Definitive CRT (organ preservation) in Esophageal cancer

Is it possible and what's new?

Dr Maryam garousi

Iran university of medical sciences

Concerns:

- Trial design
- RR assessment
- Short-term Follow up
- Adjuvant nivolumab
- Role of RT in ADC

Randomized trial

- SANO trial
- German (stahl) trial
- FFCD trial

Sano trial

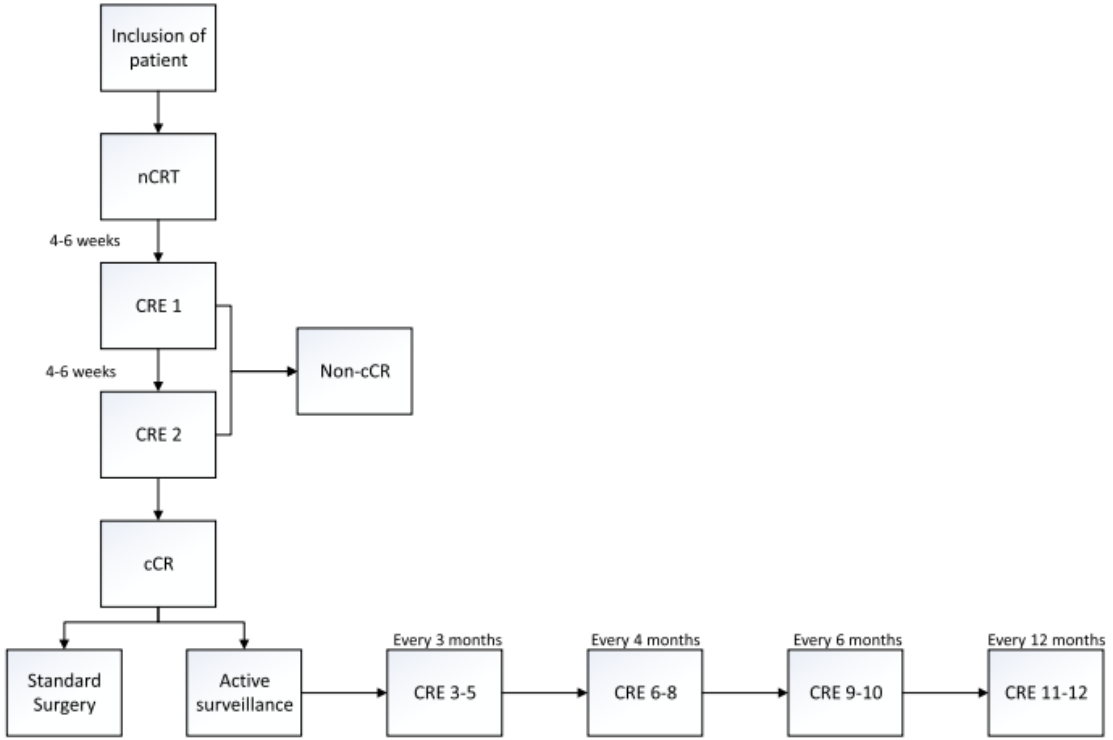
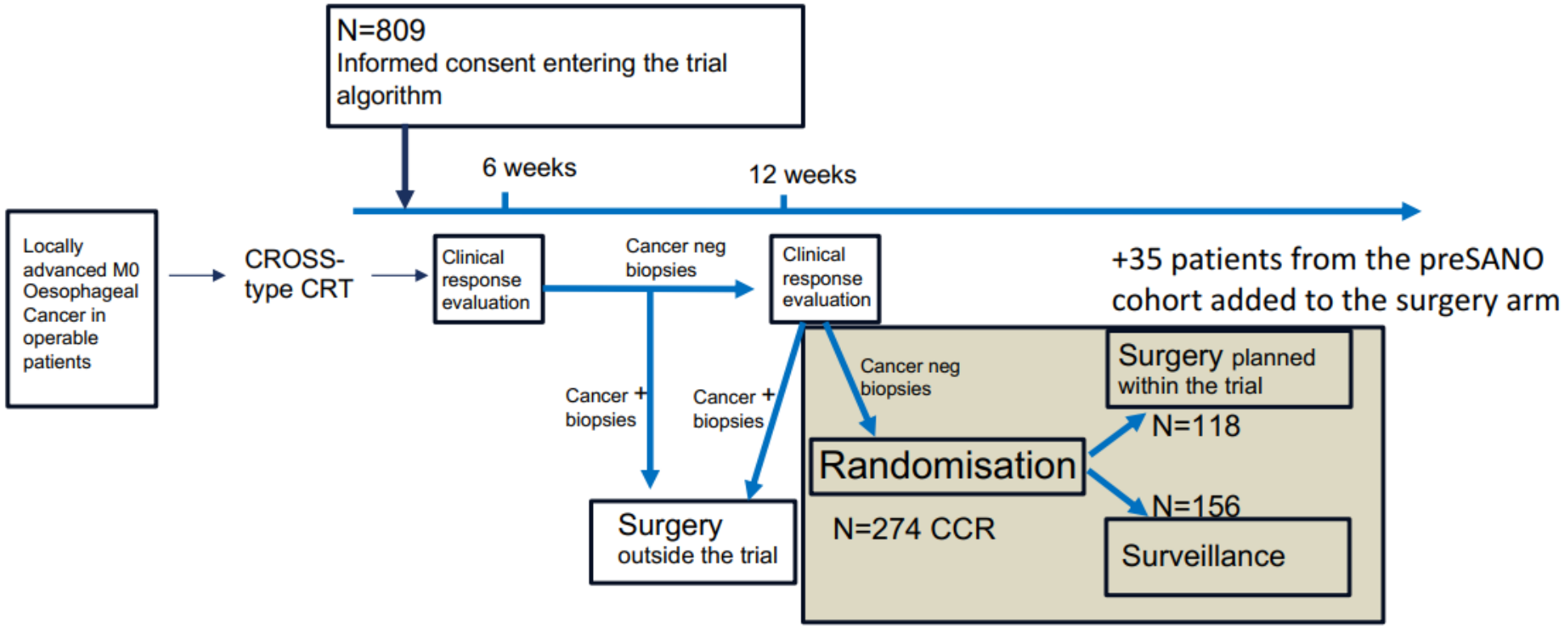


Fig. 1 Schematic overview of the SANO trial, comparing active surveillance with standard oesophagectomy in patients with oesophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy. Patients in whom no residual tumour is detected at two clinical response evaluations after neoadjuvant chemoradiotherapy are considered to have a clinically complete response. Patients who do not have a clinically complete response will undergo oesophagectomy in case no distant metastases are detected. If patients have residual disease at one of the clinical response evaluations during active surveillance (CRE 3–12), postponed oesophagectomy will be performed in case no distant metastases are detected and active surveillance will be stopped. nCRT neoadjuvant chemoradiotherapy, CRE clinical response evaluation, cCR clinically complete responder

The SANO trial



- RR assessment:
- CRE-1 : endoscopy with bite-on-bite biopsies
- CRE-2 : 18F-FDG PET/CT, followed by endoscopy with bite-on-bite biopsies and (EUS) with FNA of suspected lymph nodes.

AS

- Patients in the active surveillance arm undergo diagnostic evaluations similar to CRE-2 every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly in the fourth and fifth year.

SANO result (2years follow up)

- During active surveillance, 69 patients (35%) maintained CCR, 96 patients (48%) developed locoregional regrowths, and 33 patients (17%) developed distant metastases.
- . Median DFS for active surveillance was 35 (95% CI 31 – 41) versus 49 months (95% CI 38 – NA) for standard surgery (HR 1.35, 95% CI 0.89 – 2.03, p = 0.15).
- At 30 months after nCRT, 43% of patients with active surveillance versus 34% with standard surgery developed distant metastases (OR 1.45, 95% CI 0.85 – 2.48, p = 0.18).

The SANO trial

Three main concerns

- **Contamination of stepped-wedge cluster randomised ITT patients** (with cross-over and pre-SANO patients)
- **Mixing histologies** (SCC and adenocarcinomas) 75% adenocarcinomas, **no analyses by histological type presented yet**
- **Assumption that it's safe to delay surgery for >10 weeks** in non-CCR patients

The SANO trial

Non-complete clinical responders (N=535?)

