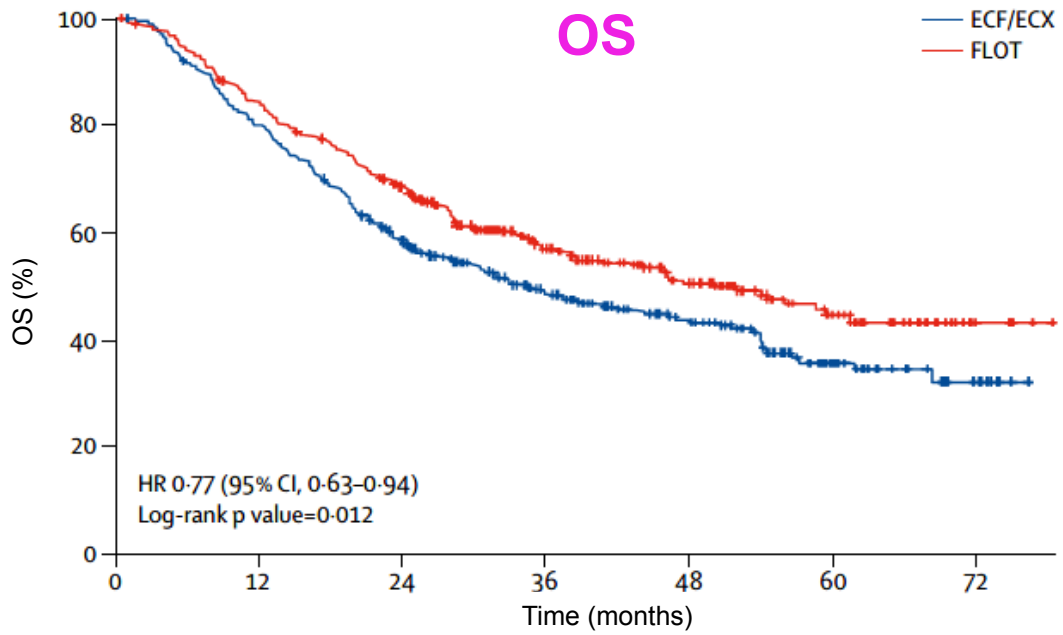
[a]ECF/ECX was administered for three preoperative cycles followed by three postoperative cycles; [b]Surgery was scheduled for 4 weeks after the last dose of preoperative chemotherapy;
[c]FLOT was administered for four preoperative cycles followed by four postoperative cycles.
D, day; DFS, disease-free survival; ECF/ECX, epirubicin and cisplatin plus either fluorouracil or capecitabine; FLOT, fluorouracil plus leucovorin, oxaliplatin and docetaxel; GEJ, gastroesophageal junction; HR, hazard ratio; IV, intravenous; mOS, median overall survival; N, node; pCR, pathological complete response; PO, orally; R, randomization; T, tumor.

1. Al-Batran SE et al. Lancet 2019;393:1948–1957; 2. ClinicalTrials.gov. NCT01216644. https://clinicaltrials.gov/ct2/show/NCT01216644. Accessed 22 March 2022.

FLOT4 AIO: FLOT vs MAGIC

- R0 resection rate with ECF/ECX vs FLOT: 78% vs 85% (p=0.0162)
- pT1 tumors in patients with ECF/ECX vs FLOT: 15% vs 25% (p=0.0008)





5-year OS-rate with FLOT vs ECF/ECX: 45% vs 36%
Median OS with FLOT vs ECF/ECX: 50 months vs 35 months

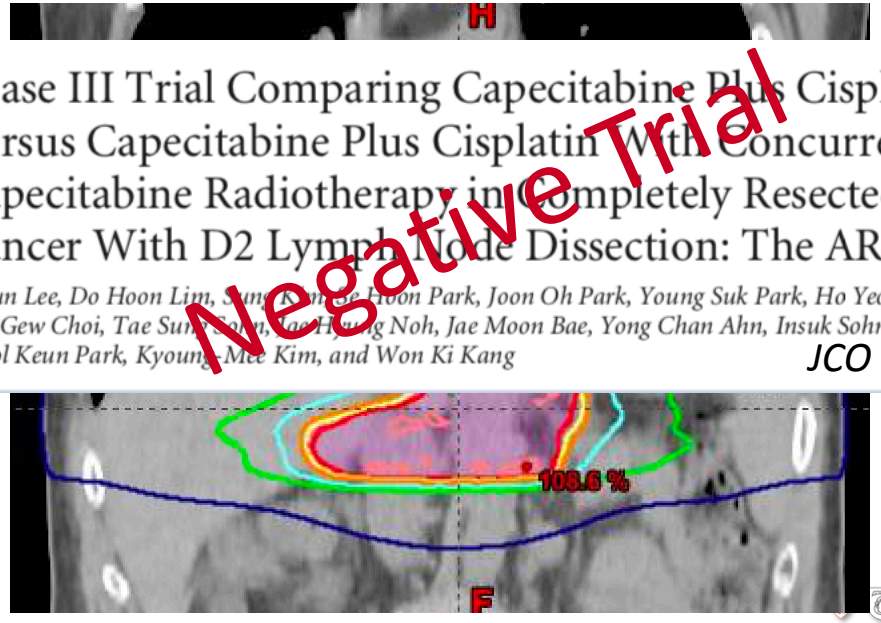
Reproduced from Al-Batran. 2019.

CI , confidence interval; DFS, disease-free survival; ECF, epirubicin, cisplatin, and fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; OS, overall survival; R0, no gross or microscopic tumor remains; T, tumor.
Al-Batran SE et al. *Lancet* 2019;393:1948–1957.

La chirurgie fait la différence

Extrapolons à partir de la littérature sur le cancer gastrique

Adjuvant Chemoradiotherapy RTOG Intergroup 0116



FU/LEU x 1 → XRT45Gy/25 +FU/LEU → FU/LEU x 2

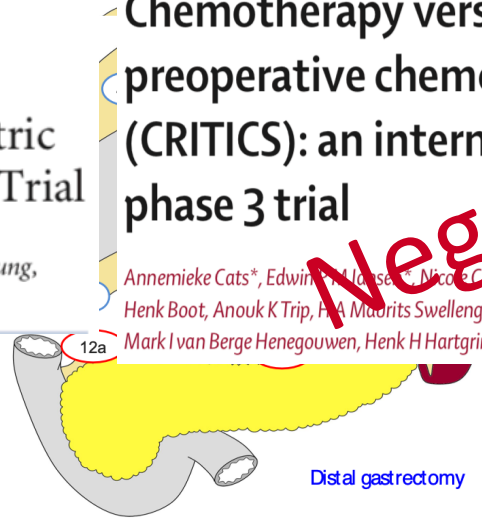
MacDonald NEJM 2001

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, Joo Ho Lee, Jae Ho Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang

