BARCELONA 2024 ESMO congress

Personalisation of surgical and systemic approaches in 2024: Optimising cure and quality of life in gastroesophageal cancer

To operate or not operate: Personalized surgical approaches in the curative setting

Pr G Piessen

CHU Lille, France, 15 september 2024

FREGAT CHU LILLE ufr3s Université de Lille FROGS

Declaration of interest

Guillaume Piessen
BMS: consulting ,board
Nestlé: consulting
Astellas pharma: consulting
Medtronic: travel, accommodation
MSD: travel, accommodation, consulting, lecture
Daiichi: consulting
Elivie : lecture
Strycker : consulting

To operate or not operate?

1. **Patient Assessment**
   Age, comorbidity, performance status
2. **Tumour Characteristics**
   Tumour size, cTNM
3. **Surgical Technique Selection**
   Extensiveness of resection and surgical approach
4. **Molecular characteristics**
5. **Patients preferences**

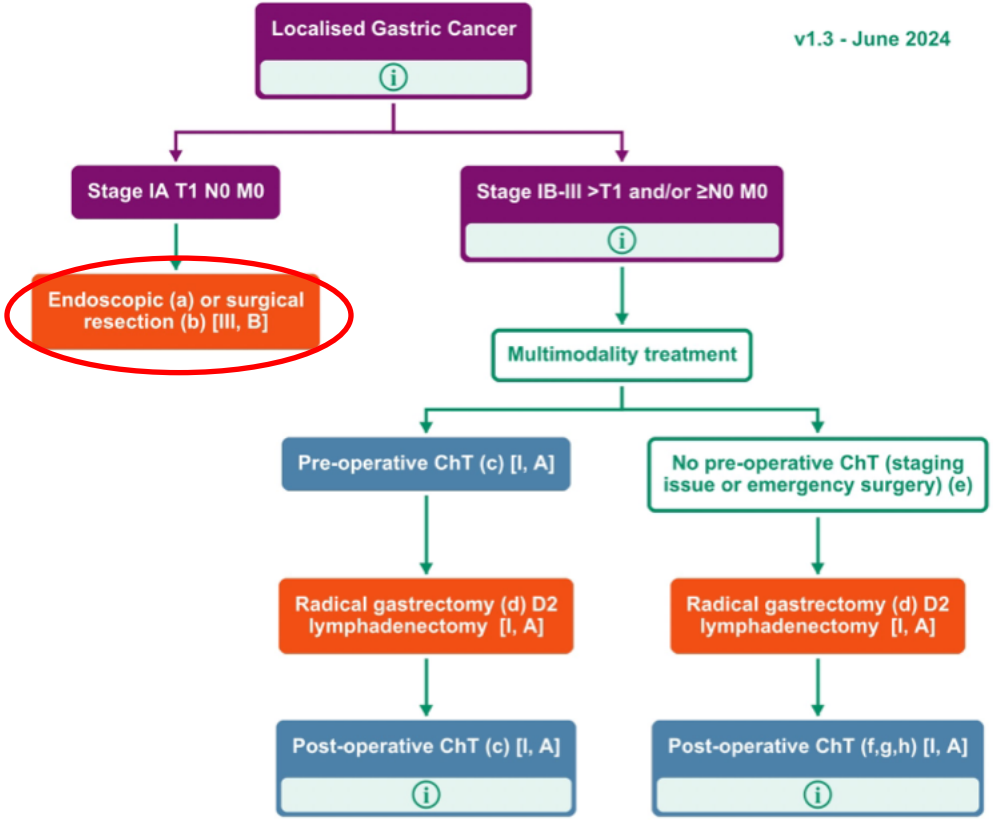
Surgery /Endoscopy

and IO

Personalized surgical approaches in the curative setting

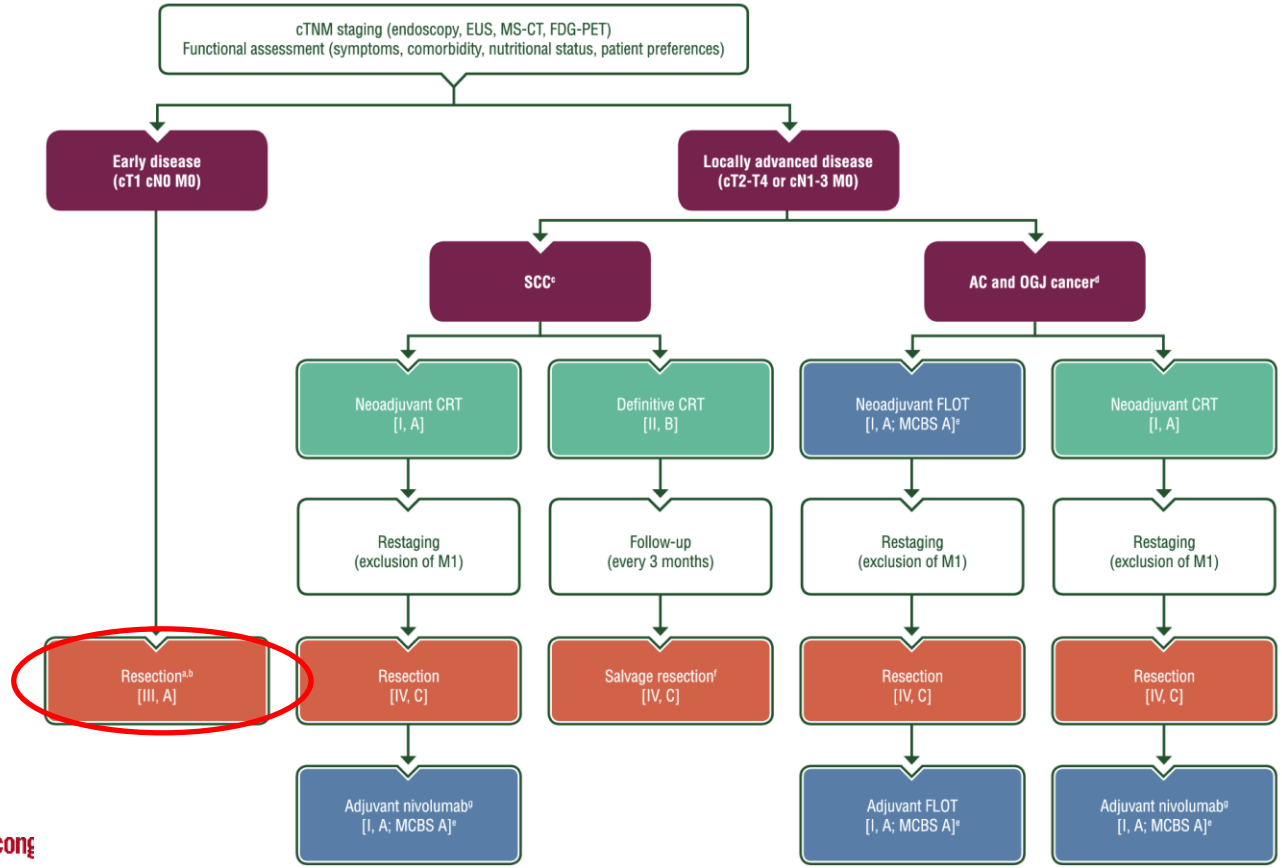
- Early
- Locally advanced
- Oligometastatic

Current ESMO guidelines: gastric cancer



Lordick et al , Ann Oncol 2022

Current ESMO guidelines: esophageal/OGC cancer



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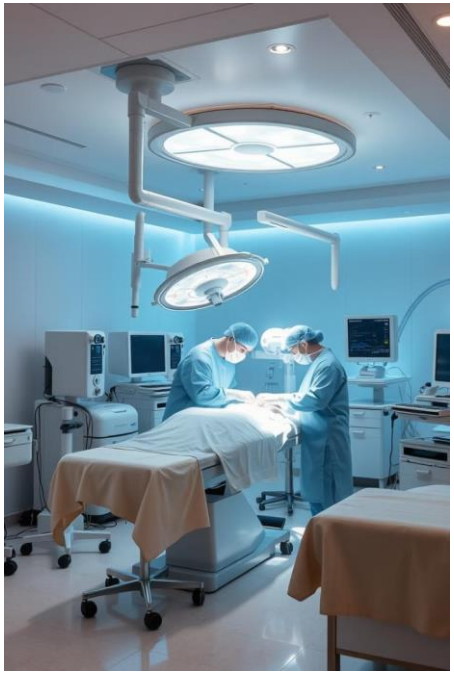
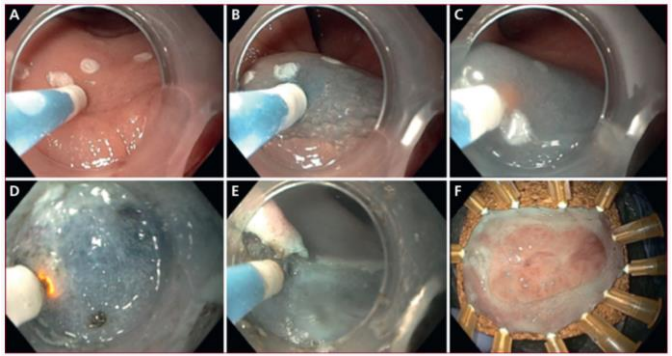
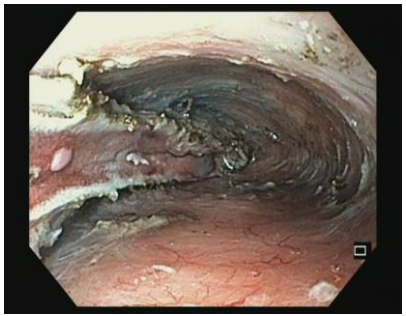
Obermmanova et al , Ann Oncol 2022

Early tumours







++ ESD, en bloc resection

Early tumours

▶ **Table 2** Univariable and multivariable subdistributional hazard regression analysis of risk factors associated with metastases (no metastases n = 170, metastases n = 78).