- Were operated outside the trial
  →no control group for these patients

- Were operated >10 weeks after completed nCRT

Can we assume that this is safe?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

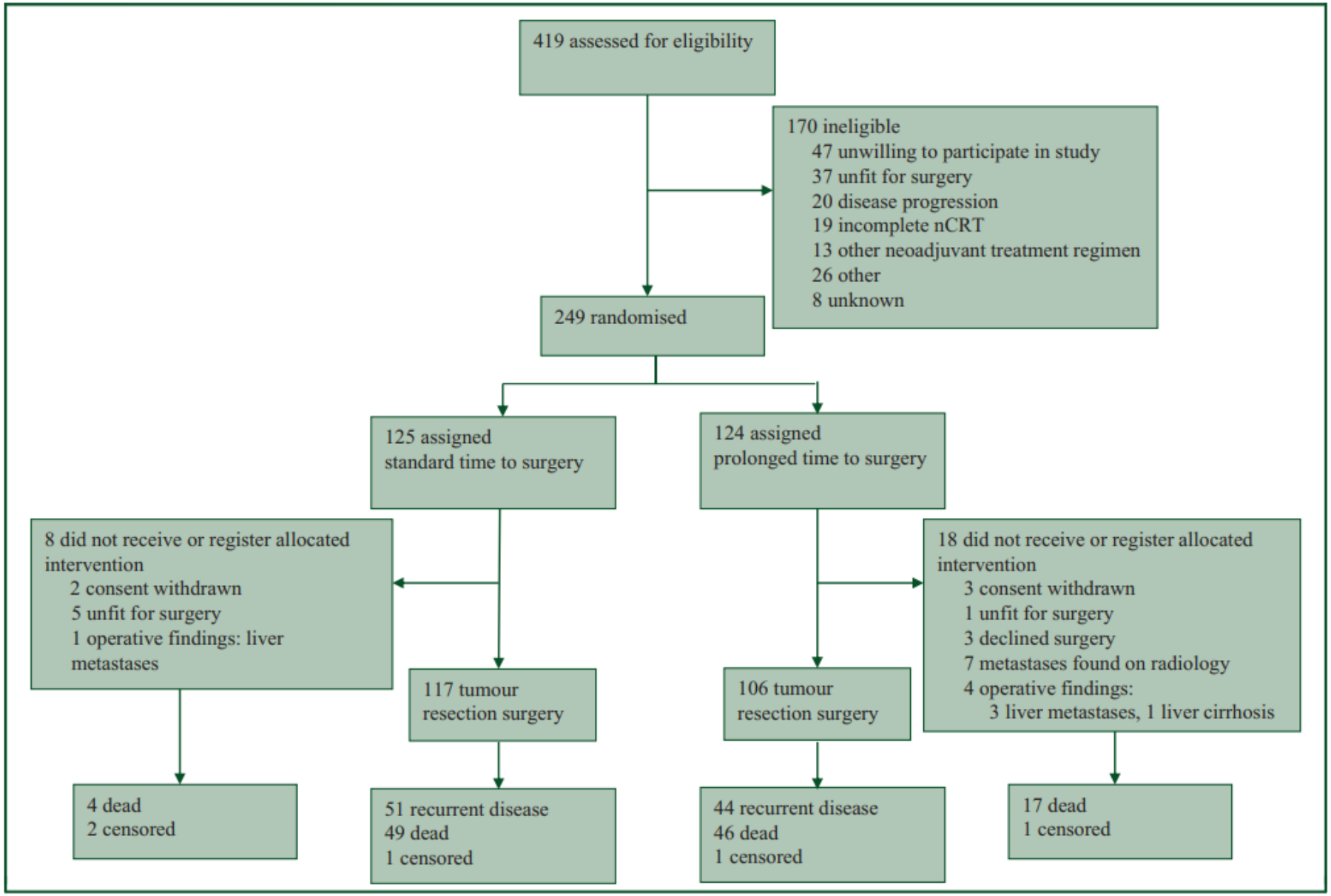
ORIGINAL ARTICLE

Oncological outcomes of standard versus prolonged time to surgery after neoadjuvant chemoradiotherapy for oesophageal cancer in the multicentre, randomised, controlled NeoRes II trial

K. Nilsson[1,2], F. Klevebro[1,2], B. Sunde[1,2], I. Rouvelas[1,2], M. Lindblad[1,2], E. Szabo[3], I. Halldestam[4], U. Smedh[5], B. Wallner[6], J. Johansson[7], G. Johnsen[8], E. K. Aahlin[9], H.-O. Johannessen[10], G. Alexandersson von Döbeln[2,11], G. O. Hjortland[12], N. Wang[13], Y. Shang[14], D. Borg[15], A. Quaas[16], I. Bartella[17], C. Bruns[17], W. Schröder[17] & M. Nilsson[1,2]*

[1]Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm; [2]Division of Surgery and Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm; [3]Department of Surgery, Faculty of Medicine and Health, Örebro University Hospital, Örebro; [4]University Hospital of Linköping, Linköping; [5]Department of Surgery, Sahlgrenska University Hospital, Gothenburg; [6]Department of Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå; [7]Department of Surgery, Skåne University Hospital, Lund, Sweden; [8]Department of Gastrointestinal Surgery, St. Olav's Hospital, Trondheim University Hospital, Trondheim; [9]Department of GI and HPB Surgery, University Hospital of Northern Norway, Tromsø; [10]Department of Gastrointestinal Surgery, Oslo University Hospital, Oslo, Norway; [11]Medical Unit of Head, Neck, Lung and Skin Cancer, Karolinska University Hospital, Stockholm, Sweden; [12]Department of Oncology, Oslo University Hospital, Oslo, Norway; [13]Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm; [14]Department of Medicine Huddinge, Karolinska Institutet, Stockholm;[15]Department of Oncology, Skåne University Hospital, Lund, Sweden; [16]Institute of Pathology, University of Cologne, Cologne; [17]Department of General, Visceral, Cancer and Transplantation Surgery, University Hospital of Cologne, Cologne, Germany

Available online 30 August 2023


419 assessed for eligibility
170 ineligible
47 unwilling to participate in study
37 unfit for surgery
20 disease progression
19 incomplete nCRT
13 other neoadjuvant treatment regimen
26 other
8 unknown
249 randomised
125 assigned
standard time to surgery
124 assigned
prolonged time to surgery
8 did not receive or register allocated intervention
2 consent withdrawn
5 unfit for surgery
1 operative findings: liver metastases
18 did not receive or register allocated intervention
3 consent withdrawn
1 unfit for surgery
3 declined surgery
7 metastases found on radiology
4 operative findings:
3 liver metastases, 1 liver cirrhosis
117 tumour resection surgery
106 tumour resection surgery
4 dead
2 censored
51 recurrent disease
49 dead
1 censored
44 recurrent disease
46 dead
1 censored
17 dead
1 censored

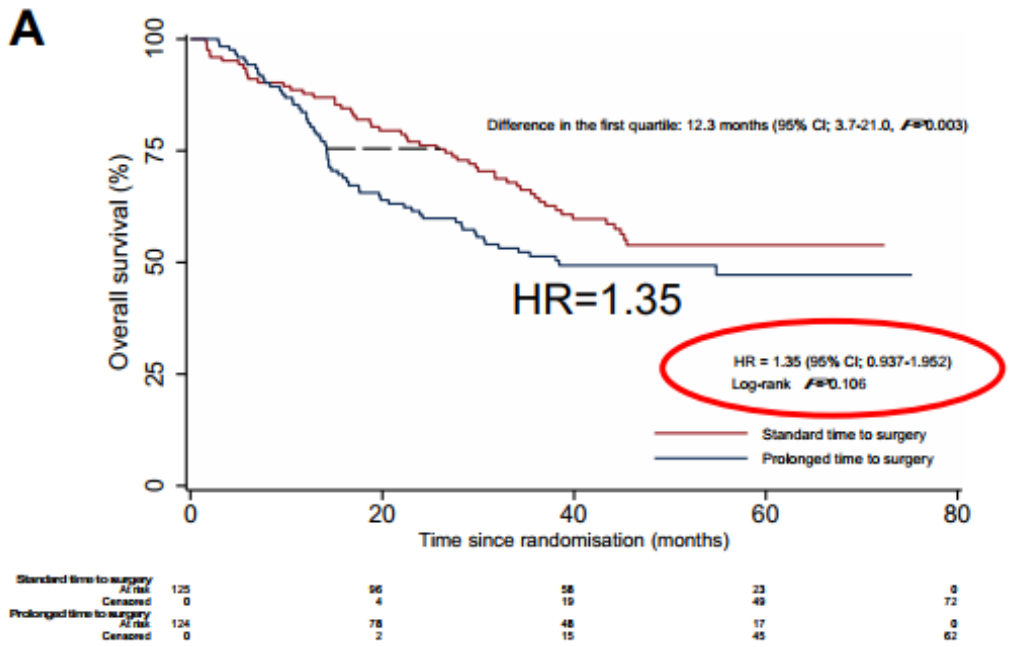
The NeoRes II trial

- Operable oesophageal cancer patients, stage II-III
- All patients had CROSS type nCRT before enrolment
- Restaging PET/CT within 10 days
- Randomised to operation at :
  4-6 vs
  10-12 weeks after nCRT
- N=249
- Primary endpoint pCR (superiority for prolonged TTS), secondary overall survival etc