JCO 2012

Negative Trial



McGILL UNIVERSITY DEPARTMENT OF SURGERY

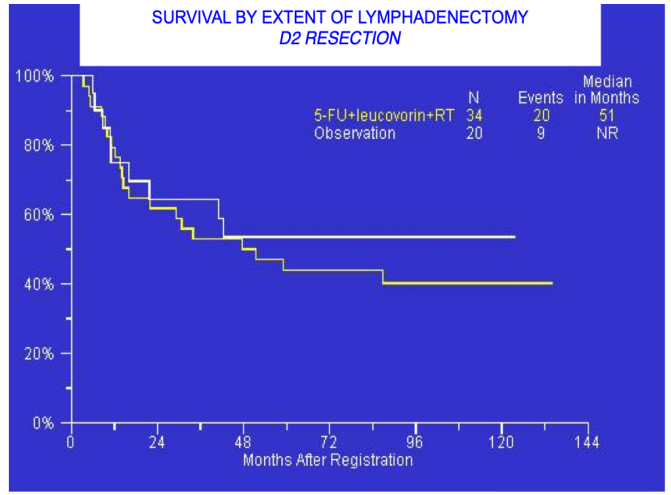
D0

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

Lancet Oncology 2018

Annemieke Cats, Edwin P M Jansen*, Nicole C T van Grieken, Karolina Sikorska, Pehr Lind, Marianne Nordsmark, Elma Meershoek-Klein Kranenbarg, Henk Boot, Anouk K Trip, H A Maurits Swellengrebel, Hanneke W M van Laarhoven, Hein Putter, Johanna W van Sandick, Mark I van Berge Henegouwen, Henk H Hartgrink, Harm van Tinteren, Cornelis J H van de Velde†, Marcel Verheij†, for the CRITICS investigators‡*

Negative Trial

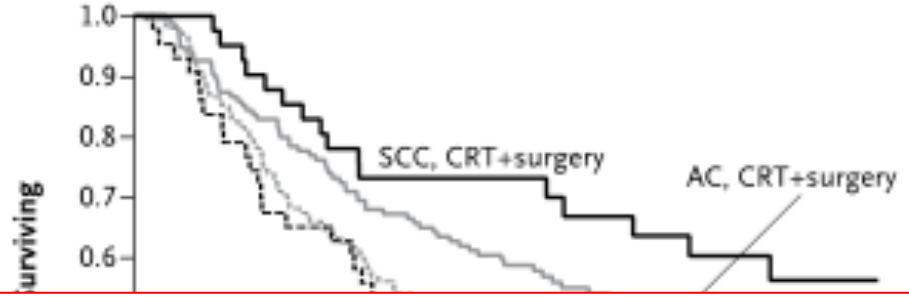


D2

La radiothérapie compense la réduction de la résection ganglionnaire

CONCLUSIONS

In conclusion, compared to surgery alone, the addition of nCRT may reduce the need for TTE with extended lymphadenectomy to improve long-term survival in patients with subcarinal esophageal adenocarcinoma.



ng-term Survival in Esophageal
nts With or Without
noradiotherapy

† Mark I. van Berge Henegouwen, MD, PhD,‡
, MD, PhD,‡ Sjoerd M. Lagarde, MD, PhD,*‡
hof, MD, PhD,¶ Katharina Biermann, MD, PhD,||
Jan B. van Lanschot, MD, PhD*,
ROSS-study group

Ann Surg 2018

Radiation Is Not a Solution for Suboptimal Surgery. A Response to the Conclusions Drawn From the Impact of Surgical Approach on Long-term Survival in Esophageal Adenocarcinoma With or Without Neoadjuvant Chemoradiotherapy Study

Cools-Lartigue, Jonathan MD, PhD; Ferri, Lorenzo MD, PhD

Annals of Surgery: July 2019 - Volume 270 - Issue 1 - p e13–e14

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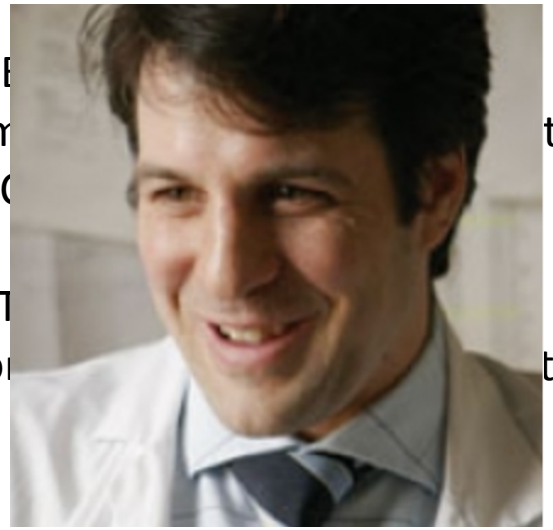
(HR 1.00, 95%



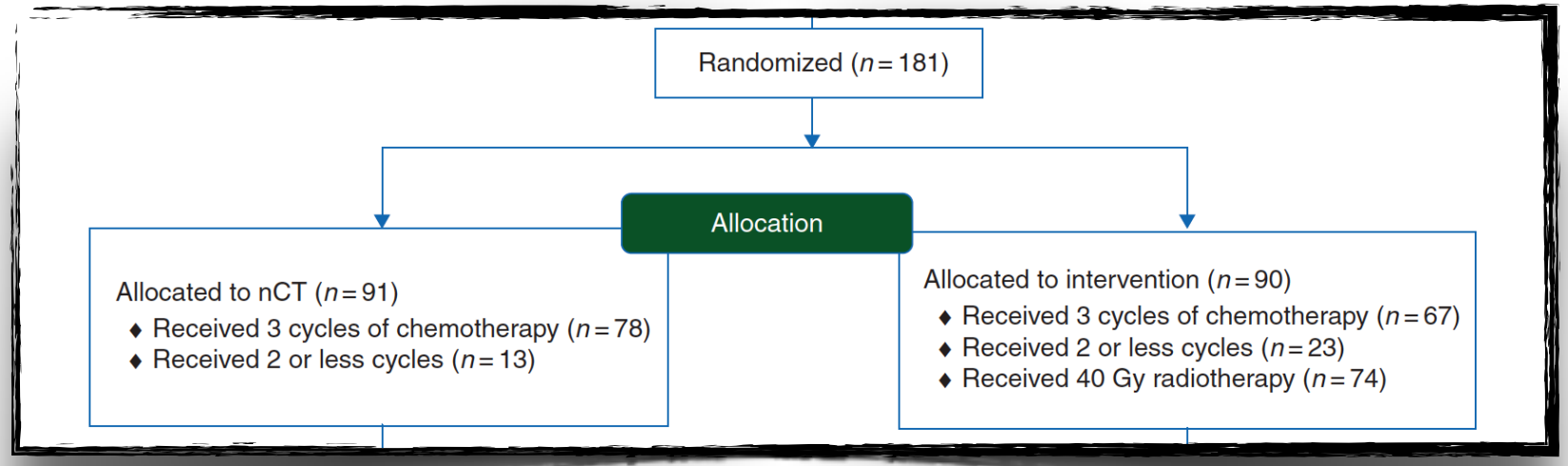
A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction

F. Klevebro[1*], G. Alexandersson von Döbeln[2], N. Wang[3], G. Johnsen[4], A.-B. Jacobsen[5], S. Friesland[2], I. Hatlevoll[6], N. I. Glenjen[7], P. Lind[8], J. A. Tsai[1], L. Lundell[1] & M. Nilsson[1]

Annals Oncology 2016

NEO-Res Trial

Randomized Phase II (pCR endpoint)
181 Pts – cT1N1, cT2-3N0-1
Mixed Histology
Squamous = 50 (27%)
ADC = 131 (73%)

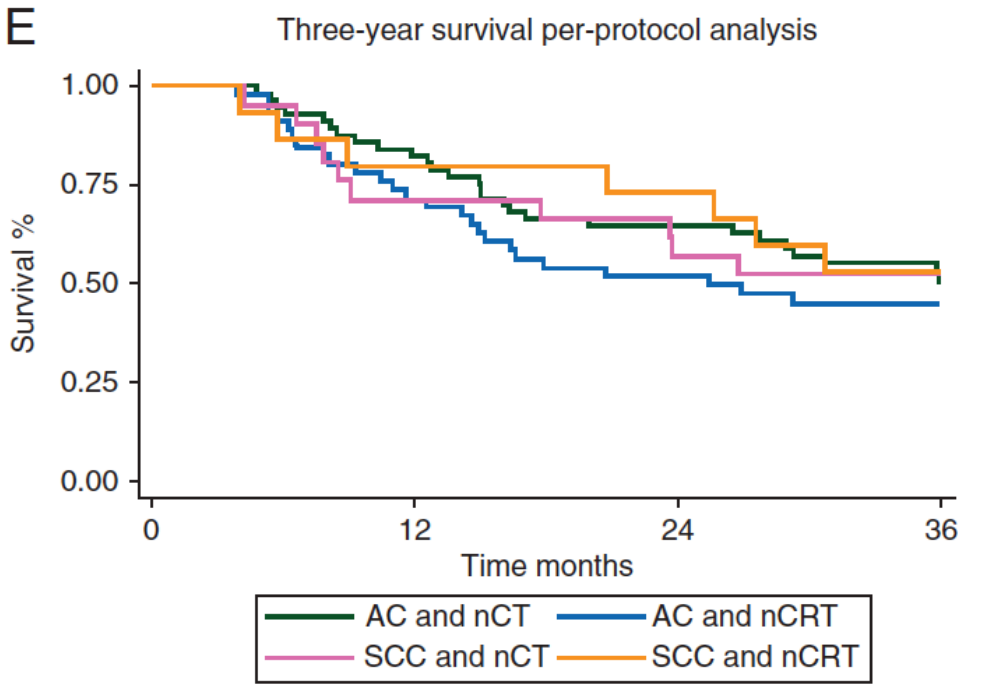


Cisplatin 75 mg/M2 day 1
5FU 1000 mg/M2 CIV day 1-5

RT 40Gy in 20
with Cycle 2-3

OS by HISTOLOGY

	nCT	nCTRT
pCR	9%	28%*
ADC	7%	22%*
SCC	16%	42%*
R0	74%	87%*
ADC	71%	89%*
SCC	76%	96%*
Local Recurrence	19%	16% NS
ADC	22%	16% NS
SCC	10%	17% NS



Number at risk

Follow up (months)	0	12	24	36
AC and nCT	66	54	39	26
AC and nCRT	65	46	39	22
SCC and nCT	25	17	14	10
SCC and nCRT	25	20	17	11

3 YR Survival

	nCT	nCTRT
	49%	47%
ADC	48%	43%
SCC	52%	56%

Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study

EXPÉRIENCE DU MONDE RÉEL

S. R. Markar[1†], B. J. Noordman[2†], H. Mackenzie[1], J. M. Findlay[3], P. R. Boshier[1], M. Ni[1], E. W. Steyerberg[4], A. van der Gaast[5], M. C. C. M. Hulshof[6], N. Maynard[3], M. I. van Berge Henegouwen[7], B. P. L. Wijnhoven[2], J. V. Reynolds[8], J. J. B. Van Lanschot[2] and G. B. Hanna[1*]

Ann Oncol 2017

10 European Centres with Established Prospective Registries

2001-2012

608 pt with Stage II/III tumours: 301 nCT and 307 nCRT

Propensity score matching and Cox regression analysis

ypT0: 27% vs 5% ; p < 0.001

ypN0 63% vs 32% ; p < 0.001:

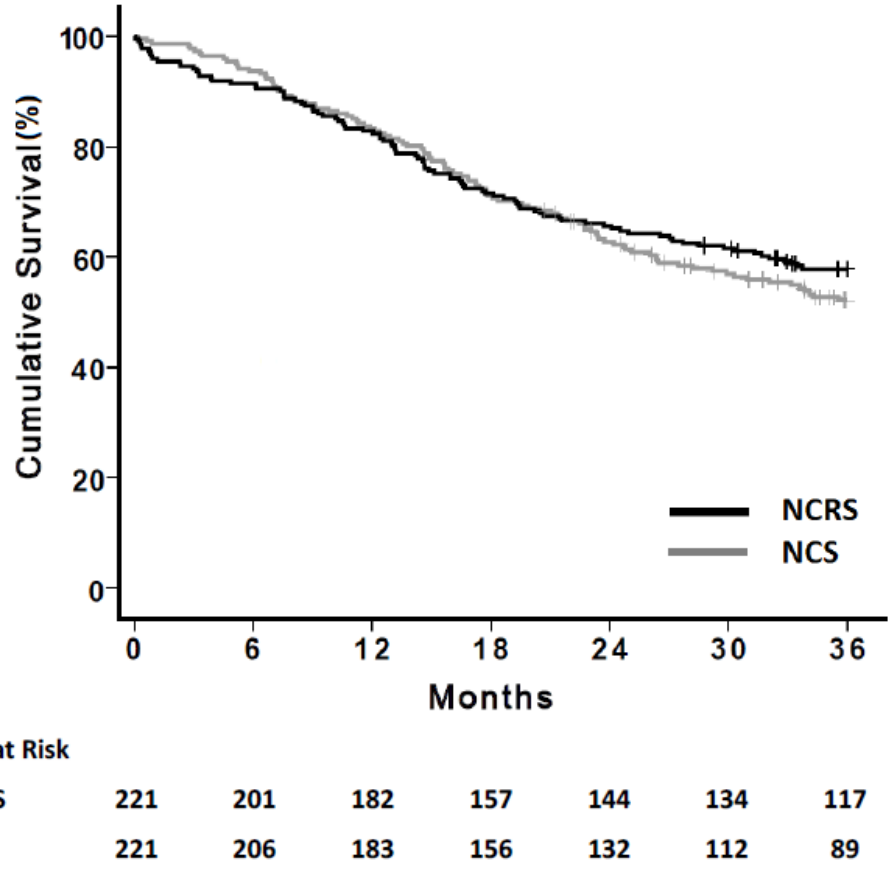
R1/R2 8% vs 22% ; p < 0.001

→ FAVOURING nCRT

3 year OS: 58% vs 53% p = 0.391

3 year DFS: 53% vs 49% p = 0.660

→ NO DIFFERENCE



Higher mean Lymph node harvest (27 vs 14) in nCT group, suggesting that surgical QA may be important, and demanding further research in both cohorts