Variable	Univariable subdistributional hazard regression analysis		Multivariable subdistributional hazard regression analysis	
	SHR (95%CI)	*P* value	SHR (95%CI)	*P* value
Sex, n (%)			–	–
▪ Female	Reference			
▪ Male	1.51 (0.74–3.10)	0.26		
Differentiation grade				
▪ G1/2 (good/moderate)	Reference		Reference	
▪ G3/4 (poor/undifferentiated)	1.78 (1.20–2.65)	<0.01	1.01 (0.66–1.55)	0.96
Submucosal invasion (per 500 µm)	1.13 (1.08–1.18)	<0.01	1.08 (1.02–1.14)[1]	<0.01
LVI				
▪ No	Reference		Reference	
▪ Yes	3.58 (2.45–5.22)	<0.01	2.95 (1.95–4.45)	<0.01
Tumor size (per 10 mm)	1.39 (1.25–1.53)	<0.01	1.23 (1.10–1.37)[2]	<0.01

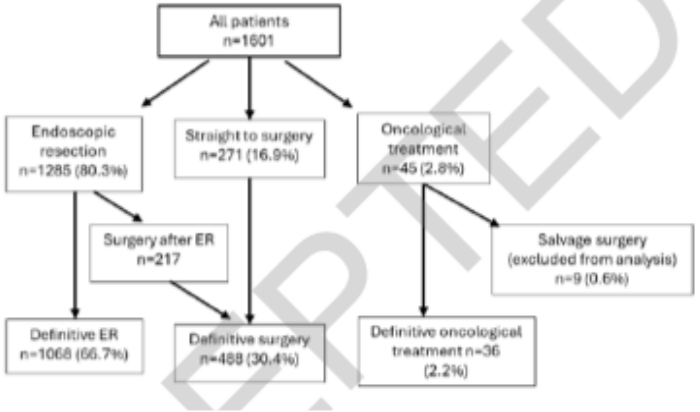
SHR, subdistribution hazard ratio; CI, confidence interval; LVI, lymphovascular invasion.
[1] For every 500 µm increase in submucosal invasion.
[2] For every 10 mm increase in tumor size.

	LVI–, % (95%CI)	LVI+, % (95%CI)	Tumor size
sm1	5.9 (2.3–11.2)	15.7 (6.0–29.3)	<20 mm
sm2	7.3 (2.6–13.8)	19.3 (6.3–36.8)	
sm3	14.1 (7.9–21.9)	34.7 (19.7–50.8)	
sm1	16.1 (6.2–29.2)	38.8 (17.0–61.4)	≥20 mm
sm2	19.4 (8.6–32.2)	45.6 (20.8–67.9)	
sm3	35.2 (25.8–44.7)	70.1 (60.5–78.7)	

▶ **Fig. 3** Score chart for 5-year metastases risk (both lymph node metastases and distant metastases) for different combinations of histopathological variables in patients with pT1b esophageal adenocarcinoma. LVI, lymphovascular invasion; CI, confidence interval; sm, submucosa.

Gotink, Endoscopy 2022

Early tumours



- CONGRESS study
  - Rate of LNM was 13.5%
  - **On ER staging**, tumour depth, LVI or signet cells were associated with LNM
  - **But non ER LN risk (R0, <SM2, no LVI, no indiff): 15.3% of LNM**
  - Highlights the need for urgent prospective study.

Pucher, Ann Surg 2024

Early tumours

ESMO and ESGE guidelines

For both histological subtypes, patients with involved deep endoscopic resection margins or significant risk factors for lymph node metastases should be offered further resective surgery with appropriate lymphadenectomy; however, chemoradiotherapy (CRT) could be considered as a treatment option for stage IA SCC with organ preservation.[49]

T1 tumours which do not meet the criteria for endoscopic resection require surgery, although less extensive surgery than other gastric cancers. Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to the site of cancer).

Complete staging with EUS and CT/PET-CT at the time of diagnosis is crucial to identify patients with synchronous LNM. In the absence of these (i. e. for pT1bN0M0 disease), the decision on further management should be guided by patient characteristics (co-morbidity, surgical risk) and patient preference. After discussion in a multidisciplinary team meeting, chemotherapy and/or radiotherapy and/or surgery, or a conservative approach consisting of intensified follow-up with EGD, EUS, and CT/PET-CT in the setting of an expert center can be considered.

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Lordick et al, Ann Oncol 2022
Obermmanova et al , Ann Oncol 2022
Weustein, Endoscopy 2023

Early tumours

Conservative approach

Prospective Endoscopic Follow-up of Patients With Submucosal Esophageal Adenocarcinoma (The PREFER Trial)

ClinicalTrials.gov ID NCT03222635

Sponsor Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)

Information provided by prof. dr. J.J.G.H.M. Bergman, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA) (Responsible Party)

- Intensive follow-up
  - gastroscopy+EUS every 3-6 months +repeated CT/PET-CT at 12 months
- Interim analysis after a median follow-up duration of 22 months
  - Showed LNM in 6/120 patients (5 %)
  - All these patients could be treated by rescue therapy
    - esophagectomy
    - selective surgical resection of the affected lymph nodes
- Predefined follow-up period of 5 years and the final results are awaited

Chan MW et al, Gastrointest Endosc 2023

Early tumours

Sentinel node

Ann Surg Oncol (2023) 30:4002–4011
https://doi.org/10.1245/s10434-023-13317-6

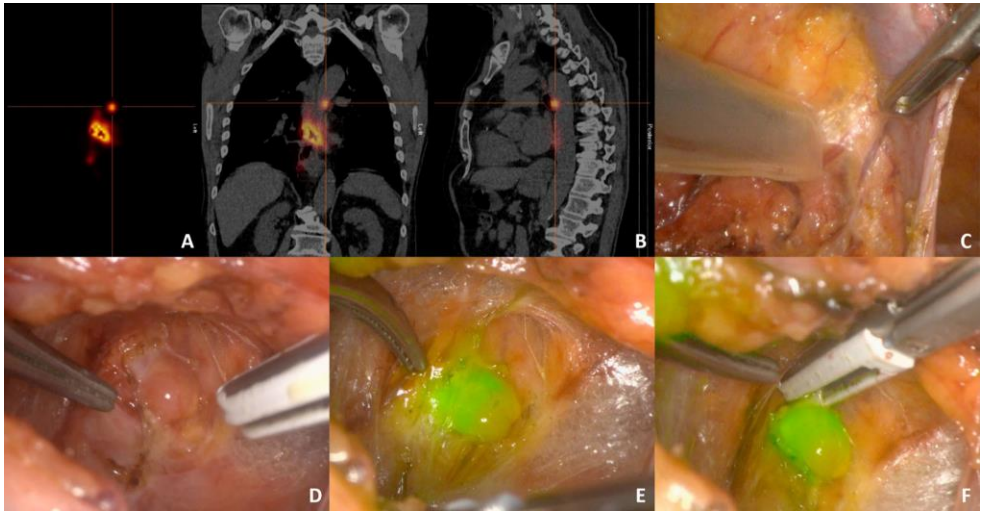
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Feasibility and Safety of Tailored Lymphadenectomy Using Sentinel Node-Navigated Surgery in Patients with High-Risk T1 Esophageal Adenocarcinoma

Charlotte N. Frederiks, MD[1,2], Anouk Overwater, MD[1,2], Jacques J. G. H. M. Bergman, MD, PhD[3], Roos E. Pouw, MD, PhD[3], Bart de Keizer, MD, PhD[4], Roel J. Bennink, MD, PhD[5], Lodewijk A. A. Brosens, MD, PhD[6], Sybren L. Meijer, MD, PhD[7], Richard van Hillegersberg, MD, PhD[8], Mark I. van Berge Henegouwen, MD, PhD[9,10], Jelle P. Ruurda, MD, PhD[8], Suzanne S. Gisbertz, MD, PhD[9,10], and Bas L. A. M. Weusten, MD, PhD[1,2]

- Hybrid tracer of technetium-99m nanocolloid and ICG
  - injected endoscopically around the scar 24H before
    - Preoperative imaging
    - Sentinel nodes identification using
      - Thoracolaparoscopic gammaprobe
      - Fluorescene
- Feasible 100%, 3 SN (1-6)
  - 10% : micrometastasis



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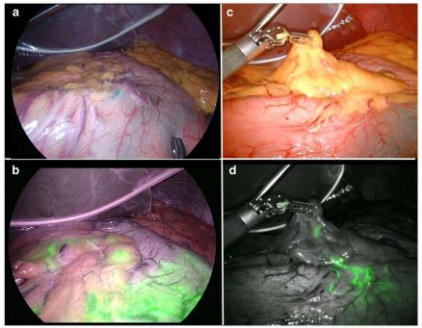
Frederiks et al, Ann Surg Oncol 2021

Early tumours

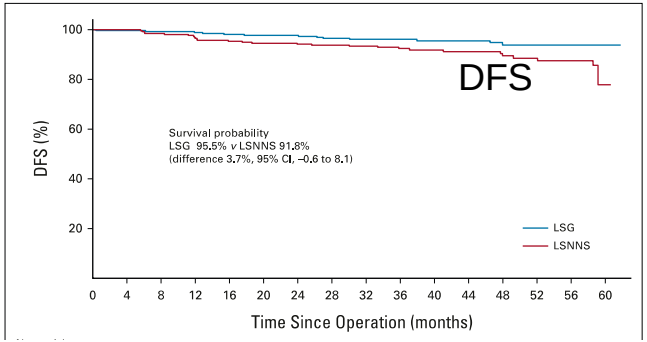
original reports

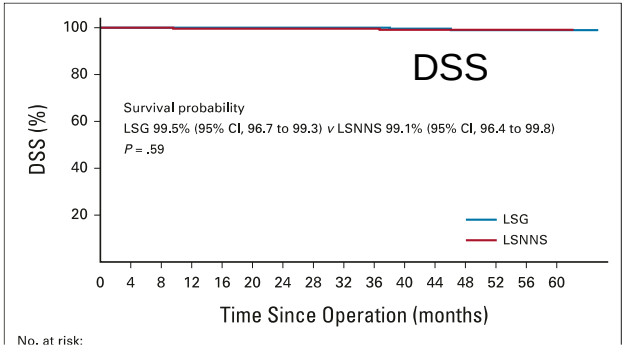
Laparoscopic Sentinel Node Navigation Surgery for Stomach Preservation in Patients With Early Gastric Cancer: A Randomized Clinical Trial