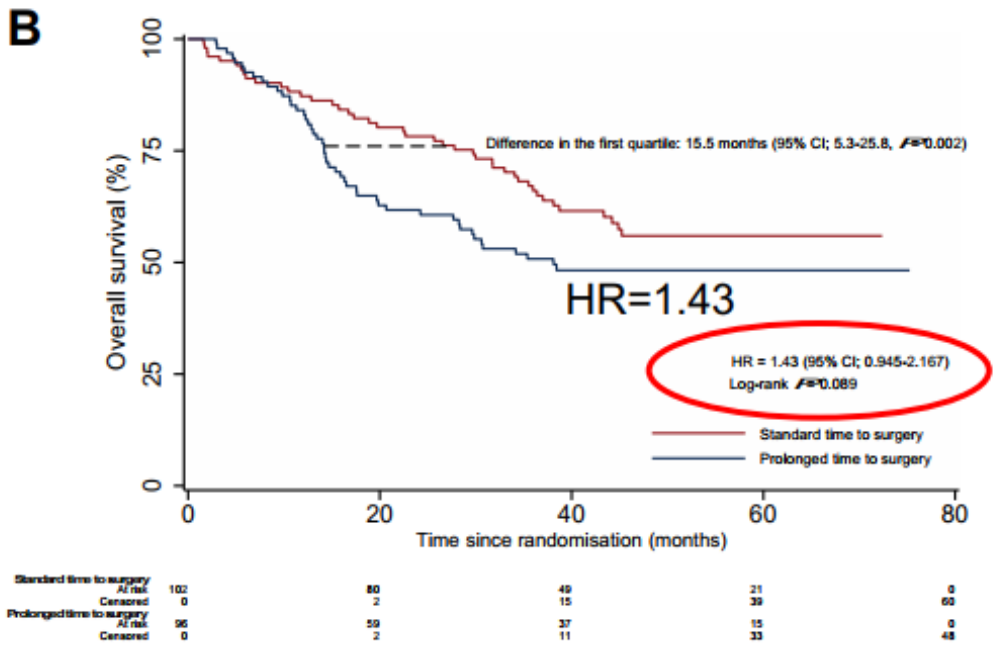
The NeoRes II trial

Overall survival (ITT analyses)

All randomised patients



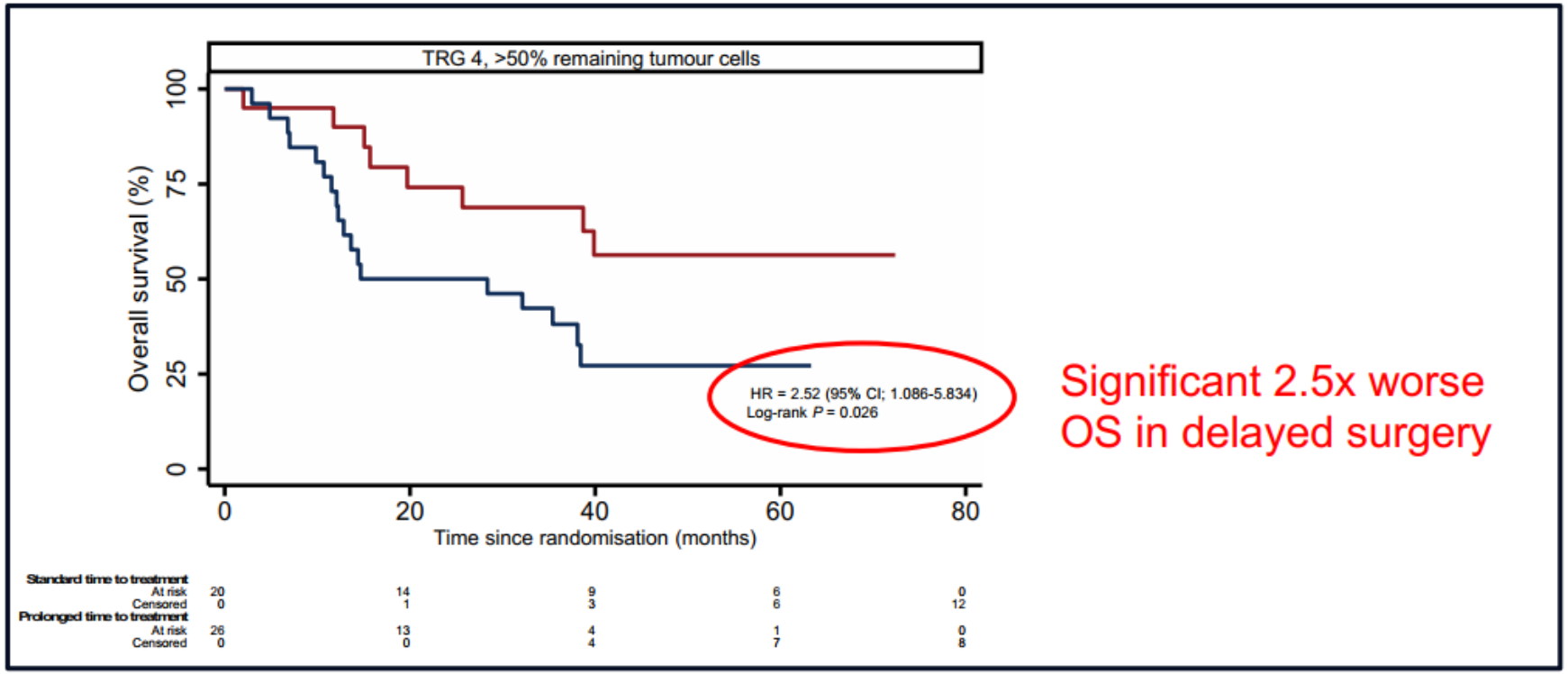
All adenocarcinoma patients



Nilsson K et al. Annals of Oncology 2023

The NeoRes II trial

Overall survival, TRG 4 (path non-responders)



Significant 2.5x worse OS in delayed surgery

Nilsson K et al. Annals of Oncology 2023

The SANO trial

Non-complete clinical responders (N=535?)

- Were operated outside the trial
  →no control group for these patients
- Were operated >10 weeks after completed nCRT

Can we assume that this is safe?

No, does not appear to be safe

SANO does not provide valid and generalizeable evidence to guide clinical practice

Old trials

- Stahl trial
- FFCD trial

VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus

Michael Stahl, Martin Stuschke, Nils Lehmann, Hans-Joachim Meyer, Martin K. Walz, Siegfried Seeber, Bodo Klump, Wilfried Budach, Reinhard Teichmann, Marcus Schmitt, Gerd Schmitt, Claus Franke, and Hansjochen Wilke

From the Departments of Medical Oncology and Hematology and Surgery, Kliniken Essen-Mitte; Institute for Medical Informatics, Biometry and Epidemiology, Department of Radiation Oncology, and Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen Medical School, Essen; Department of Surgery, Klinikum Solingen, Solingen; Departments of Gastroenterology, Radiation Oncology, and Surgery, University Clinic, Tübingen; and Departments of Gastroenterology, Radiation Oncology, and Surgery, University Clinic, Düsseldorf, Germany.

Submitted July 27, 2004; accepted December 21, 2004.

Supported by the Stiftung Deutsche Krebshilfe.

Presented in part at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001; and at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 3, 2003.