Courtesy of John Reynolds, Trinity College Dublin

NEO-AEGIS

(NEOadjuvant trial in Adenocarcinoma of the Esophagus and esophago-Gastric junction International Study):
PRELIMINARY RESULTS OF PHASE III RCT OF CROSS VS PERI-OPERATIVE CHEMOTHERAPY(MODIFIED MAGIC OR FLOT PROTOCOL) (CTRIAL-IE 10-14) (NCT01726452)

John V. Reynolds
Academic Head of Surgery, Trinity College Dublin, Ireland
Cancer Trials Ireland and Trinity St. James's Cancer Institute

ASCO 2021

ADENOCARCINOMA
Esophageal and AEG I-III
cT2-3N0-3M0

R

EC(O)F(X) x 3 or FLOT x 4 → Surgery → EC(O)F(X) x 3 Or FLOT x 4 — Arm A

Neo CRT (CROSS) wCP-RT(41.4Gy)+Surgery — Arm B

Non-inferiority

[(n= 540) -powered as per first futility analysis (n=71 deaths) in December 2018]

Primary endpoint:
Overall survival

Secondary end points:
Disease free survival
Time to treatment failure
TRG
R0
Toxicity
Postoperative complications

Stopped for futility at 362

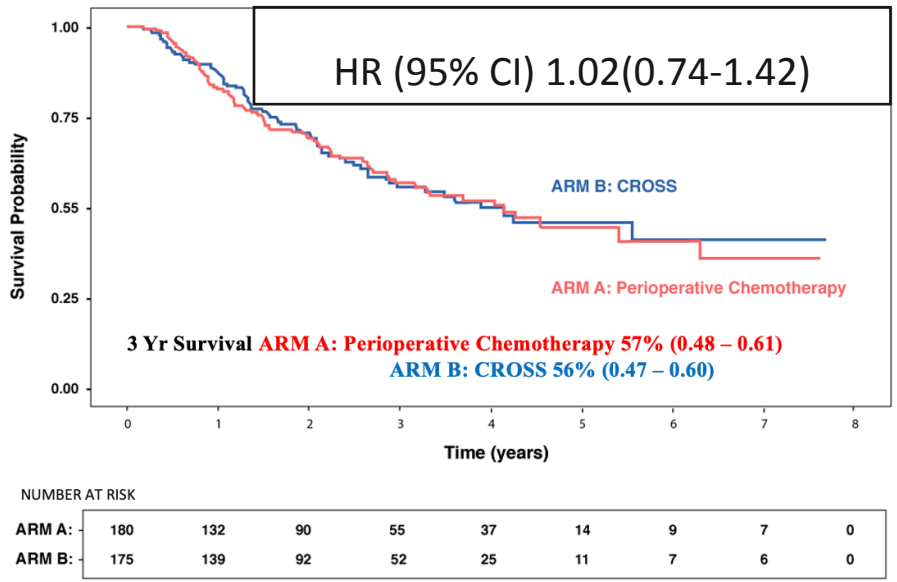
Results: Demographics and Surgical Approach

	ARM A (Chemo) N = 184	ARM B (CROSS) N = 178
Median (range) age	64 (35-83)	64 (45-81)
Male	91.8%	88.8%
MAGIC/FLOT	157/27	-
cT3	84%	84%
cN 1-3	60.3%	56%
Surgical Approach		
Transthoracic Esophagectomy	75%	80%
Transhiatal	1.2%	4.3%
Extended gastrectomy	5.8%	5.1%
MIE	18%	11.7%

Pathological Outcomes
ALL IN FAVOUR OF nCRT

ypN0 (p=0.004)
pCR (p=0.001)
R0 (p< 0.001)
TRG (p< 0.001)

Overall Survival



Courtesy of John Reynolds, Trinity College Dublin

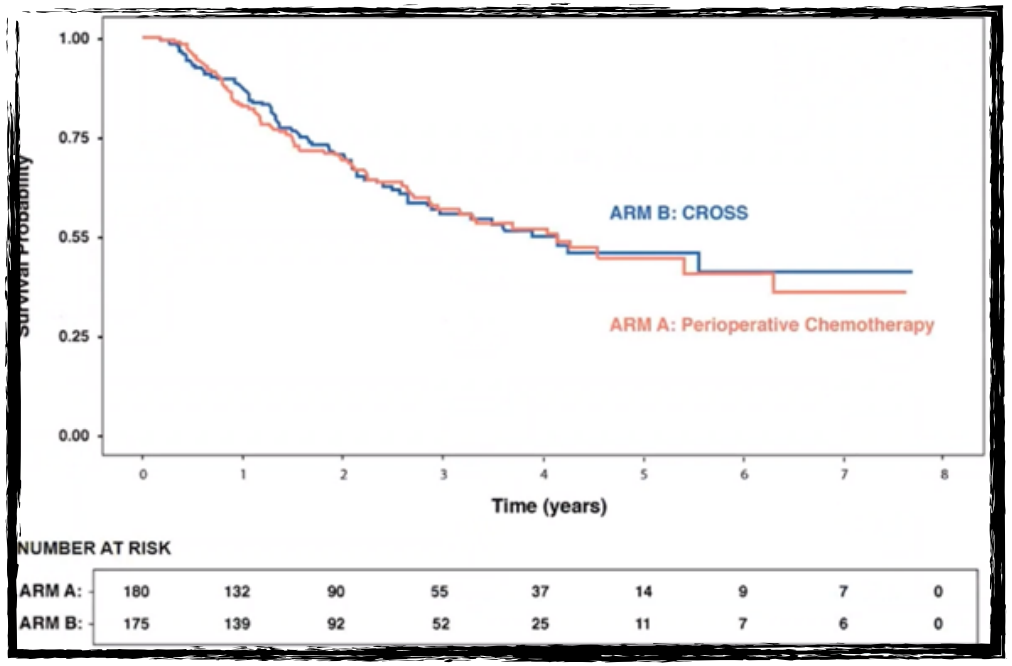
Neo-AEGIS trial: CROSS vs MAGIC (II)

Results: Pathologic response, TRG and R status

	ARM A (Chemo)	ARM B (CROSS)
ypN0	44.5%	60%
ypT3	59.6%	52%
Change from cN1-ypN+	-5%	-20%
R0	82%	95%
pCR	5%	16%
TRG1	5.3%	17.3%
TRG 2	6.7%	24.4%
Major Path Response	12%	31.7%
TRG 3	23.4%	32.1%
TRG 4	41.6%	22.4%
TRG 5	22.8%	3.8%