Young-Woo Kim, MD[1]; Jae-Seok Min, MD[2]; Hong Man Yoon, MD[1]; Ji Yeong An, MD[2,3]; Bang Wool Eom, MD[2]; Hoon Hur, MD[4]; Young Joon Lee, MD[4]; Gyu Seok Cho, MD[1]; Young-Kyu Park, MD[4]; Mi Ran Jung, MD[4]; Ji-Ho Park, MD[4]; Woo Jin Hyung, MD[2]; Sang-Ho Jeong, MD[2]; Myeong-Cherl Kook, MD[2]; Mira Han, MS[4]; Byung-Ho Nam, PhD[2,3,5]; and Keun Won Ryu, MD, PhD[2]



- Stage IA<3cm, randomized between conventional surgery and SN
- Dual ICG and Technetium- 99m human serum albumin tracers intraoperatively injected
  - Conservative surgery if SN negative : success 81%
  - Conventional surgery otherwise
- Negative trial on DFS (5%) but similar DSS/OS
- Improved QOL and nutrition





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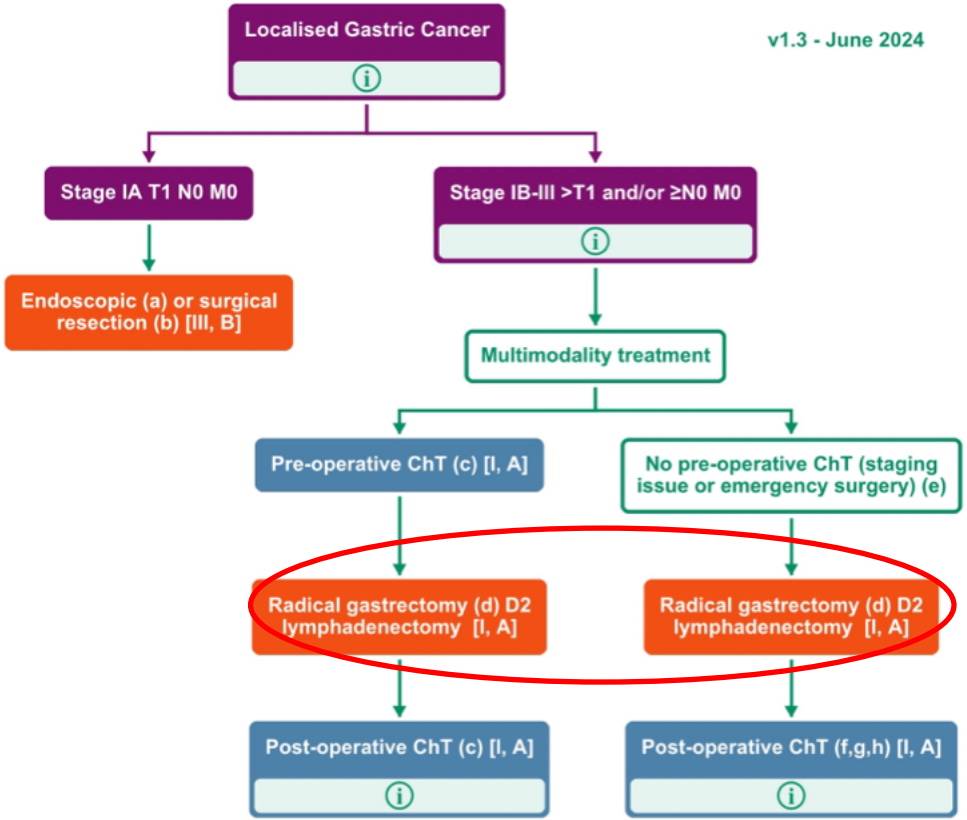
Kim et al, J Clin Oncol 2022

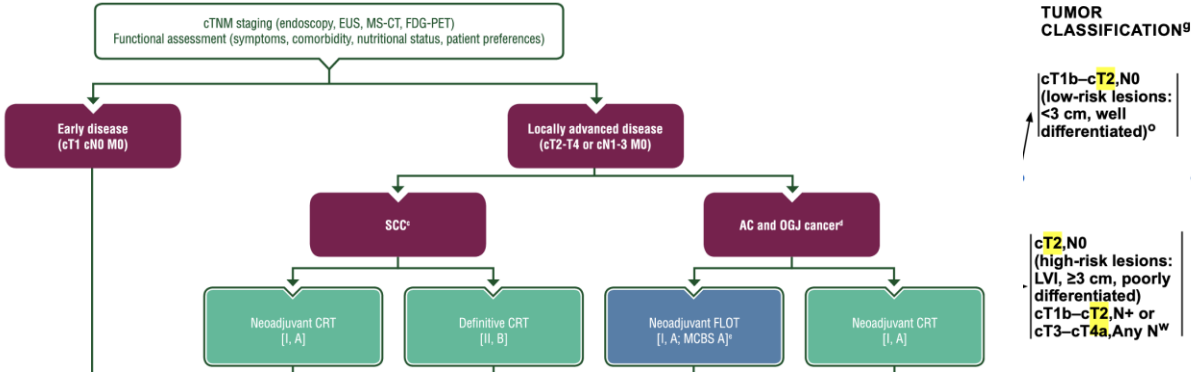
Current ESMO guidelines: gastric cancer



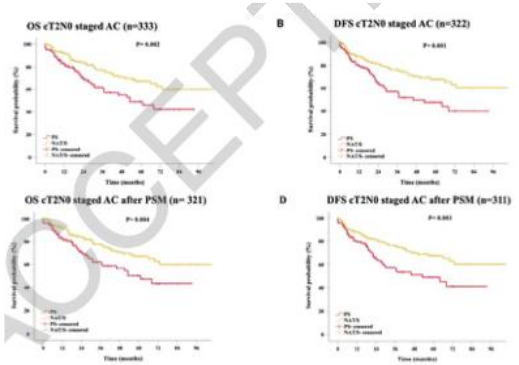
Lordick et al , Ann Oncol 2022

Locally advanced tumours

cT2N0



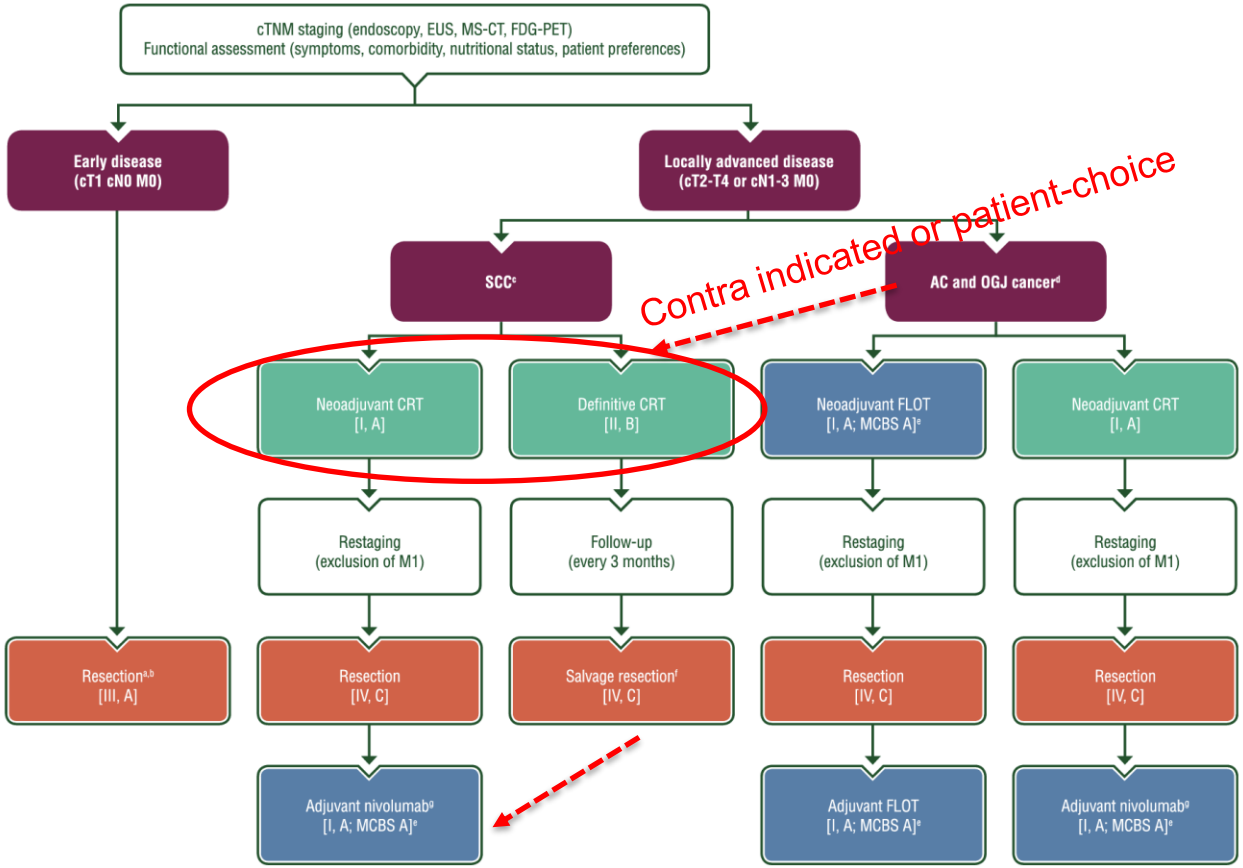
- Recent multicentric international study
  - 35% understagged on pT and 36% understagged on pN
    - Inacurracy of work-up so NAT for every patients
  - But 49% overstagged



- Endoscopic reassessment in ct2 patients: 60 % dowstagged
  - Among them 80% of success of endoscopic resection
  - 40 % restagged and treated with success with endoscopy alone

Obermannova et al, Ann Oncol 2022
NCCN 2023
Markar et al, Eur J Cancer 2016
Wirsik et al, Ann Surg 2024
Van de Ven et al, Endoscopy 2022

Current ESMO guidelines: esophageal/OGC cancer



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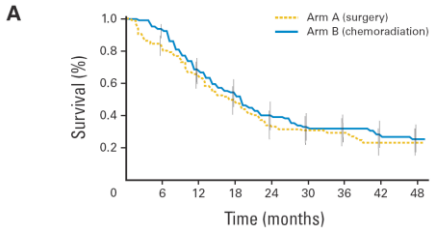
Obermmanova et al , Ann Oncol 2022