Authors' disclosures of potential conflicts of interest are found at the end of

ABSTRACT

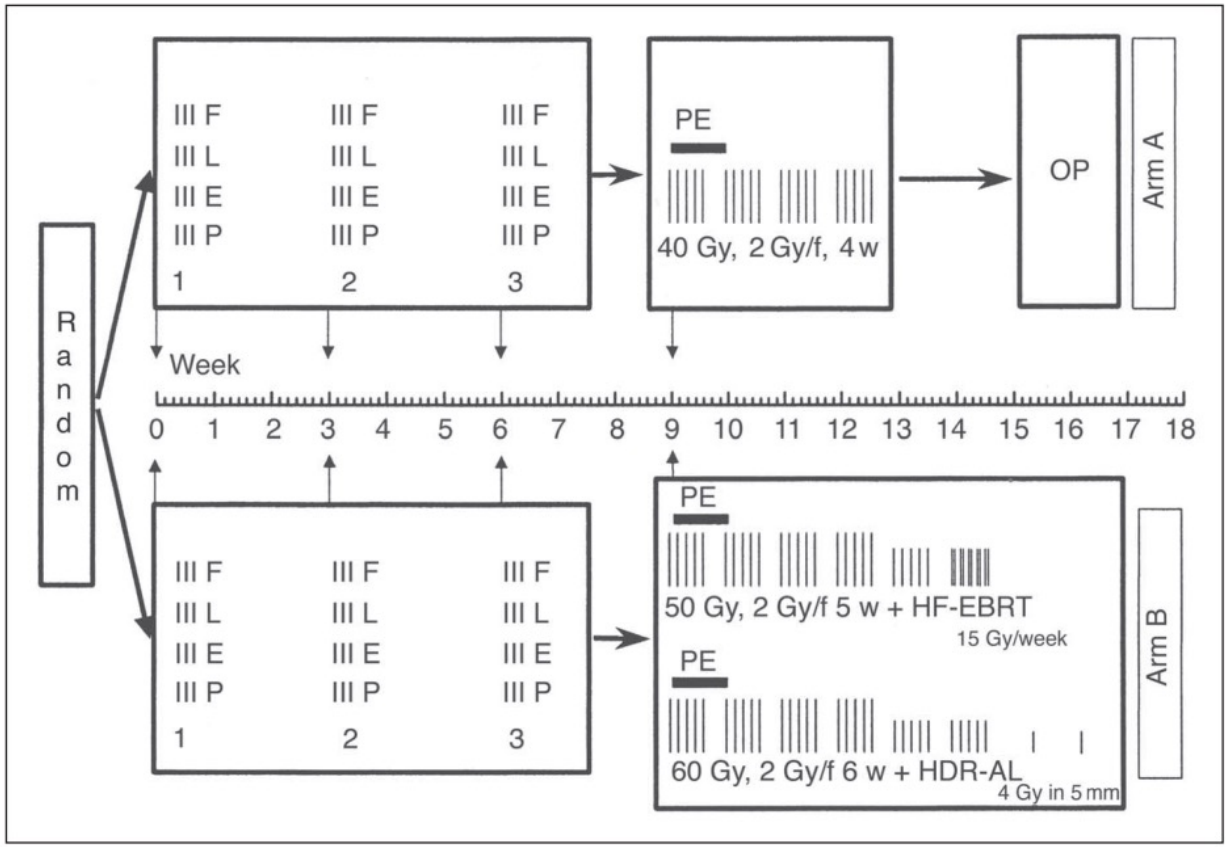
Purpose
Combined chemoradiotherapy with and without surgery are widely accepted alternatives for the curative treatment of patients with locally advanced esophageal cancer. The value of adding surgery to chemotherapy and radiotherapy is unknown.

Patients and Methods
Patients with locally advanced squamous cell carcinoma (SCC) of the esophagus were randomly allocated to either induction chemotherapy followed by chemoradiotherapy (40 Gy) followed by surgery (arm A), or the same induction chemotherapy followed by chemoradiotherapy (at least 65 Gy) without surgery (arm B). Primary outcome was overall survival time.

Results
The median observation time was 6 years. The analysis of 172 eligible, randomized patients (86 patients per arm) showed overall survival to be equivalent between the two treatment groups (log-rank test for equivalence, $P < .05$). Local progression-free survival was better in the surgery group (2-year progression-free survival, 64.3%; 95% CI, 52.1% to 76.5%) than in the chemoradiotherapy group (2-year progression-free survival, 40.7%; 95% CI, 28.9% to 52.5%; hazard ratio [HR] for arm B *v* arm A, 2.1; 95% CI, 1.3 to 3.5; $P = .003$). Treatment-related mortality was significantly increased in the surgery group than in the chemoradiotherapy group (12.8% *v* 3.5%, respectively; $P = .03$). Cox regression analysis revealed clinical tumor response to induction chemotherapy to be the single independent prognostic factor for overall survival (HR, 0.30; 95% CI, 0.19 to 0.47; $P < .0001$).

Conclusion
Adding surgery to chemoradiotherapy improves local tumor control but does not increase survival of patients with locally advanced esophageal SCC. Tumor response to induction

Trial design



- 2year local control:
- 64%vs 40%

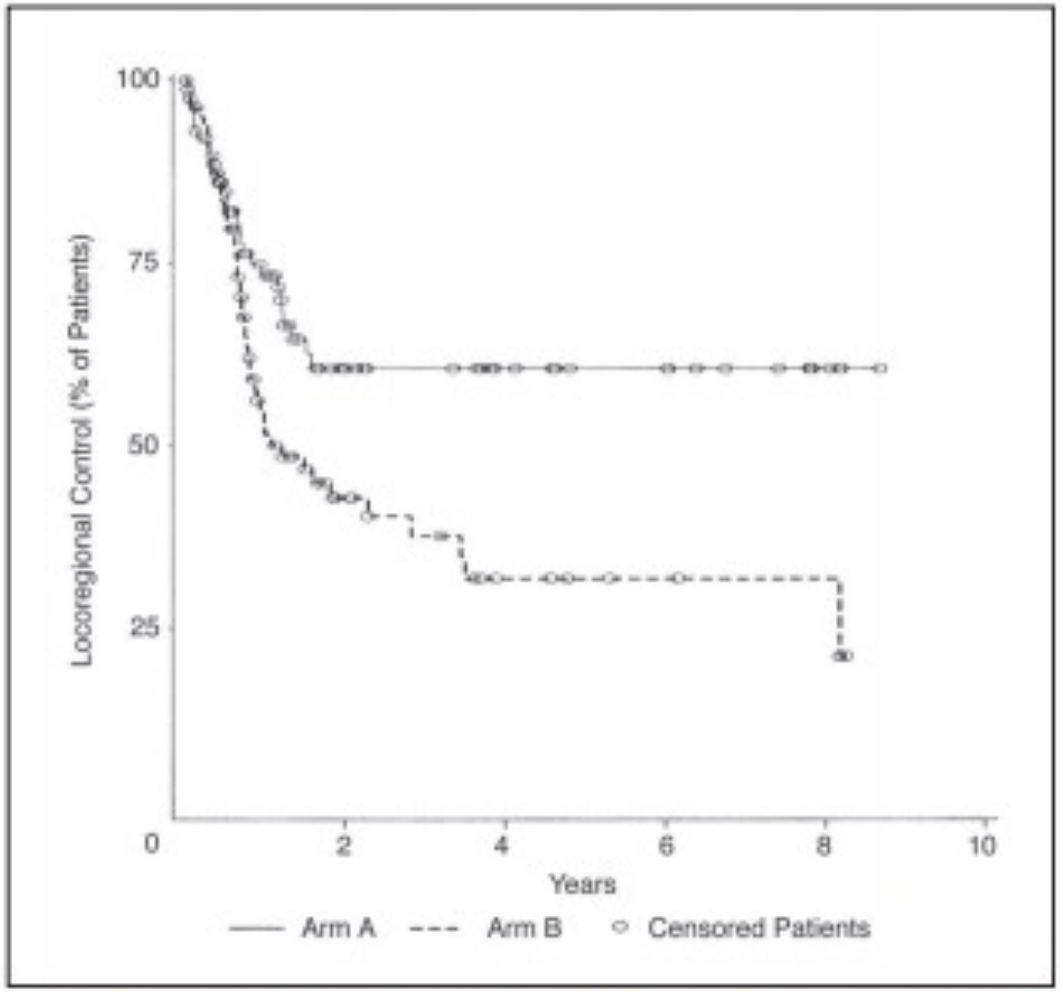


Fig 4. Kaplan-Meier plots showing the freedom from locoregional progression among patients allocated to preoperative chemoradiation and surgery (arm A) or chemoradiation without surgery (arm B).