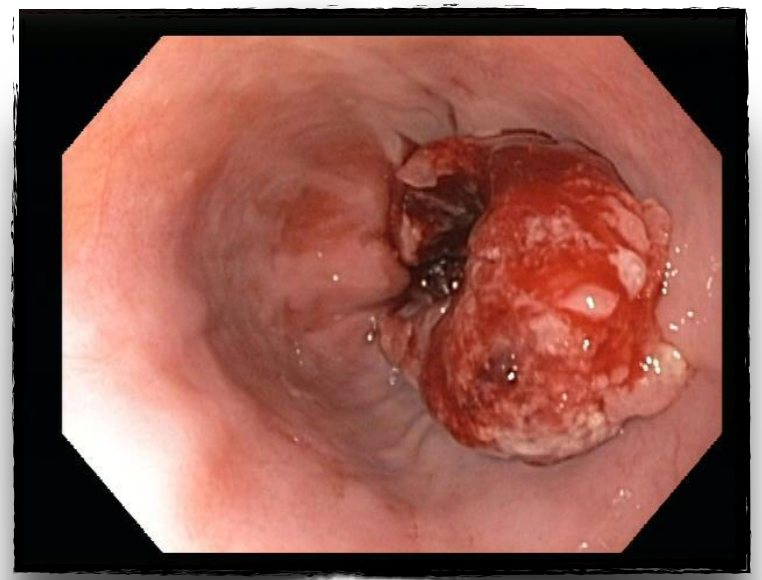
Only?

OS



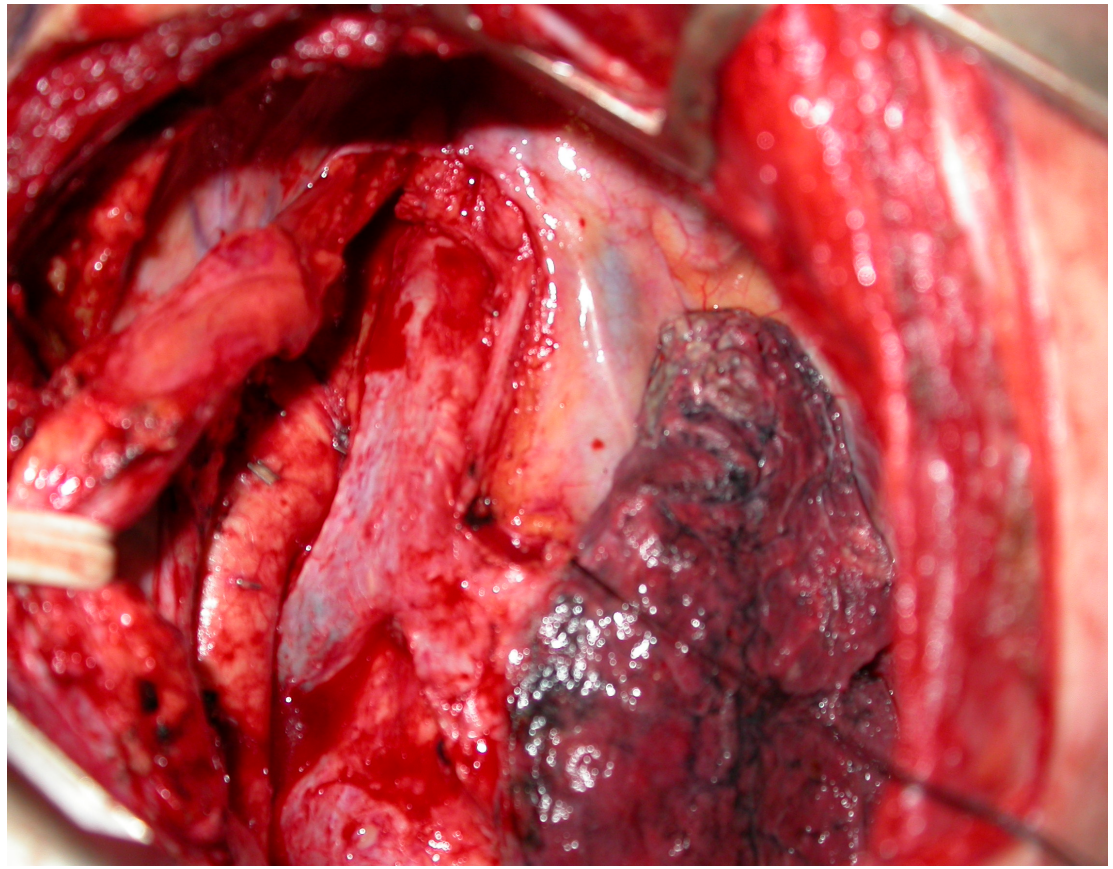
- **Improved local control does not translate into better survival**
- **FLOT is better than ECF but CROSS is not!!**

ECF, epirubicin, cisplatin, and fluorouracil; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; OS, overall survival; pCR, pathologic complete response; TRG, tumor regression grading; R, residual tumor.
Al-Batran SE et al. *Lancet* 2019;393:1948–1957.



1) Quelle opération puis-je proposer
2) CROSS=MAGIC
   FLOT>MAGIC
   FLOT>CROSS…
3)Le radiation ajoute-t-il quelque chose ?

L'œsophagectomie offre une chance de guérison



En Bloc Esophagectomy

BUT..

High risk of complications

Benchmarking Complications Associated With Esophagectomy

Donald E. Low, MD, FACS, FRCSC, Madhan Kumar Kuppusamy, MD, FRCS,* Derek Alderson, FRCS,†*
Ivan Cecconello, MD, PhD,‡ Andrew C. Chang, MD,§ Gail Darling, MD, FRCSC, FACS,¶
*Andrew Davies, MD, FRCS,|| Xavier Benoit D'Journo, MD, PhD,** Suzanne S. Gisbertz, MD, PhD,††*
S. Michael Griffin, OBE, MD, FRCSEd, FRCS,‡‡ Richard Hardwick, MD, FRCS,§§
*Arnulf Hoelscher, MD, FACS, FRCS,¶¶ Wayne Hofstetter, MD,|||| Blair Jobe, MD, FACS,****
Yuko Kitagawa, MD, PhD, FACS,††† Simon Law, MS, PhD, FRCS,‡‡‡ Christophe Mariette, MD, PhD,§§§
*Nick Maynard, MS, FRCS,¶¶¶ Christopher R. Morse, MD,|||||| Philippe Nafteux, MD, PhD,*****
Manuel Pera, MD, PhD,†††† C. S. Pramesh, MD, FRCS(Edin),‡‡‡‡ Sonia Puig, MD,§§§§
*John V. Reynolds, MCh, FRCSI,¶¶¶¶ Wolfgang Schroeder, FACS,||||||| Mark Smithers, FRACS, FRCS,******
and B. P. L. Wijnhoven, MD, PhD†††††