Locally advanced tumours

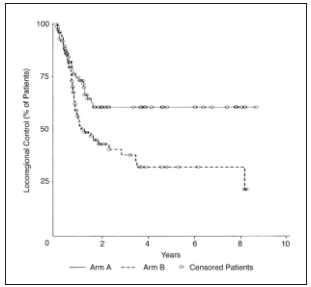
2 RCT (GESG and FFCD9102)

- Only middle/upper third SCC
- 90% SCC, randomisation of clinical responders

- Non inferiority in terms of 2 years OS



- Better locoregional control in the surgery arm
  - at the price of a higher risk of early mortality

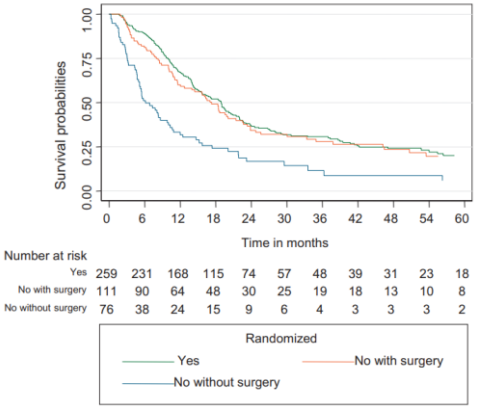


Stahl et al, J Clin Oncol 2005
Bedenne et al, J Clin Oncol 2007

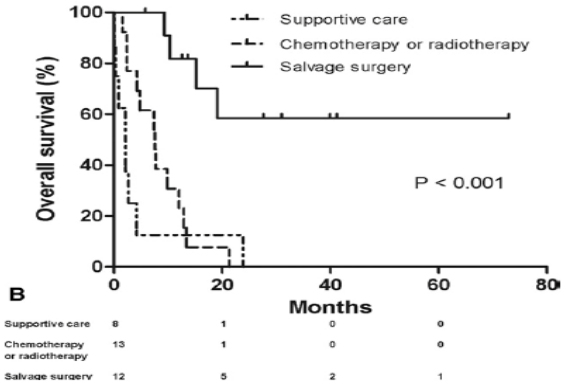
Locally advanced tumours

Definitive chemoradiotherapy (possibly followed by resection)		
Main goal of dCRT	To cure esophageal cancer without surgery	96
Indications for treatment with dCRT	T4b carcinoma, proximal tumor, patients unfit for surgery and patients who refuse surgery	93
Chemotherapy regimen	A combination of platinum along with taxane, platinum in combination with 5-FU derivate, or platinum combined with vinorelbine	82
Total dose of radiotherapy	50.4 Gy	91
Surgery after dCRT	Salvage surgery	96

- Persistent tumour



- Recurrence tumour



phase II
SCC stage II/III (T4 excluded)
5FU-cisplat and 50,4 Gy
59% cCR

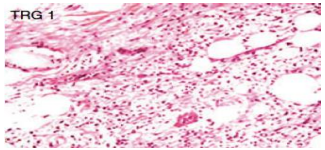
Endoscopic salvage 5%
<200µm
Salvage resection 27%
76% R0, 40% at 3 years

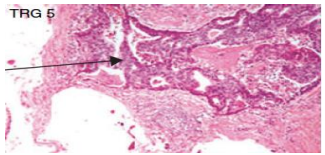
Van der Zijden et al. , Ann Surg Oncol 2024
Vincent Eur J Cancer 2015
Yoo Ann thorac Surg 2012
Takeuchi et al. Int Journal of radiation oncology 2022

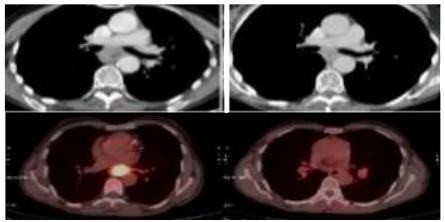
Locally advanced tumours

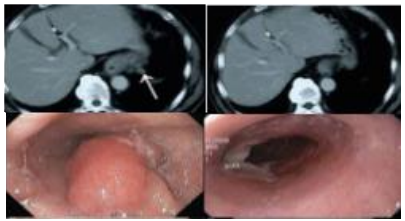
Concept of response evaluation

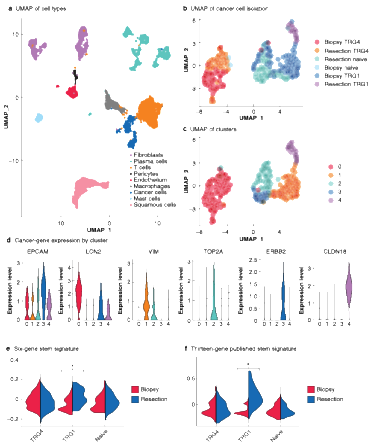
- How to predict?





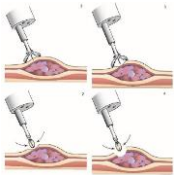






Using scRNA sequencing, rare population of residual cancer celles withing the scar tissue of ypT0N0 patients

Diagnostic tests which should be performed during response evaluations	Diagnostic CT-scan	76
	^{18}F-FDG PET/CT scan	89
	Upper endoscopy with (bite-on-bite) biopsies	96
	Endoscopic ultrasonography with fine-needle aspiration of suspicious lymph nodes	91
	PET/CT combined with diagnostic CT-scan	75



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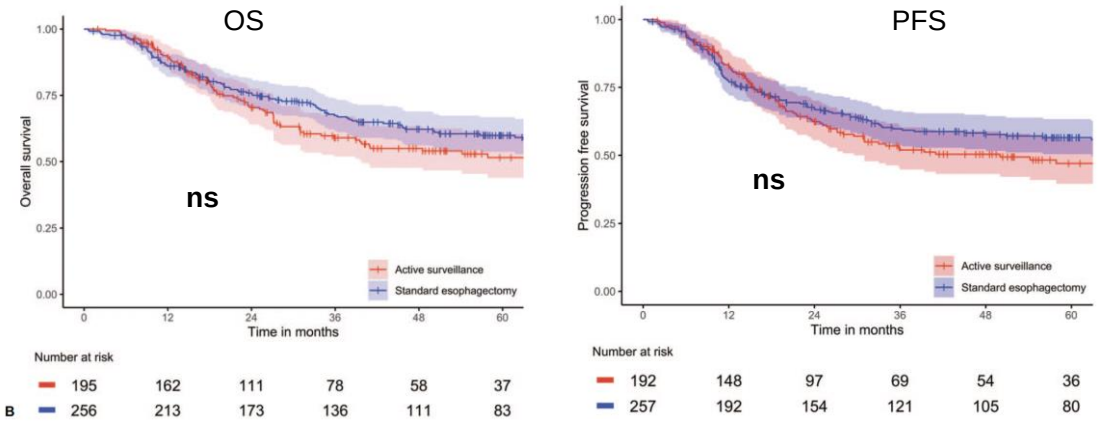
64% ypT0N0

In other words: 36% residual tumor

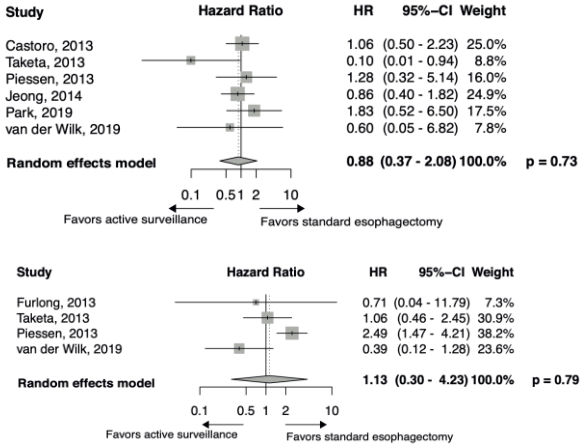
Van der Zijden et al , Ann Surg Oncol 2024
Noordman, Lancet Oncol 2022
Piessen et al, Ann Surg 2013
Walker et al. Br J Surg 2024

Locally advanced tumours

Metaanalysis (7 studies) individual data



Similar results regardless of histological type



Surveillance arm : Local recurrence : 34% at 2 years and 40% at 5 years / 95% R0 salvage surgery

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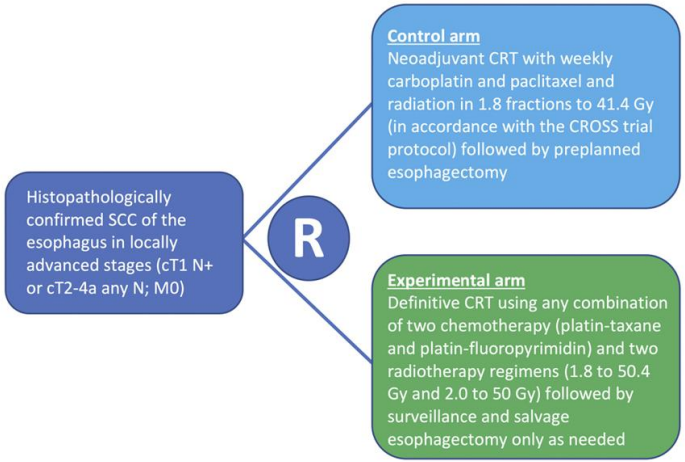
Van der Wilk, Ann Surg 2022

Locally advanced tumours

Neoadjuvant Chemoradiotherapy and Surgery for Esophageal Squamous Cell Carcinoma Versus Definitive Chemoradiotherapy With Salvage Surgery as Needed: The Study Protocol for the Randomized Controlled NEEDS Trial



Main hypothesis 1:
Overall survival after dCRT with surveillance and salvage surgery when needed is **non-inferior** to OS after nCRT + surgery

Main hypothesis 2:
HRQoL is better after dCRT + surveillance and salvage surgery only when needed

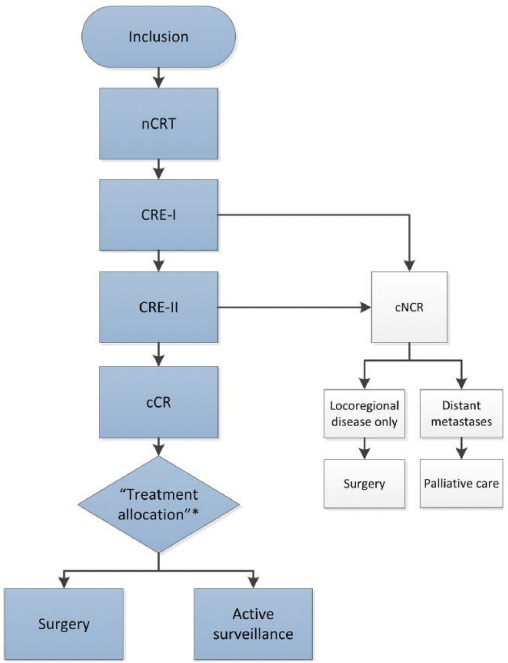
Main hypothesis 3:
Eating restrictions are better after dCRT + surveillance and salvage surgery only when needed