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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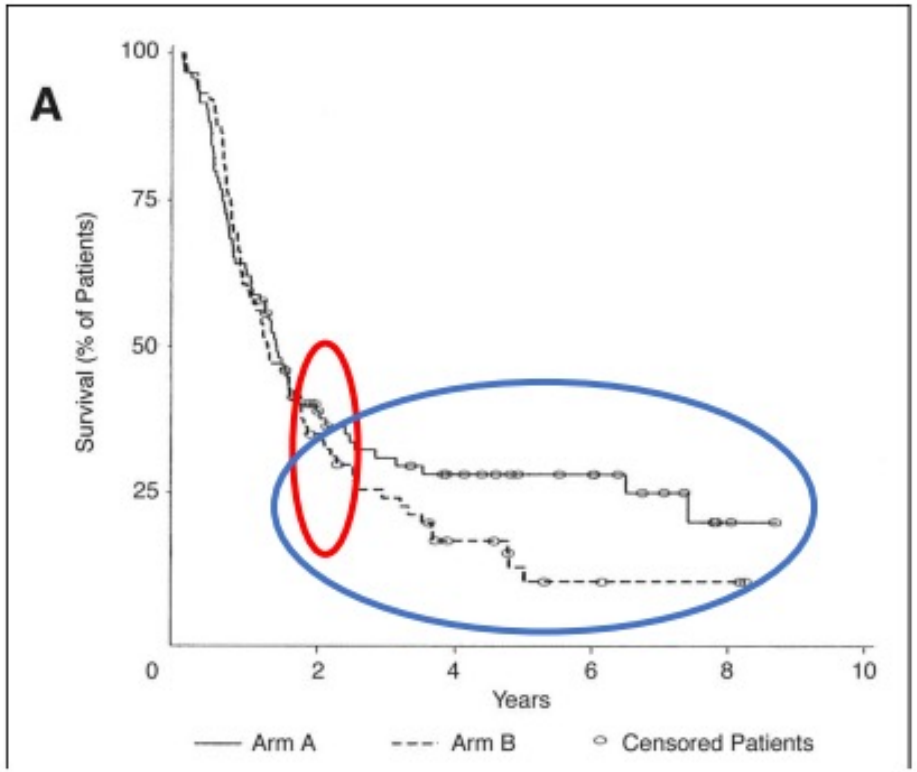

Overall survival

- Primary endpoint OS at two years
  - Arm A: 39.9%
  - Arm B: 35.4%
  - =Delta 0.045 (<0.15)
  - **Equivalence**
  - Overall survival throughout follow-up:
    - Just under stat signficance level
      - **Trial very underpowered for this more relevant endpoint**

VOLUME 23 · NUMBER 10 · APRIL 1 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus

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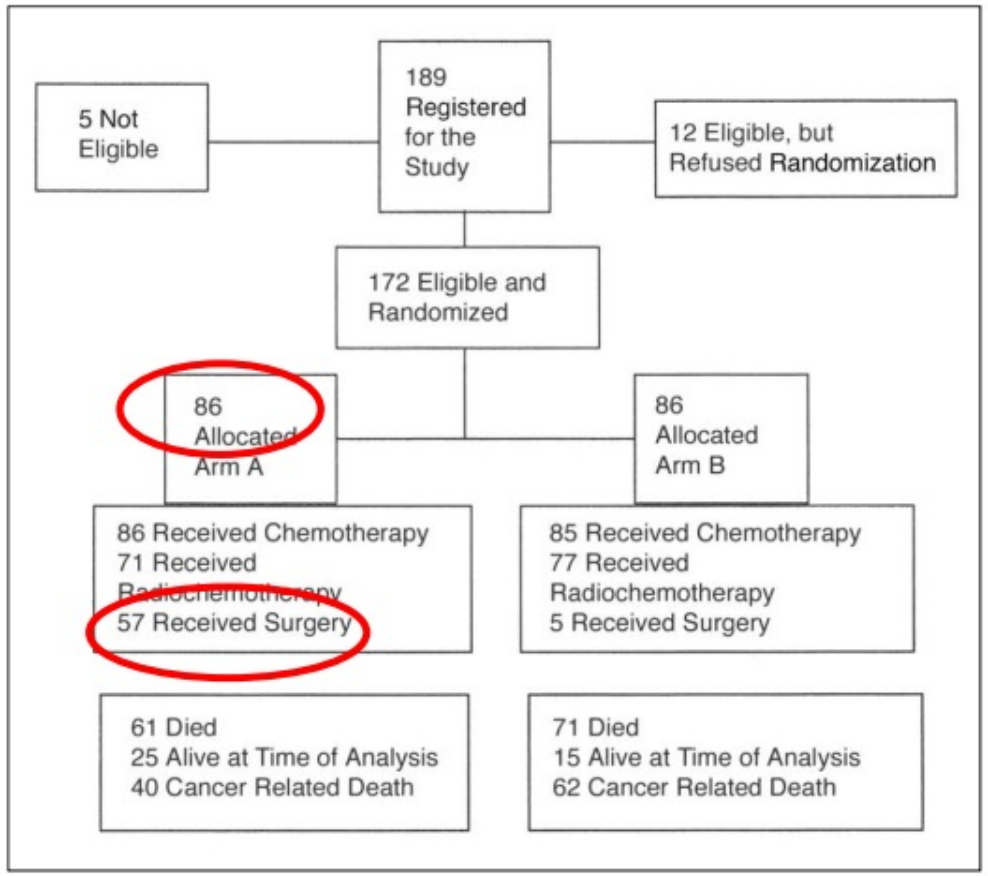


- Out of 86 patients allocated to planned surgery only 57 **(66%) were operated**
- 7 out of 57 **(12.3%)** operated patients **died postop**

Treatment related mortality

- Surgical mortality: 11%
- Surgical morbidity: 70%

- This survival benefit in nCRT may be attributed to the lower mortality in the nCRT group than in the nCRT.
- The morbidity and mortality have greatly reduced in the recent decade.

- In the MD Anderson Cancer Center (UICC), comparison between the early (1987–2000) and modern eras (1997–2010) showed that the mortality rate decreased from **6 to 3%** for planned surgery .

Stahl trial concerns:

- Trial design
- Short-term F/U
- High surgery-related mortality

FFCD trial

VOLUME 25 · NUMBER 10 · APRIL 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102

Laurent Bedenne, Pierre Michel, Olivier Bouché, Chantal Milan, Christophe Mariette, Thierry Conroy, Denis Pezet, Bernard Roullet, Jean-François Seitz, Jean-Philippe Herr, Bernard Paillot, Patrick Arveux, Franck Bonnetain, and Christine Binquet

From the University Hospital Le Bocage; Anticancer Center Georges-François Leclerc, Dijon; University Hospital Charles-Nicolle, Rouen; University Hospital Robert-Debré, Reims; University Hospital Claude-Huriez, Lille; Anticancer Center Alexis Vautrin, Vandoeuvre; University Hospital Hôtel-Dieu, Clermont-Ferrand; University Hospital Dupuytren, Limoges; Université de la Méditerranée, Marseille; and Clinique Sainte-Marie, Chalon, France.

Submitted October 24, 2005; accepted October 11, 2006.