2704 Esophagectomies

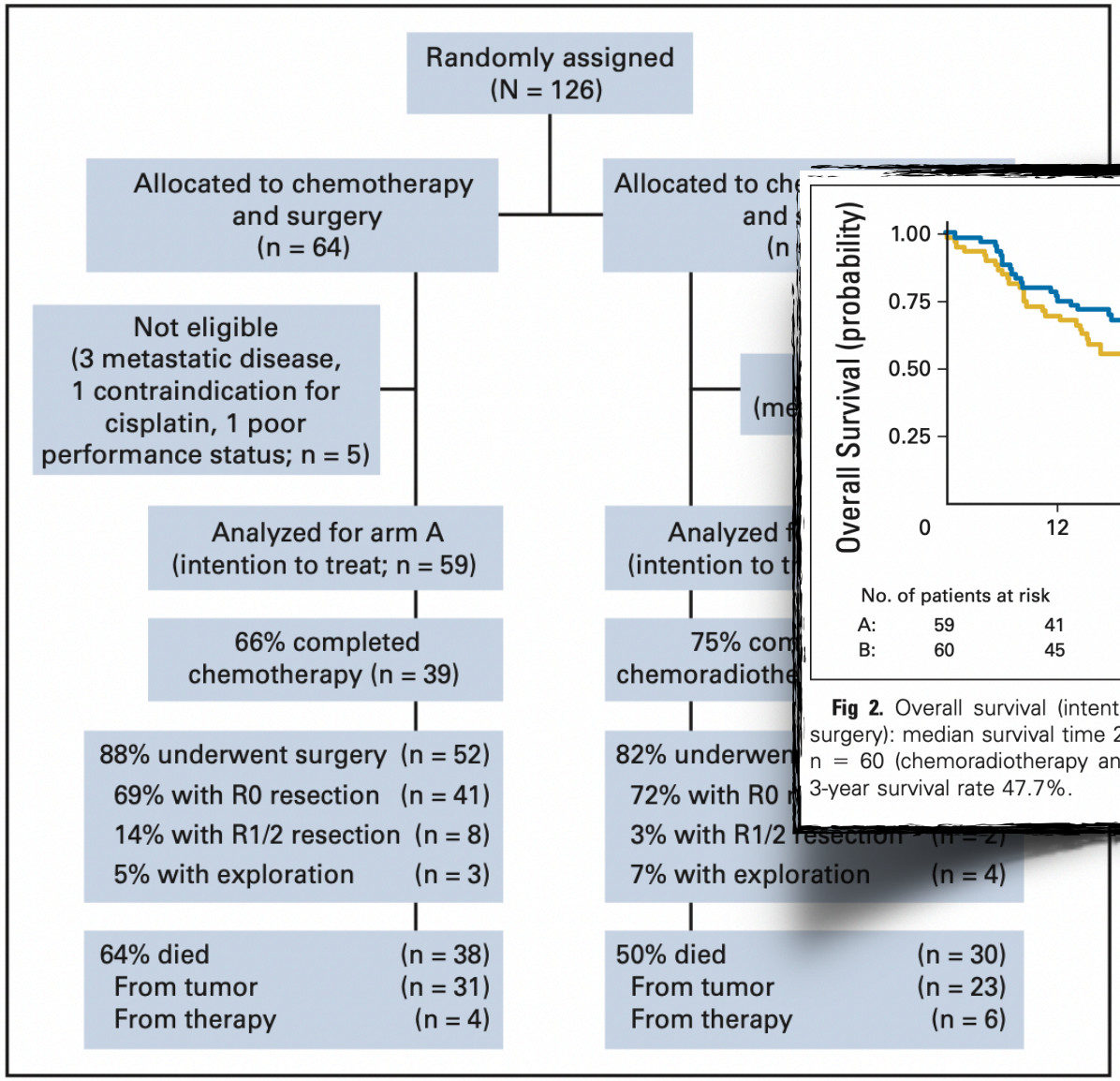
24 high volume centres from 14 countries

≈60% Complication Rate

≈20% Major Complications

Annals of Surgery 2019

La radiothérapie augmente les complications post-opératoires



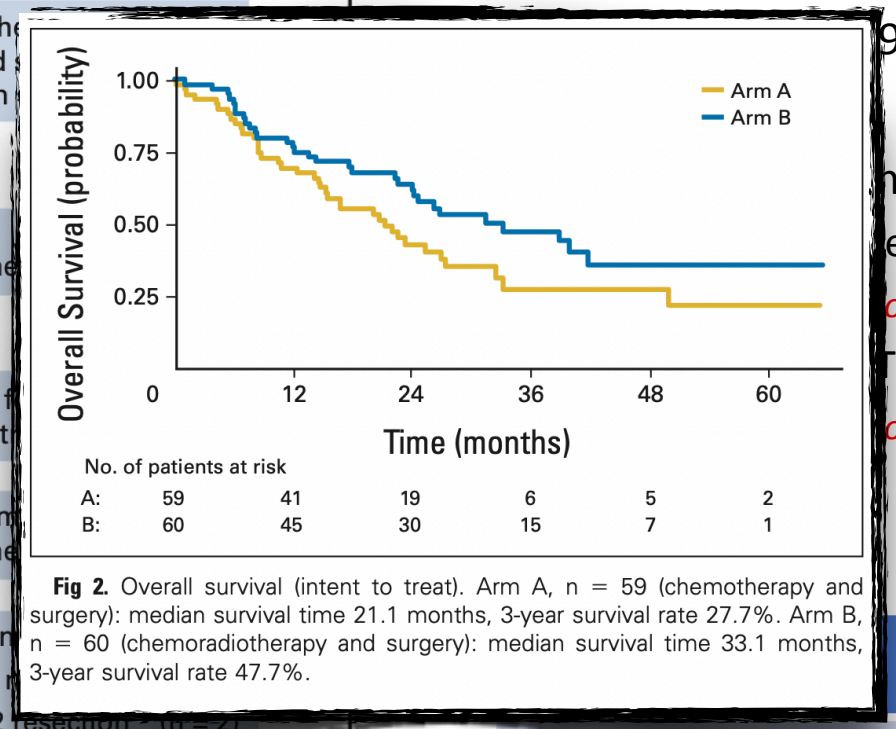


Fig 2. Overall survival (intent to treat). Arm A, n = 59 (chemotherapy and surgery): median survival time 21.1 months, 3-year survival rate 27.7%. Arm B, n = 60 (chemoradiotherapy and surgery): median survival time 33.1 months, 3-year survival rate 47.7%.

901 – Surgery vs nCRT+Surgery

and 2 only

istology

ery Alone – 43.8 month survival

operative mortality)

T + Surgery – 31.8 month survival

operative mortality)

	nCT	nCRT
NeoRes – *Klevbro 2016*	2.6%	6.5%
POET – *Stahl 2009*	3.8%	10.2%

La radiothérapie augmente les complications post-opératoires

Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study

S. R. Markar[1†], B. J. Noordman[2†], H. Mackenzie[1], J. M. Findlay[3], P. R. Boshier[1], M. Ni[1], E. W. Steyerberg[4], A. van der Gaast[5], M. C. C. M. Hulshof[6], N. Maynard[3], M. I. van Berge Henegouwen[7], B. P. L. Wijnhoven[2], J. V. Reynolds[8], J. J. B. Van Lanschot[2] and G. B. Hanna[1*]

Table 3. Comparative analysis of short-term outcomes and three-year recurrence from unmatched and propensity-matched groups.