PHRC-K 2023
125 patients
France

Nilsson et al, Frontiers Oncol 2022

Locally advanced tumours

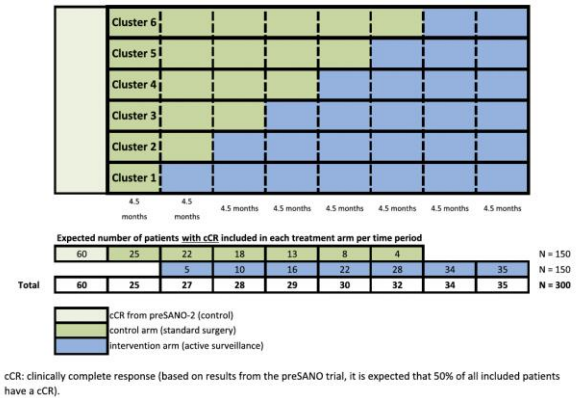
PreSANO ans SANO trial



STUDY PROTOCOL Open Access

Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial

Bo Jan Noordman[1*], Bas P. L. Wijnhoven[1], Sjoerd M. Lagarde[1], Jurjen J. Boonstra[2], Peter Paul L. O. Coene[3], Jan Willem T. Dekker[4], Michael Doukas[5], Ate van der Gaast[6], Joos Heisterkamp[7], Ewout A. Kouwenhoven[8], Grard A. P. Nieuwenhuijzen[9], Jean-Pierre E. N. Pierie[10], Camiel Rosman[11], Johanna W. van Sandick[12], Maurice J. C. van der Sangen[13], Meindert N. Sosef[14], Manon C. W. Spaander[15], Roelf Valkema[16], Edwin S. van der Zaag[17], Ewout W. Steyerberg[18], J. Jan B. van Lanschot[1] and on behalf of the SANO-study group

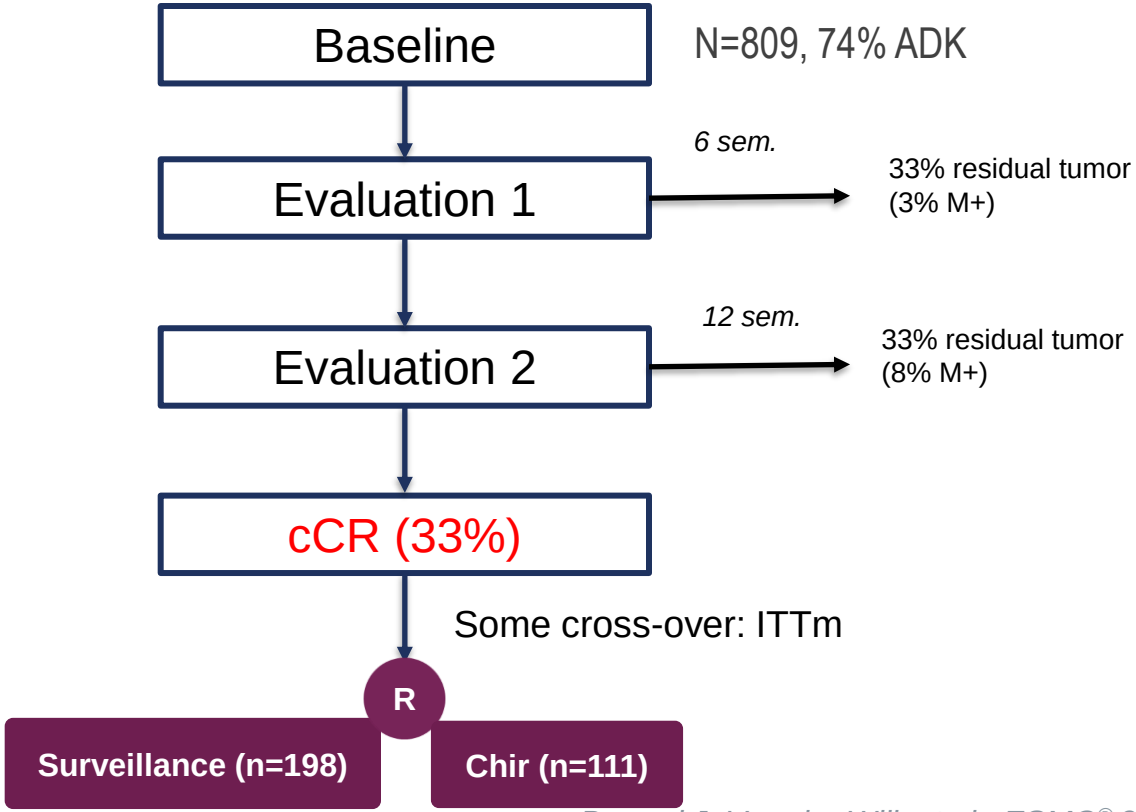


phase III multicentric « stepped-wedge cluster » RCT
ADC and SCC
n=300 cCR randomised
H0 non-inferiority (< 15% at 2 years) en OS

Noordman, BMC Cancer 2018

Locally advanced tumours

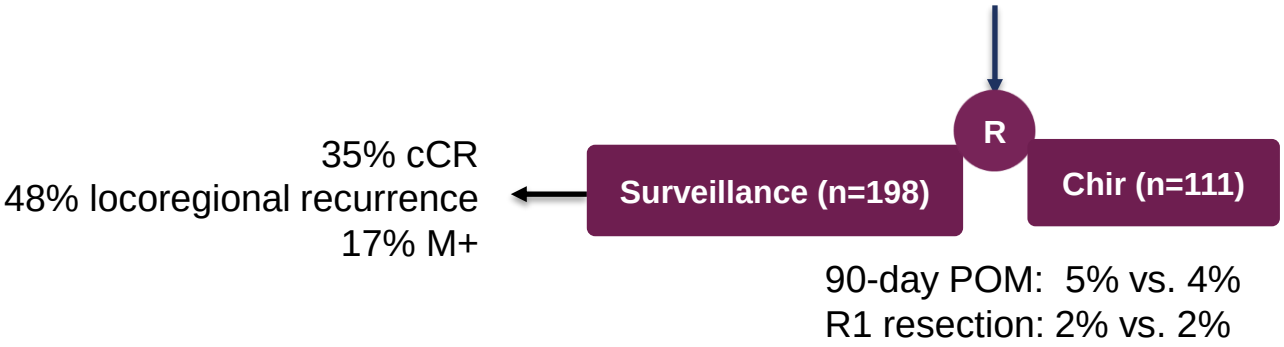
SANO trial: Active surveillance vs. Systematic surgery



Berend J. Van der Wilk et al., ESMO® 2023, Abs # LBA75

Locally advanced tumours

SANO trial: Active surveillance vs. Systematic surgery



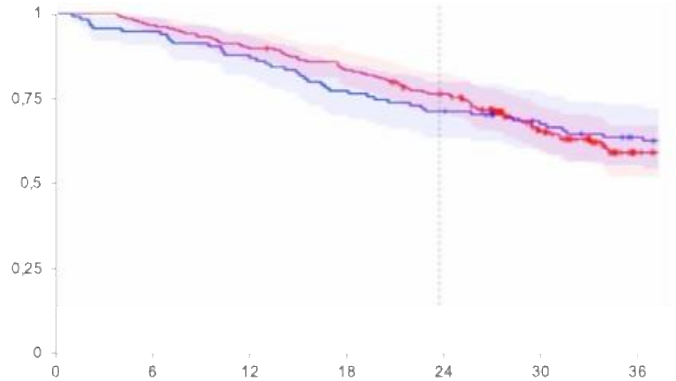
Overall: 12% organ preservation at 2 years

Berend J. Van der Wilk et al., ESMO® 2023, Abs # LBA75

Locally advanced tumours

SANO trial: Active surveillance vs. Systematic surgery

- Median follow-up 38 months
  - At 2 years, median OS was not inferior in AS, HR 1.14 (0.74-1.78), p=0.55



  - Median DFS : 35 vs. 49 months, HR 1.35, 95% CI 0.89-2.03, **p=0.15**
  - Risk of metastasis at 30 months: 43% vs. 34% (OR 1.45, 95% CI 0.85-2.48, **p= 0.18**
- HRQOL was statistically significantly better at 6 months (p=0.002) and 9 months (p=0.007)

Berend J. Van der Wilk et al., ESMO® 2023, Abs # LBA75

Locally advanced tumours

Perspectives

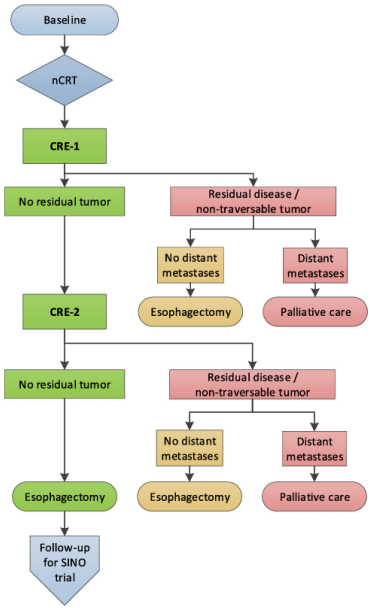


Fig. 1 Flow chart of the preSINO trial. nCRT: neoadjuvant chemoradiotherapy; CRE-1: first clinical response evaluation, four to six weeks after completion of nCRT; CRE-2: second clinical response evaluation, 10–12 weeks after completion of nCRT

STUDY PROTOCOL Open Access

Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma (preSINO trial): a prospective multicenter diagnostic cohort study