Supported by grants from the Ligue Nationale Contre le Cancer, the Fonds de Recherche de la Société Nationale Française de Gastroentérologie, the Programme Hospitalier pour la Recher-

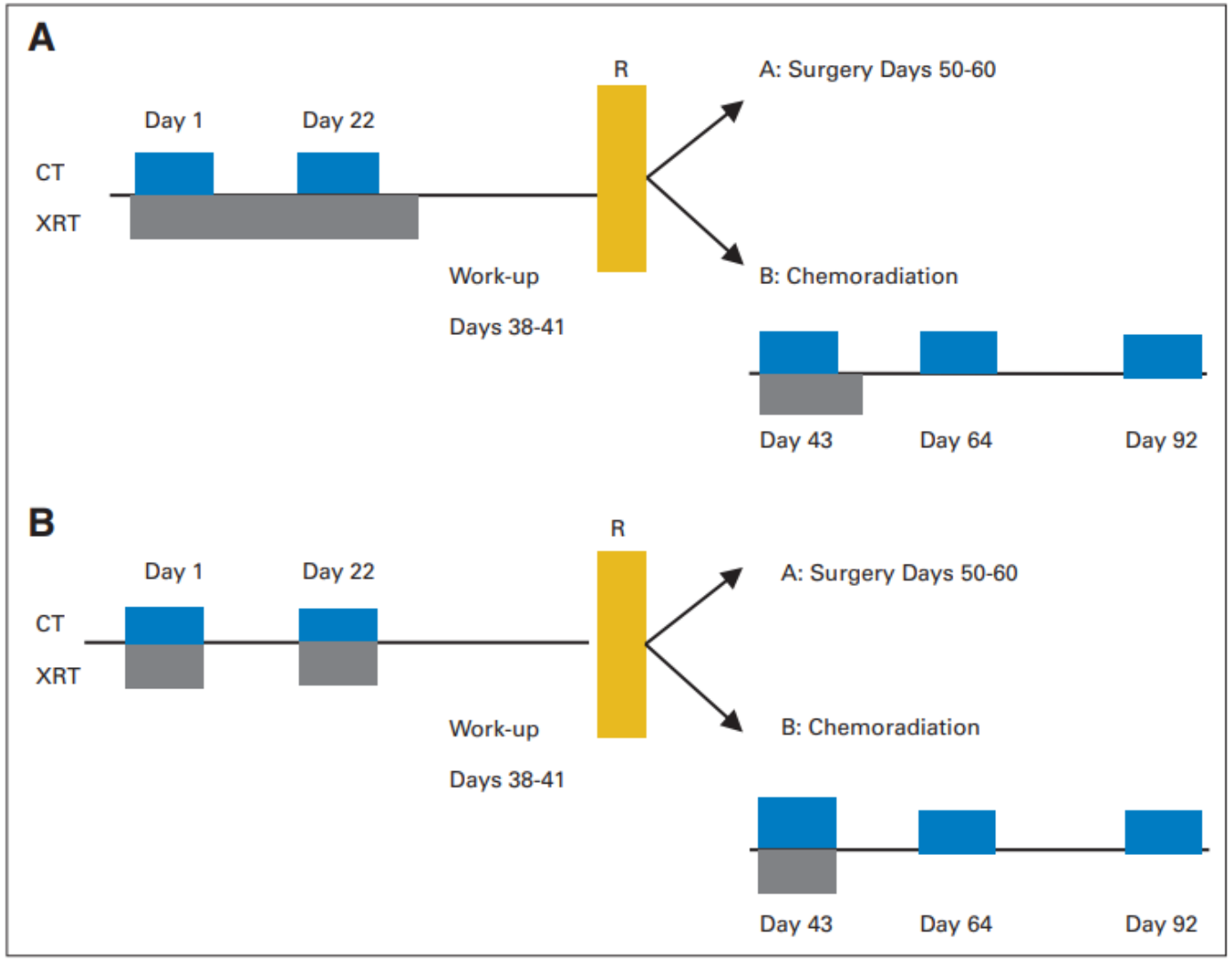
A B S T R A C T

Purpose
Uncontrolled studies suggest that chemoradiation has similar efficacy as surgery for esophageal cancer. Therefore, a randomized trial was carried out to compare, in responders only, chemoradiation alone with chemoradiation followed by surgery in patients with locally advanced tumors.

Patients and Methods
Eligible patients had operable T3N0-1M0 thoracic esophageal cancer. Patients received two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. Patients with response and no contraindication to either treatment were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy). Chemoradiation was considered equivalent to surgery if the difference in 2-year survival rate was less than 10%.

Results
Of 444 eligible patients, 259 were randomly assigned; 230 patients (88.8%) had epidermoid

Trial design



Mortality rate

- 3m mortality: 9% vs 1%
- 6m mortality: 16% vs 6%

Other finding:

Salvage oesophagectomy:

	<55 Gy	≥55 Gy	P
Inhospital mortality	**4.3%**	**17.5%**	<0.001

- Dysphagia and Palliative Procedures:
- 24% vs 46%
- Loco-regional recurrence:
- 33% vs 43%

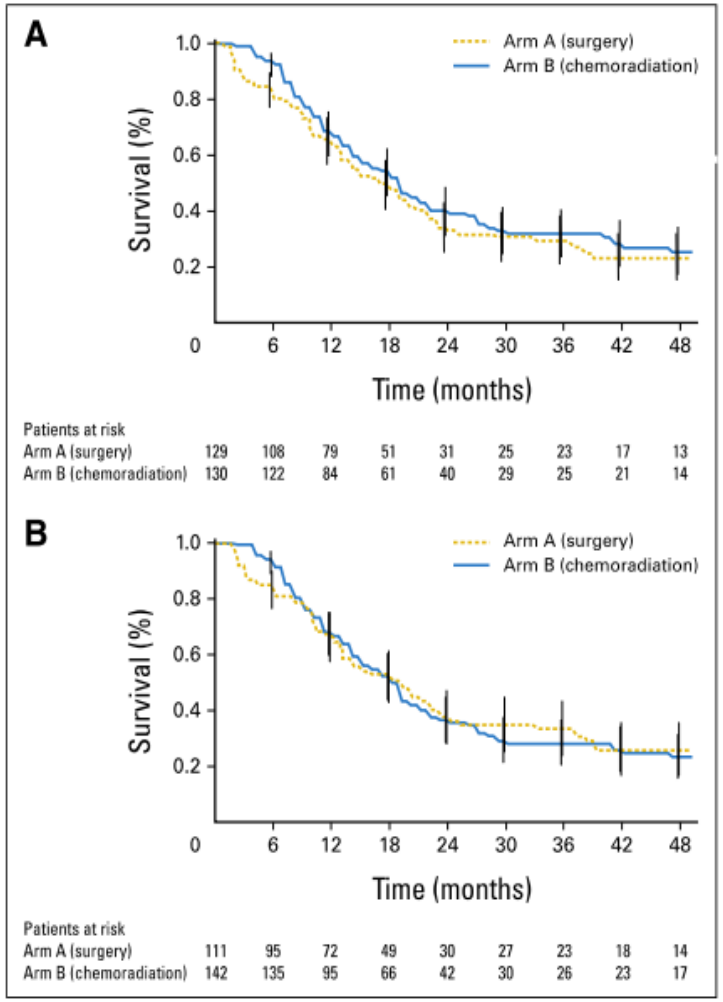


Fig 3. Overall survival of the patients with esophageal cancer responding to induction chemoradiation who were randomly assigned to either surgery (arm A) or continuation of chemoradiation (arm B). (A) Survival in intent-to-treat analysis. (B) Survival in per-protocol analysis. The 95% CIs of the survival rates are indicated on the figures.

No difference in survival

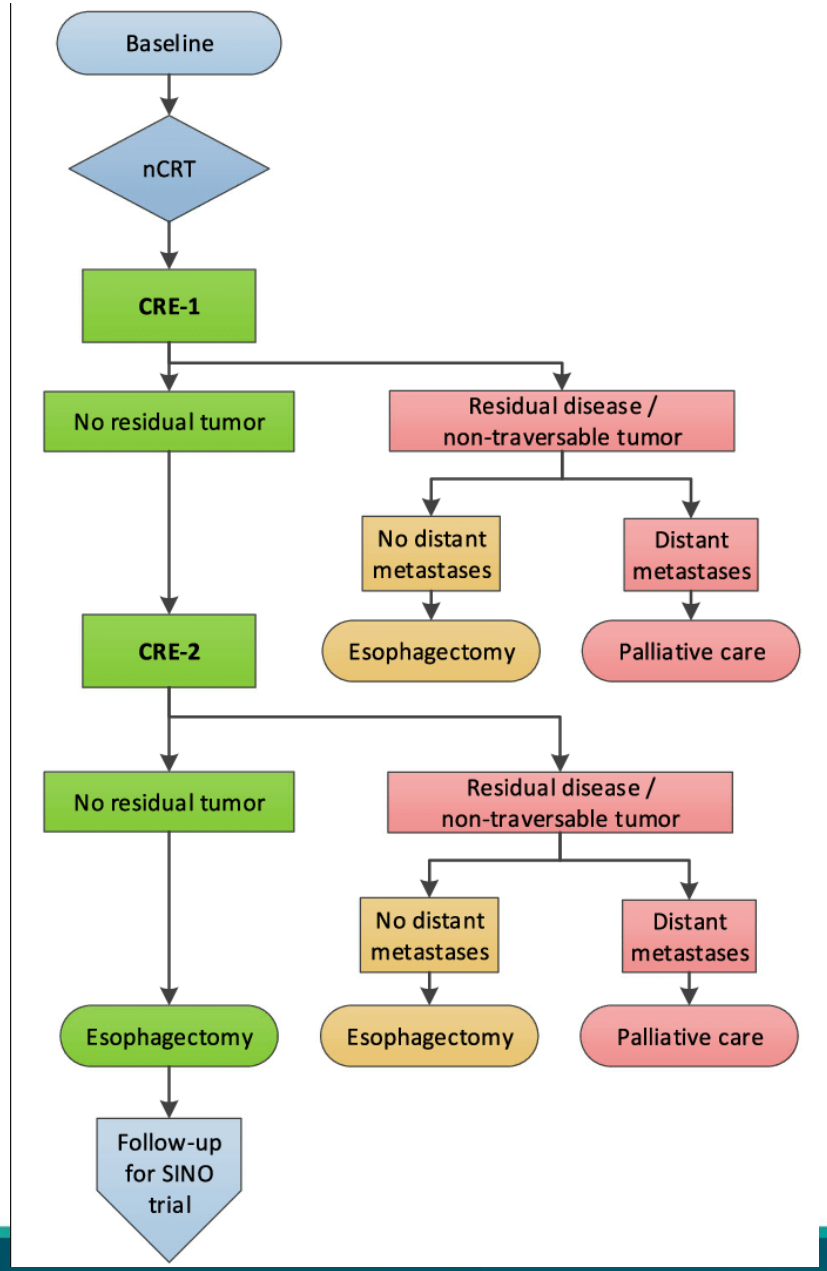
- **9.3% postop mortality**
- **77%** of operated patients (considered to be clinical responders) **had residual disease**