	Before matching			After matching		
	NCRS (n=301) (%)	NCS (n=307) (%)	P value	NCRS (n=221) (%)	NCS (n=221) (%)	P value
30-day mortality	9 (3)	5 (1.6)	0.263	9 (4.1)	3 (1.4)	0.140
90-day mortality	15 (5)	7 (2.3)	0.074	13 (5.9)	5 (2.3)	0.090
Anastomotic leak [a]	61 (20.4)	15 (5.6)	<0.001	51 (23.1)	13 (6.8)	<0.001
Pulmonary complications [a]	135 (44.9)	103 (38.9)	0.15	101 (45.7)	72 (38.3)	0.134
Cardiac complications [a]	58 (19.3)	56 (21.1)	0.581	43 (19.5)	36 (19.1)	>0.999
Chyle leak [a]	22 (7.3)	24 (9.1)	0.448	17 (7.7)	13 (6.9)	0.850
Reoperation	27 (9.1)	20 (6.5)	0.108	22 (10.2)	14 (6.5)	0.050
Recurrence						
Locoregional	15 (5.0)	19 (6.2)	0.542	10 (4.5)	14 (6.3)	0.660
Distant	73 (24.3)	70 (22.8)		56 (25.3)	60 (27.1)	
Mixed	30 (10.0)	22 (7.2)		19 (8.6)	14 (6.3)	

NCRS, neoadjuvant chemoradiotherapy and surgery; NCS, neoadjuvant chemotherapy and surgery.
[a]Missing data.

EXPÉRIENCE DU MONDE RÉEL

2-3 fold Mortality (NS)
3 fold Leak (Sig)

Sheraz Markar 2017

Pembrolizun
alone for firs
cancer (KEYN
phase 3 stud

Jong-Mu Sun, Lin Shen, Manis
Sung-Bae Kim, Byoung Chul C
Luis Antunes, Christos Fountz
Investigators*