Xiaobin Zhang[1†], Ben M. Eyck[2†], Yang Yang[1], Jun Liu[3], Yin-Kai Chao[4], Ming-Mo Hou[5], Tsung-Min Hung[6], Qingsong Pang[7], Zhen-Tao Yu[8], Hongjing Jiang[9], Simon Law[9], Ian Wong[9], Ka-On Lam[10], Berend J. van der Wilk[2], Ate van der Gaast[11], Manon C. W. Spaander[12], Roelf Valkema[13], Sjoerd M. Lagarde[2], Bas P. L. Wijnhoven[2], J. Jan B. van Lanschot[2] and Zhigang Li[1*]

- Asian vs. European SCC: less histological response after CROSS

Table 3 Pathological characteristics of the two matched cohorts

	Overall (*n* = 266)	Asia (*n* = 133)	Netherlands (*n* = 133)	P§
pCR*	95 (35.7)	37 (27.8)	58 (43.6)	0.010
ypT category†				0.004
ypT0	112 (42.1)	45 (33.8)	67 (50.4)	
ypT1	31 (11.7)	21 (15.8)	10 (7.5)	
ypT2	40 (15.0)	16 (12.0)	24 (18.0)	
ypT3	81 (30.5)	50 (37.6)	31 (23.3)	
ypT4	2 (0.8)	1 (0.8)	1 (0.8)	
ypN category†				0.239
ypN0	163 (61.3)	74 (55.6)	89 (66.9)	
ypN1	68 (25.6)	39 (29.3)	29 (21.8)	
ypN2	28 (10.5)	15 (11.3)	13 (9.8)	
ypN3	7 (2.6)	5 (3.8)	2 (1.5)	
No. of positive lymph nodes, median (i.q.r.)	0 (0–1)	0 (0–1)	0 (0–1)	0.119
ypT0 N+	17 (6.4)	8 (6.0)	9 (6.8)	1.000
Histological regression				< 0.001
No response	6 (2.3)	0 (0)	6 (4.5)	
Partial response	145 (54.5)	88 (66.2)	57 (42.9)	
Complete response	112 (42.1)	45 (33.8)	67 (50.4)	
Not assessed	3 (1.1)	0 (0)	3 (2.3)	

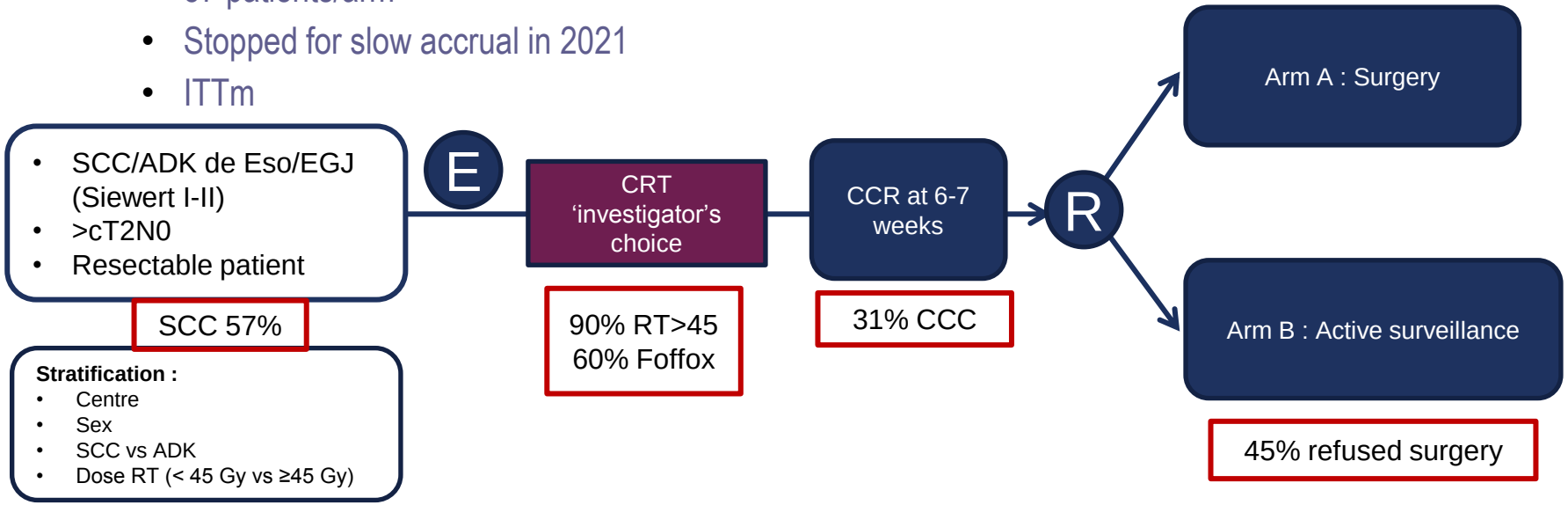
- Genetic? Microbiome?

Zhang, BMS Cancer 2020
Eyck, Br J Surg 2022

Locally advanced tumours

PRODIGE 32 - ESOSTRATE – FFCD1401

- Phase 2 trial randomized: 1 year survival at least 70%
  - 57 patients/arm
  - Stopped for slow accrual in 2021
  - ITTm



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Drouillart et al, JFHOD 2024

Locally advanced tumours

PRODIGE 32 - ESOSTRATE – FFCD1401 : Active Surveillance vs. S

- After a median follow-up of 50,2 months
  - 1-year OS: 78% vs. 100%
  - 3 -year OS: 58,5% vs. 69,0%
  - 3-year treatable RFS: 47,8 % vs. 51,8 %
  - 25% presented a LRC in AS group
- Surgery
  - R0 resection rate :86% vs.100%
  - Complications grade 3-4 (Dindo-Clavien) :43% vs. 47%
  - no 90 day POM

Promising results but difficult to randomize surgery
Oncogical Safety?

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Drouillart et al, JFHOD 2024

Locally advanced tumours

Potential limits of an organ preservation strategy

- AFC cohort
  - Radiotherapy dose > 55 Gy and volume center
    - influenced mortality (x7 and x3) and morbidity

- DICE study 2867 patients
  - Risk of POM
    - 0-50 (ref.)
    - 51-100 HR=1.54, 95%CI 1.04-2.29
    - 101-200 HR=2.14, 95%CI 1.37-3.35
    - > 200 HR=3.06, 95%CI 1.64-5.69

Variable	Overall (N = 848)	After Matching: SALV (n = 308)	After Matching: NCRS (n = 308)	OR (95% CI)	P
In-hospital mortality, No. (%)	76 (9.0)	26 (8.4)	35 (11.4)	0.719 (0.414 to 1.250)	.241
In-hospital morbidity, No. (%)	514 (60.6)	196 (63.6)	188 (61.0)	1.117 (0.818 to 1.525)	.506
Anastomotic leak, No. (%)	111 (13.1)	53 (17.2)	33 (10.7)	1.732 (1.110 to 2.703)	.015
Conduit necrosis, No. (%)	6 (0.7)	4 (1.3)	1 (0.3)	—	NA*
Surgical site infection, No. (%)	123 (14.5)	57 (18.5)	38 (12.3)	1.614 (1.058 to 2.461)	.026
Chylothorax, No. (%)	26 (3.1)	10 (3.3)	10 (3.3)	1.000 (0.404 to 2.474)	> .999
Postoperative hemorrhage, No. (%)	5 (0.6)	1 (0.3)	3 (1.0)	—	NA*
Gastroparesis, No. (%)	10 (1.2)	3 (1.0)	3 (1.0)	—	NA*
Pulmonary, No. (%)	353 (41.6)	132 (42.9)	127 (41.2)	1.069 (0.786 to 1.454)	.672
Cardiovascular, No. (%)	115 (13.6)	42 (13.6)	43 (14.0)	0.973 (0.612 to 1.547)	.908
Thromboembolic, No. (%)	25 (2.9)	9 (2.9)	10 (3.3)	0.900 (0.374 to 2.167)	.814
Neurologic, No. (%)	25 (2.9)	5 (1.6)	8 (2.6)	0.998 (0.876 to 1.113)	.405
Clavien-Dindo score, No. (%)				—	.201
I	64 (7.5)	21 (6.8)	30 (9.7)		
II	168 (19.8)	68 (22.1)	45 (14.6)		
IIIa	51 (6)	20 (6.5)	21 (6.8)		
IIIb	49 (5.8)	23 (7.5)	18 (5.8)		
IVa	86 (10.1)	33 (10.7)	30 (9.7)		
IVb	20 (2.4)	5 (1.6)	9 (2.9)		
V	76 (9)	26 (8.4)	35 (11.4)		

Chidambaram et al, Ann Surg 2023
Markar, J Clin Oncol 2015

Locally advanced tumours

Potential limits of an organ preservation strategy

- Less histological response with 41 Gy, ++ Adk
- No adjuvant Nivolumab in the Surveillance arm

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])

N = 794 → R 2:1

- n = 532 → **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W
- n = 262 → **Placebo** Q2W × 16 weeks then Q4W

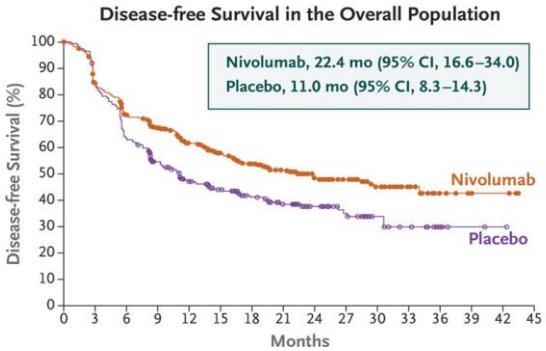
Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2-44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)