Surgical pathology result

- No residue: 23%
- Microscopic residue: 16%
- Macroscopic residue: 61%

- **Current response assessment is enough?**

Pre SANO trial



- First clinical response: endoscopy with biopsies and EUS with measurement of maximum tumor thickness.
- Second clinical response evaluation : PET–CT, endoscopy with biopsies, EUS with measurement of maximum tumor thickness, and FNA of suspicious lymph nodes.
- All patients eventually underwent surgery. The primary endpoint of this study was the association of cCR with pCR.

- In this study, **31%** of tumor regression grade (TRG) 3 or TRG4 were missed by **endoscopy with regular biopsies and FNA.**
- **10%** were missed by **bite on-bite biopsies plus FNA.**
- **28%** were missed by **EUS plus FNA.**
- **15%** were missed by **PET-CT.**

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Meeting Abstract: 2009 ASCO Annual Meeting I

FREE ACCESS | Gastrointestinal (Noncolorectal) Cancer | May 20, 2009

The association of PET response with complete pathological response (CPR) and residual nodal disease (RND) after induction chemoradiotherapy (CRT) and resection of esophageal cancer: A review of 493 cases

Authors: S. A. Barnett, N. P. Rizk, P. S. Adusumilli, B. J. Park, M. S. Bains, R. M. Flores, K. A. Goodman, D. H. Ilson, T. J. Akhurst, and V. W. Rusch | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 27, Number 15_suppl • https://doi.org/10.1200/jco.2009.27.15_suppl.4552

PET Scan and Path CR: Esophageal Cancer

- 493 pts, AC and Squamous, treated with preop chemo RT
- PET scan prior to therapy, after chemort
- PET response not associated with pCR or nodal disease
- Squamous cancer patients: SUV response correlated with pCR
  - SUV reduction < 50% pCR 29%, 50-75% pCR 44%
  - SUV reduction > 75%: pCR 85%

Rizk J Clin Oncol 27: Abstr 4552; 2009

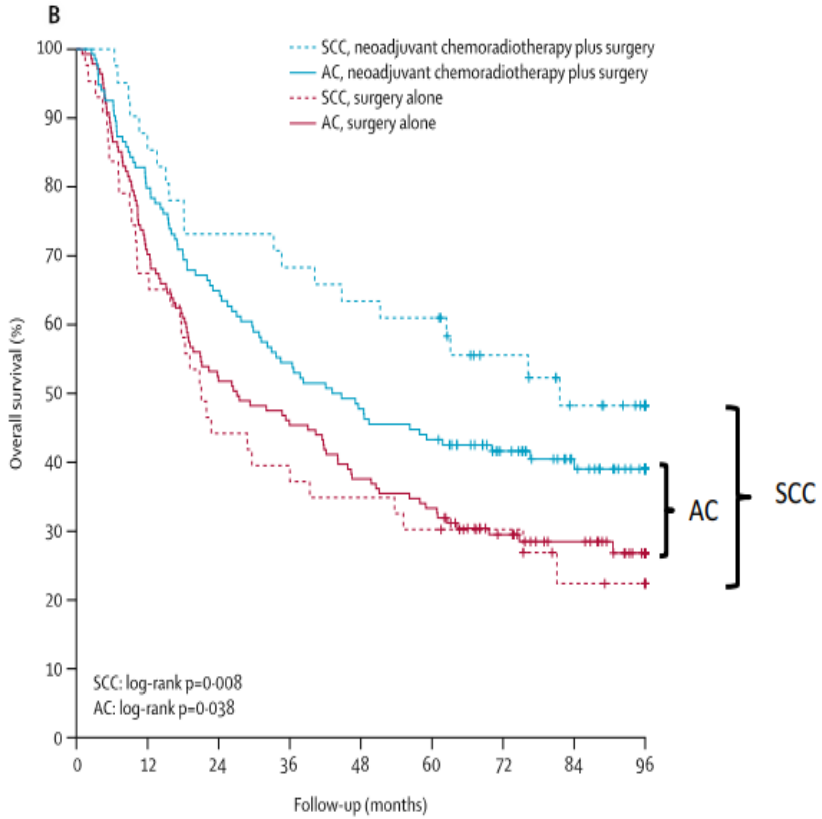
PCR rate in ADC

- **Cross**
- **neoAgis**

PCR rate

Neoadjuvant chemoradiotherapy + surgery:

The CROSS trial



Long-term survival data

- Esophageal SCC + adenocarcinoma +junctional type I and II
- N=368
- Neoadjuvant paclitaxel + carboplatin + 41.4 Gy vs surgery alone

- **nCRT: significant survival advantage in adenocarcinoma**

- pCR adenocarcinoma = **23%**

- Neo-AEGIS trial = **14 %**
  (Reynolds et al Lancet Gastrohep 2023)

Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-023-00991-8

RESEARCH

Survival Benefit of Induction Chemotherapy with Paclitaxel and Carboplatin Followed by Chemoradiation Versus Postoperative Treatment in Locally Advanced Gastric Cancer: A Retrospective Cohort Study

Payam Azadeh[1] · Sahar Gholizadeh pasha[1] · Ali Yaghobi Joybari[1] · Zeinab Abiar[2] · Sam Alahyari[3] · Farzad Taghizadeh-Hesary[4,5]

Accepted: 19 November 2023
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Results A total of 102 patients were included in the study (63.7% male, mean age ± standard deviation 56 ± 13 years). Among these, 45 patients received neoadjuvant treatment, and 57 received adjuvant treatment. The neoadjuvant group had a higher proportion of patients with advanced disease (stage III: 91.1% vs. 57.9%, P = 0.001). In the neoadjuvant group, 20 patients (44.4%) achieved a complete pathologic response, and all underwent curative surgery. The neoadjuvant group exhibited a lower 3-year recurrence rate (13 [28.9%] vs. 33 [57.9%], P = 0.003) and a higher 3-year overall survival rate (36 [80%] vs. 32 [56.1%], P = 0.003).

Conclusions Patients receiving induction chemotherapy with paclitaxel and carboplatin followed by chemoradiation demonstrated enhanced disease control and survival compared to standard adjuvant regimens. In addition, patients treated with the applied preoperative regimen in this study showed higher pathologic response and overall survival rates than in previous studies.