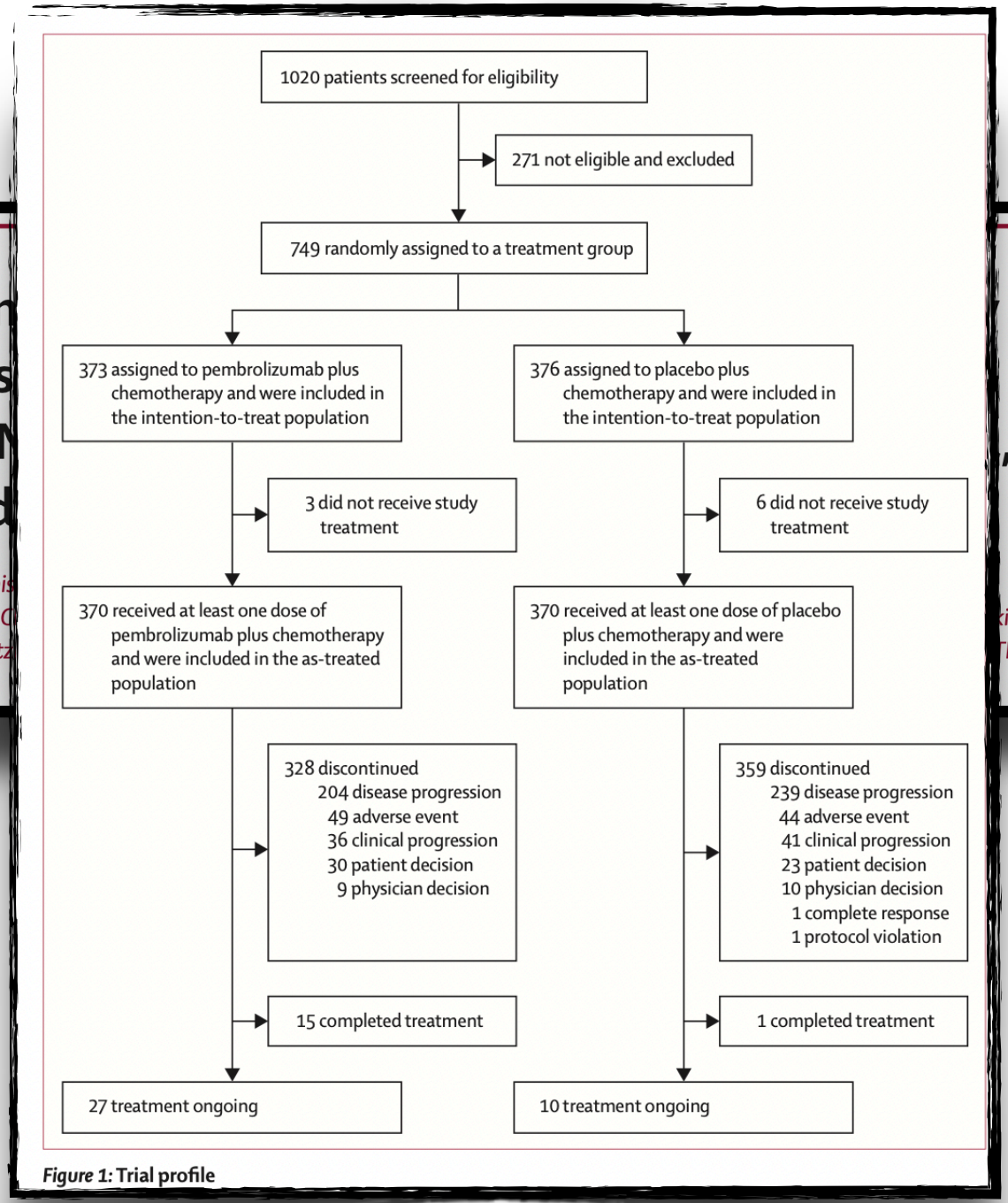


Figure 1: Trial profile

ki Hara,
TE-590

Non curable, locally advanced or metastatic EC

Cisplatin, 5FU

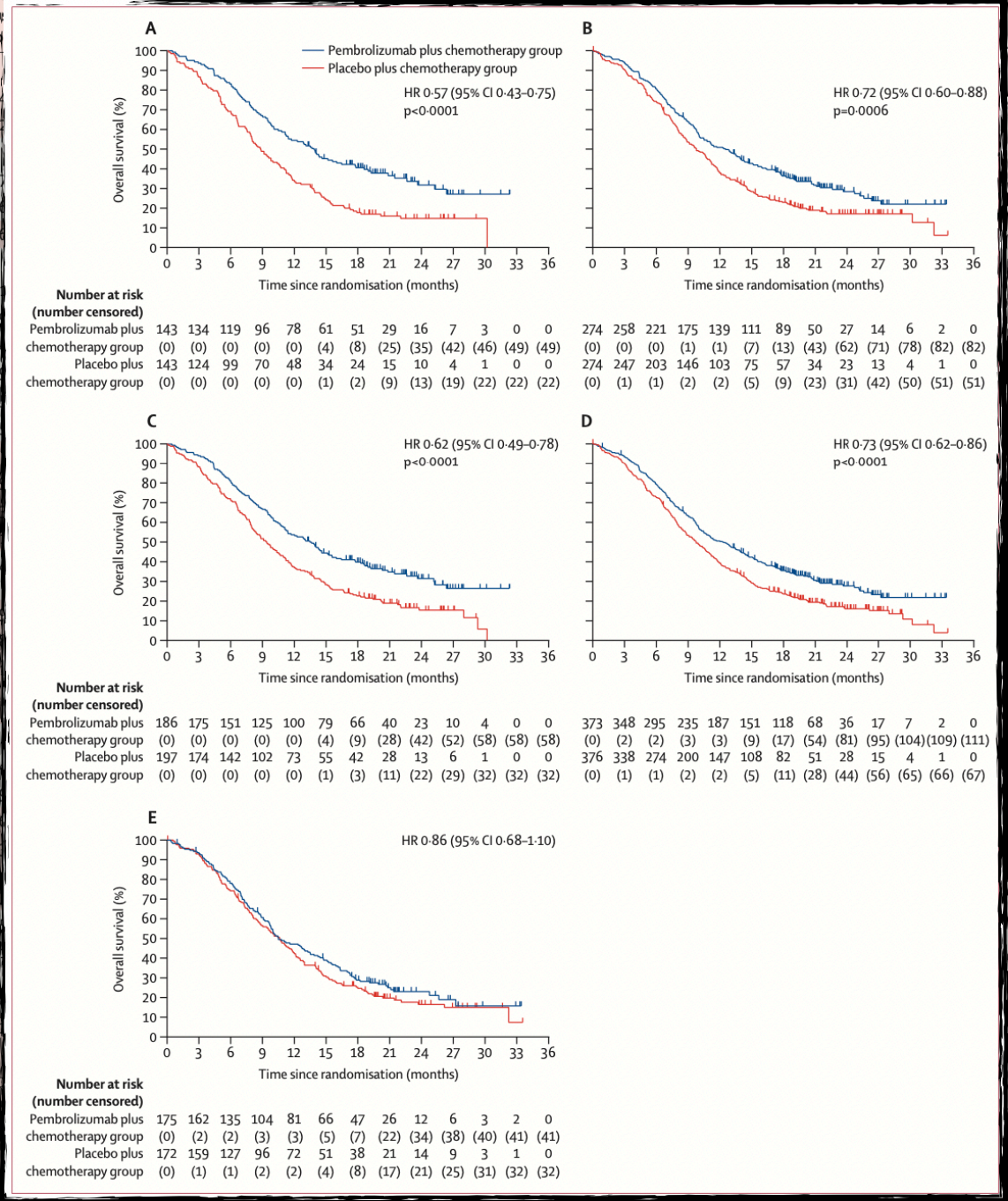
Cisplatin, 5FU, + Pembrolizumab

75% ESCC
38% CPS>10
25% ADC
12% CPS>10

	Pembrolizumab plus chemotherapy group	Placebo plus chemotherapy group
Age, years		
Median (range)	64	
≥65	17	
Sex		
Female	6	
Male	30	
Asia region*	19	
Race		
Asian	20	
White	13	
Missing	1	
Native American		
African American		
Other†		
ECOG performance status		
0	14	
1	22	
2		
Oesophageal squamous cell carcinoma	27	
Adenocarcinoma	9	
Oesophageal adenocarcinoma	5	
Siewert type 1 gastro-oesophageal junction adenocarcinoma‡	4	
Disease status		
Metastatic	34	
Unresectable locally advanced	2	
PD-L1 CPS ≥10	18	
Oesophageal squamous cell carcinoma	14	
Adenocarcinoma	4	
PD-L1 CPS <10	17	
Oesophageal squamous cell carcinoma	12	
Adenocarcinoma	5	
PD-L1 status not evaluable or missing	1	

Data are n (%) unless otherwise stated. EC
Group. CPS=combined positive score. *Co
Hong Kong, Japan, South Korea, and Taiwa
ethnicities. ‡58 patients were HER2-negat
32 had unknown HER2 status.

Table 1: **Baseline characteristics in the intention-to-treat population**



HR (95% CI)
0·76 (0·61–0·95)
0·69 (0·53–0·89)
0·89 (0·59–1·35)
0·70 (0·58–0·84)
0·72 (0·55–0·94)
0·73 (0·59–0·90)
0·64 (0·51–0·81)
0·83 (0·66–1·05)
0·74 (0·54–1·02)
0·72 (0·60–0·88)
0·62 (0·49–0·78)
0·86 (0·68–1·10)
0·73 (0·62–0·86)
0·69 (0·56–0·85)
0·62 (0·48–0·80)
0·74 (0·49–1·12)
0·63 (0·53–0·75)
0·57 (0·45–0·74)
0·71 (0·58–0·87)
0·59 (0·47–0·73)
0·70 (0·56–0·89)
0·63 (0·46–0·87)
0·65 (0·54–0·78)
0·51 (0·41–0·65)
0·80 (0·64–1·01)
0·65 (0·55–0·76)

10·0

vours placebo plus
emotherapy

Merci

- Questions?

1) Lequel des énoncés suivants est vrai?
A) La chimiothérapie est inférieure chez tous les patients atteints de cancer de l'œsophage en ce qui concerne la survie globale
B) La radiothérapie offre un meilleur contrôle local et à distance par rapport à la chimiothérapie
C) La radiothérapie et la chimiothérapie sont des stratégies néoadjuvantes appropriées chez des patients sélectionnés de manière appropriée
D) La radiothérapie doit être abandonnée dans la prise en charge du cancer de l'œsophage en raison de complications.

2) L'essai CROSS reflète lequel des éléments suivants :
A) L'adénocarcinome de l'œsophage est très radiosensible
B) Le carcinome épidermoïde de l'œsophage est marqué par une récidive étendue à distance
C) Amélioration du contrôle locorégional et à distance chez tous les patients atteints de cancer de l'œsophage par rapport à la chirurgie seule
D) Amélioration marquée de la survie des patients atteints d'adénocarcinome par rapport aux patients atteints d'un cancer de l'œsophage

3) Lequel des énoncés suivants est vrai
A) Le cancer de l'œsophage fait référence à une maladie homogène
B) Les deux sous-types histologiques prédominants, l'œsophage épidermoïde et l'adénocarcinome, sont des distinctions avec une épidémiologie, un comportement clinique et une génétique différents
C) L'essai FLOT 4 a prouvé la supériorité de l'ECF sur FLOT dans la prise en charge du denocarcinome de l'œsophage.
D) L'expérience du monde réel a confirmé la supériorité de la chimioradiothérapie sur la chimiothérapie seule dans le cancer de l'œsophage en ce qui concerne la survie