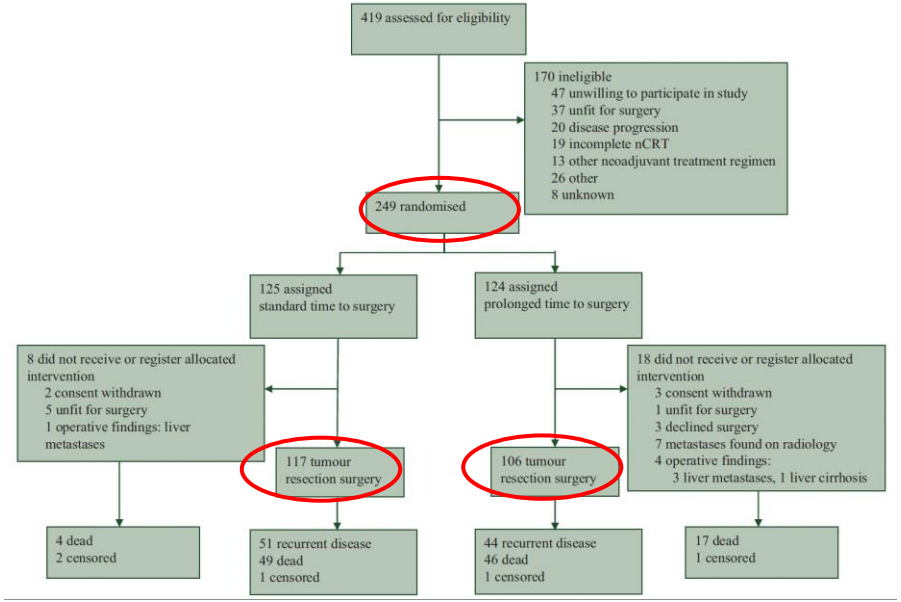
- In progress: SANO-3 cohort and Skyscraper

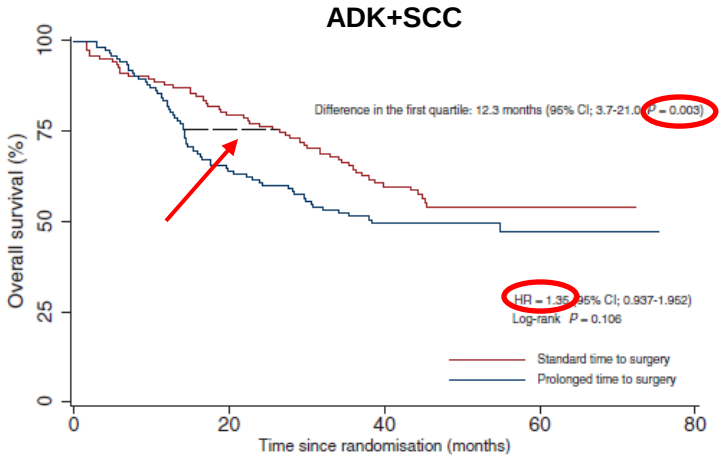
Chidambaram et al, Ann Surg 2023
Mantziari et al, Ann Surg Oncol 2024
Kelly et al, New England J Med 2021

Locally advanced tumours

Potential limits of an organ preservation strategy

- NeoRes2:





→ **+35% risk of death**

In conclusion, prolonged TTS did not improve histological complete response or other pathological endpoints, while there was a strong trend towards worse overall survival, suggesting caution in routinely delaying surgery for >6 weeks after nCRT.

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→ **ypT0N0 rate (ADK) : 26% vs. 21% p=0,429**

Nilsson et al, Annals Oncology 2023

Locally advanced tumours

Perspectives

- Intensification of RCT with induction CT or ICI
  - CROC trial (SCC), RACE-trial (ADC)
- CT
  - Triplet
    - JCOG1109 NeXT) : 16% pCR ypT0(SCC)
    - ESOPEC: pCR 16.8%
  - CT intensified with IO (Dante, Keynote-585,Matterhorn)
    - In PDL1 + and dMMR/MSI high patients
- IO in dMMR/MSI high
  - Neonipiga trial 59% (Nivolumab+Ipilimumab)
  - Dewi trial in progress (Dostarlimab)

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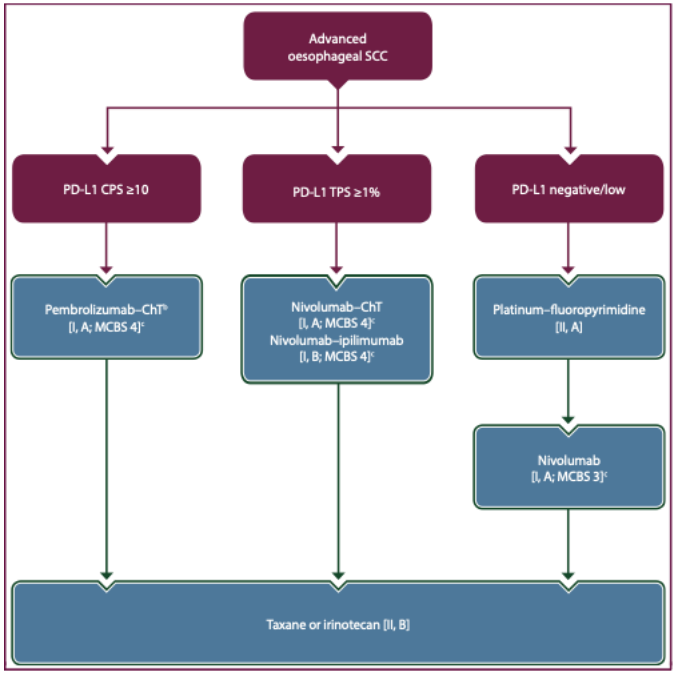
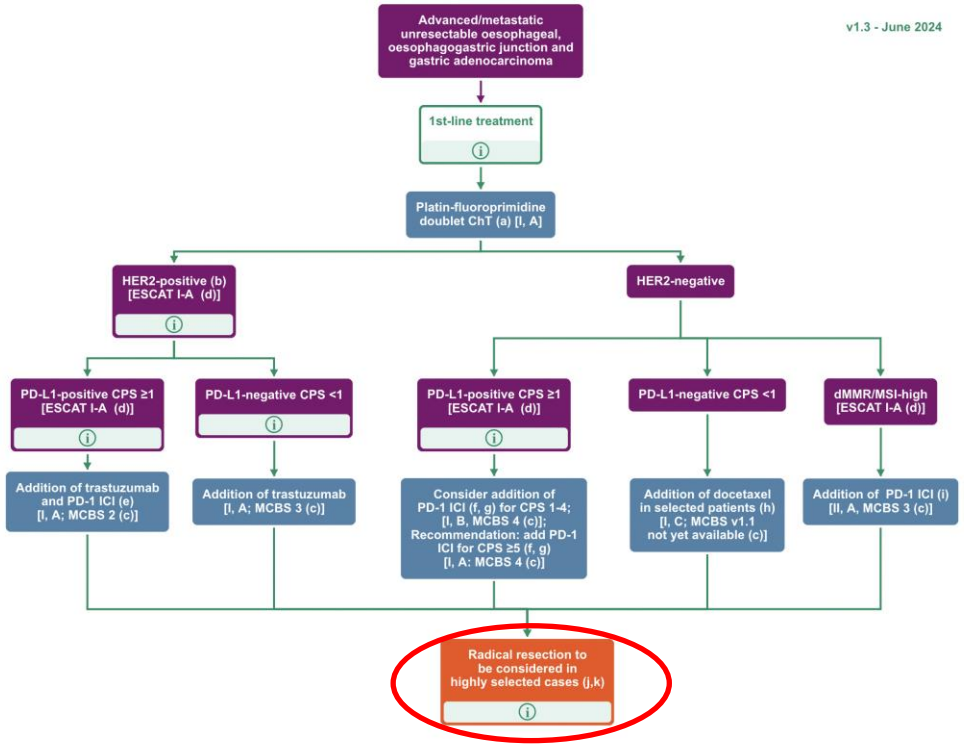
Clin trial UMIN000008086
Lorenzen et al, BMC Cancer 2020
Leong et al, ESMO2024
Lang et al, Oncologist 2022
Li et al, Eur Cancer 2021
Kato et a, Lancet 2024
Lorenzen et al, J Clin oncol 2024
Shitara, Lancet Oncol 2023
Elizabeth Smyth et al., ESMO® 2023, Abs # LBA73
André et al, J Clin Oncol 2022

Current ESMO guidelines: metastatic setting





Surgery cannot be recommended outside the context of a **clinical trial** or in very selected cases, after **a sufficiently long period of systemic treatment (standard of care)** and **after critical discussion in a multidisciplinary tumour board at a high-volume tertiary referral centre**

Lordick et al, Ann Oncol 2022
Obermmanova et al , Ann Oncol 2022

Oligometastatic disease

The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction – a phase III trial of the German AIO/CAO-V/CAOGI

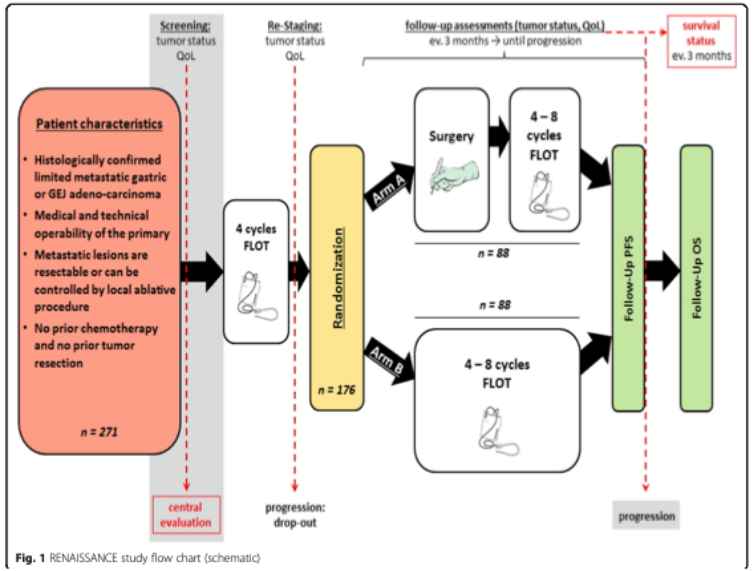
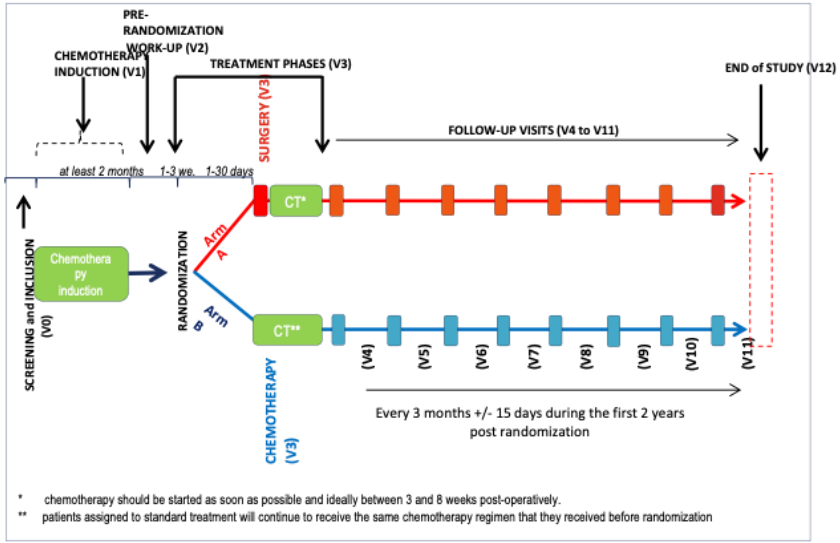


Fig. 1 RENAISSANCE study flow chart (schematic)

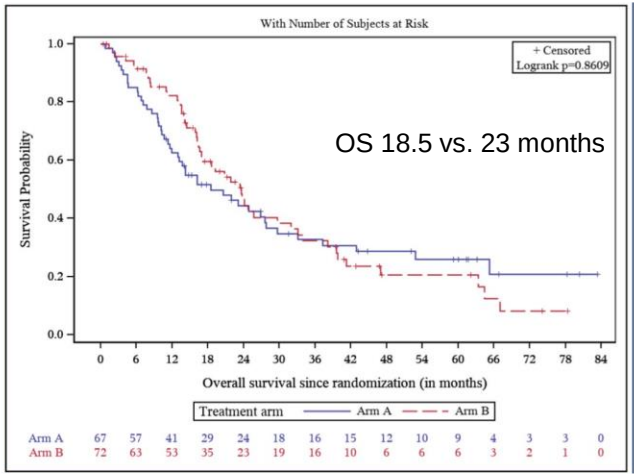
PRODIGE 47 - SURGIGAST



* chemotherapy should be started as soon as possible and ideally between 3 and 8 weeks post-operatively.
** patients assigned to standard treatment will continue to receive the same chemotherapy regimen that they received before randomization

Oligometastatic disease

Renaissance trial



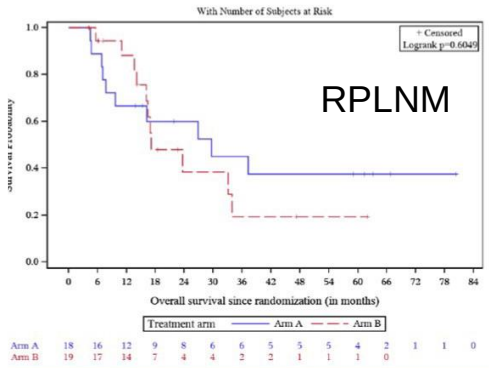
- >90% T3,N+
- A lower exposition ot CT in the surgery arm
  - Cycle 5: 66% vs. 83%
  - Cycle 8: 43% vs. 74%
  - Cycle 12: 4% vs. 39%
  - At progression second line: 52% vs. 82%
- A cross over
  - 91% resection in arm A vs. 21% resection in arm B
- Post operative outcomes
  - morbidity 55% including 16% reoperation
  - 90-d POM 8%
- **Only 50% of patients undergoing surgery had surgery of primary tumour + metastatic site**
- **R0?**

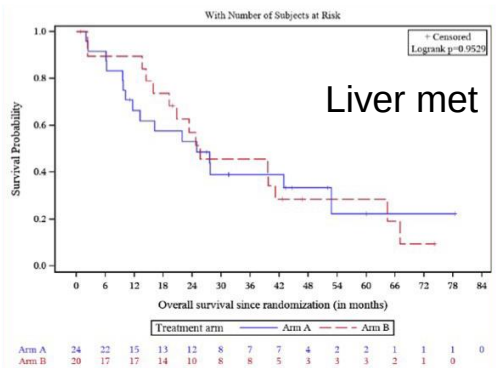
SE. Al Batran et al., ASCO® 2024, Abs #4001

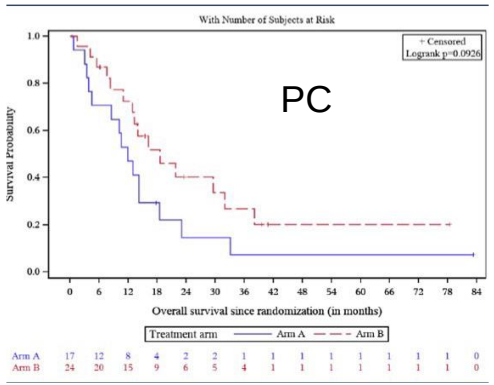
Oligometastatic disease

Renaissance trial

3 main cohorts
Liver metastasis: 49 patients (32%)
Peritoneal carcinomatosis: 41 patients (29%)
RPLNM: 28 patients (20%)







	Subgroup analysis : median OS (3 y OS)		
	RPLN	Liver met	Peritoneal carcinomatosis
Arm A (N=67)	**29.6 (45%)**	**24.9 (39%)**	**11.9 (7%)**
Arm B (N=72)	**17 (19%)**	**25.7 (46%)**	**18.6 (27%)**

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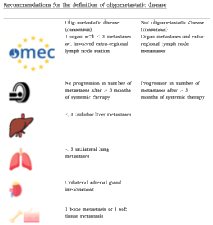
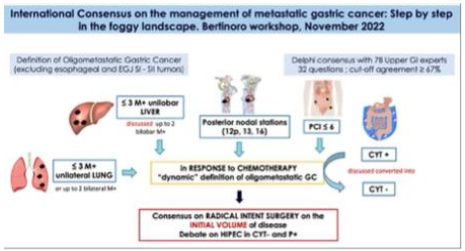
SE. Al Batran et al., ASCO® 2024, Abs #4001

Oligometastatic disease

Renaissance trial : reflexions

- More restricted definition of oligometastatic diseases
  - OMEC and Bertinoro projects
- Best available combination (CT +/- IO and/or targeted therapy)
- Increase duration of neoadjuvant treatment
  - Under reflection OMEC5
- Better selection: ctDNA?
- Less morbidity
  - Radiation, thermal ablation ?





Kroese, Eur J cancer 2023
Morgagni Gastric Cancer 2024
A. Zaanan et al., ASCO® 2024, Abs #4028

Oligometastatic disease

Renaissance trial : reflexions

- ESO-shangai 13
  - SCC, mostly metachronous, lung/LN
  - Best CT, IO regimen +/- local intervention
    - 89% RT
  - Median PFS: 15.3 vs. 6.4 mois , HR 0.26 (0.16-0.42)
  - Toxicity > grade 2 (47% vs. 41% p=0·538)

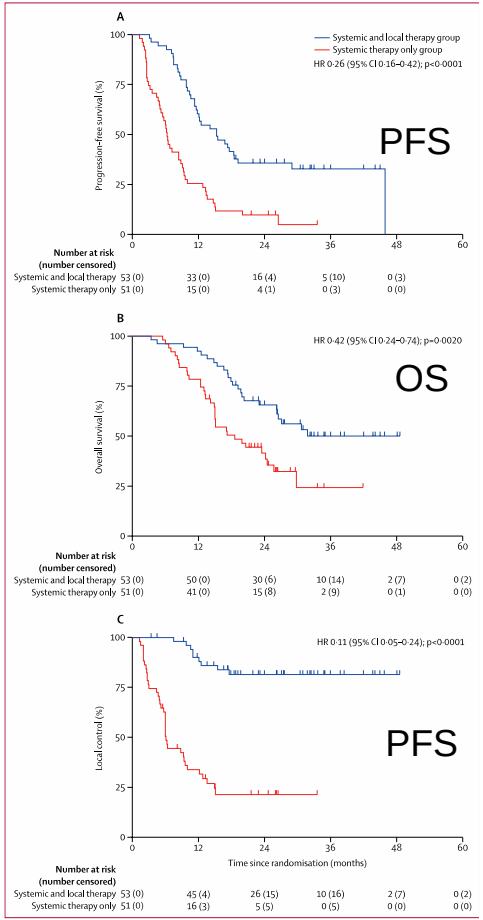


Figure 2: **Kaplan-Meier plots for survival**
(A) Progression-free survival. (B) Overall survival. (C) Local control.

Liu, Lancet Gastroenterolhepatol 2024

Oligometastatic disease

Renaissance trial : reflexions

- Dedicated trial for peritoneal carcinomatosis
  - Periscope II (Pr Van Sandick)
  - Convergence trial (Pr Jimmy SO Bok Yan)
    - Permits peritoneal directed treatment in addition
  - Restrictive criteria
    - Limit of PCI 7
    - Response to induction ttt
  - Optimal control group
    - Best combination available
  - Optimal surgery
    - Cytoreductive surgery+HIPEC


STUDY PROTOCOL Open Access

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II)

HIPEC according to PERISCOPE I

Oxaliplatin 460 mg/m² (41–42∘C) 30 min,

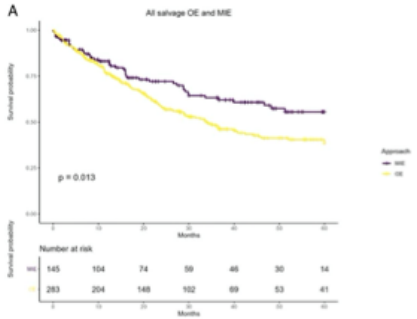
Docetaxel 50 mg/m² (37∘C) 90min

Koemans, BMC Cancer 2019
Van Der Kaiij Br J Surg 2020

Regardless of tumour stage

The best quality surgery

- Only curative surgery
- Prehabilitation and enhanced recovery
- In the good place
  - volume and adequate multidisciplinary team
- By a skilled surgeon
- With the optimal surgical technic
  - To improve short terms
  - And even long terms results



Birkmeyer et al , New England J Med 2003
Deroyar et al , J Clin Oncol 2013
Pasquier et al, Ann Surg 2016
Nuytens et al, JAMA Surg 2022
Markar et al, Ann Surg 2024

To operate or not operate: Personalized surgical approaches in the curative setting

Conclusion

- Surgery used to be the corner stone of treatment of oesogastric cancer
- Consistently challenged by the endoscopists and the oncologists
- Moved to a personalized surgical approach
- Concept of treatment response to tailor the approach : present and futur tools
- Molecular testing to provide personalize treatment but tumour heterogeneity : room for surgery
- Multidisciplinary Team Approach and Shared Decision-Making

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Thank you for your attention

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