Take home message

- AS require careful follow up
- Longer follow up of trials is needed
- Role of RT in ADC
- Trials based on histology is required
- Accuracy of RR assessment is not enough yet(lead to un-resectable tumor)

Ongoing trial

THE NEEDS TRIAL

Protocol publication 2022

frontiers | Frontiers in Oncology

METHODS
published: 13 July 2022
doi: 10.3389/fonc.2022.917961

OPEN ACCESS

Edited by:
Zhendong Jin,
Second Military Medical University, China

Reviewed by:
Alessandro Gonfiotti,
University of Florence, Italy
Teng MAO,
Shanghai Jiao Tong University, China

***Correspondence:**
Magnus Nilsson
magnus.nilsson@ki.se

Specialty section:
This article was submitted to Gastrointestinal Cancers: Gastric & Esophageal Cancers, a section of the journal Frontiers in Oncology

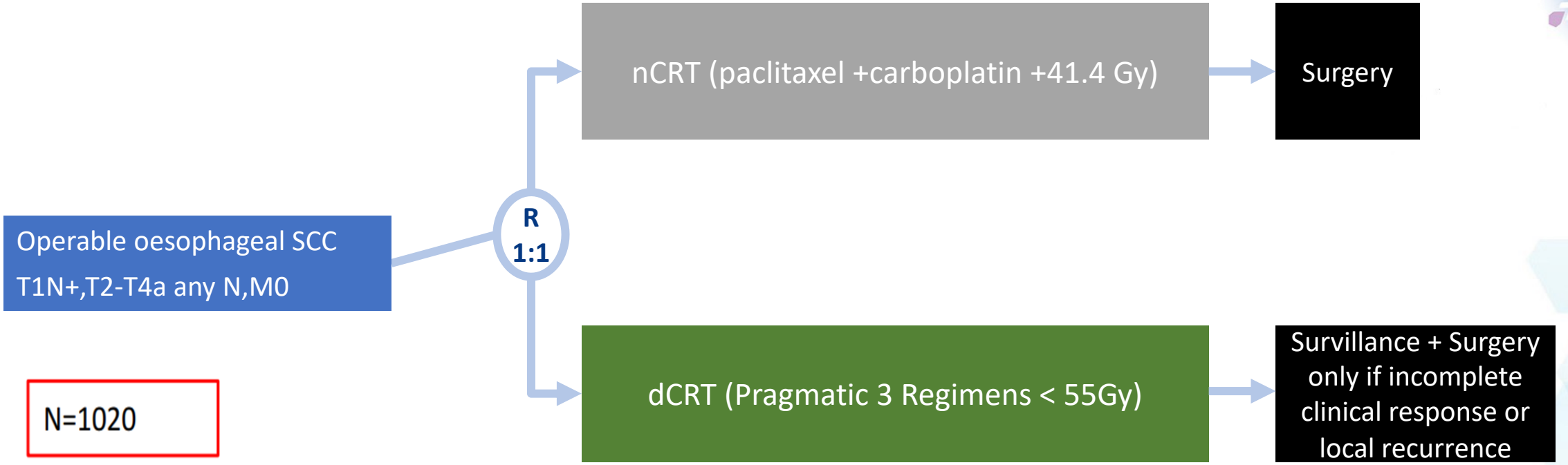
Received: *11 April 2022*
Accepted: *08 June 2022*
Published: *13 July 2022*

Citation:
Nilsson M, Olafsdottir H,

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

Magnus Nilsson[1,2], Halla Olafsdottir[1,3], Gabriella Alexandersson von Döbeln[1,3], Fernanda Villegas[4], Giovanna Gagliardi[4], Mats Hellström[5], Qiao-Li Wang[1], Hemming Johansson[5,6], Val Gebski[7], Jakob Hedberg[8], Fredrik Klevebro[1,2], Sheraz Markar[9,10], Elizabeth Smyth[11], Pernilla Lagergren[10,12], Ghazwan Al-Haidari[13], Lars Cato Rekstad[14], Eirik Kjus Aahlin[15], Bengt Wallner[16], David Edholm[17], Jan Johansson[18], Eva Szabo[19], John V. Reynolds[20], CS Pramesh[21], Naveen Mummudi[21], Amit Joshi[21], Lorenzo Ferri[22], Rebecca KS Wong[23,24], Chris O'Callaghan[25], Jelena Lukovic[23,24], Kelvin KW Chan[26], Trevor Leong[27], Andrew Barbour[28], Mark Smithers[28], Yin Li[29], Xiaozheng Kang[29], Feng-Ming Kong[30], Yin-Kai Chao[31], Tom Crosby[32], Christiane Bruns[33], Hanneke van Laarhoven[34], Mark van Berge Henegouwen[35], Richard van Hillegersberg[36], Riccardo Rosati[37], Guillaume Piessen[38], Giovanni de Manzoni[39] and Florian Lordick[40]*

NEEDS trial



N=1020

PRIMARY ENDPOINT

- to demonstrate that dCRT with salvage esophagectomy as needed is non-inferior to nCRT followed by surgery

SECONDARY ENDPOINTS

- To study prespecified HRQOL endpoints relevant to esophageal cancer and effects of treatment for this disease, repeatedly during treatment and survivorship.
- To determine event free survival, loco-regional and distal relapse rates and histological response after chemoradiotherapy in the surgical specimen in the control arm

NCCN Guidelines Version 5.2024
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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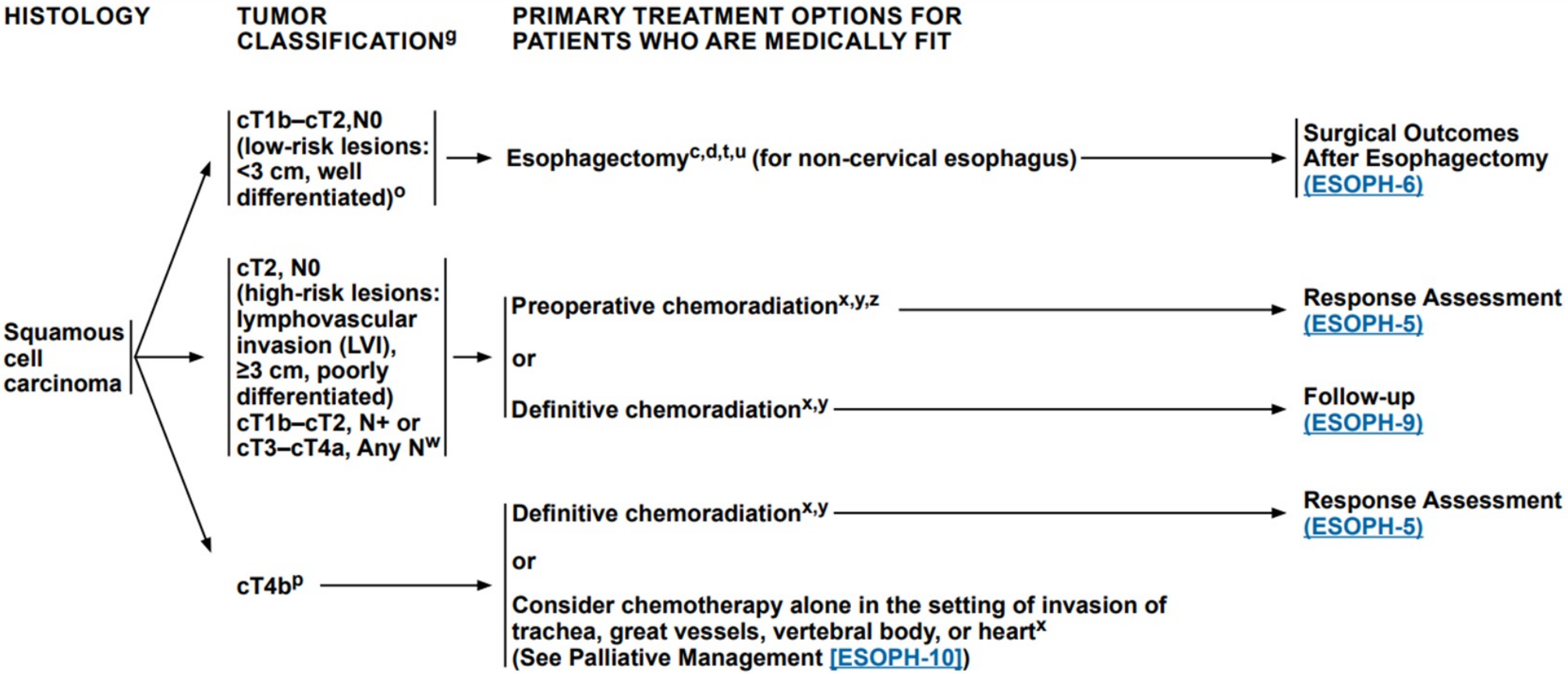
Discussion



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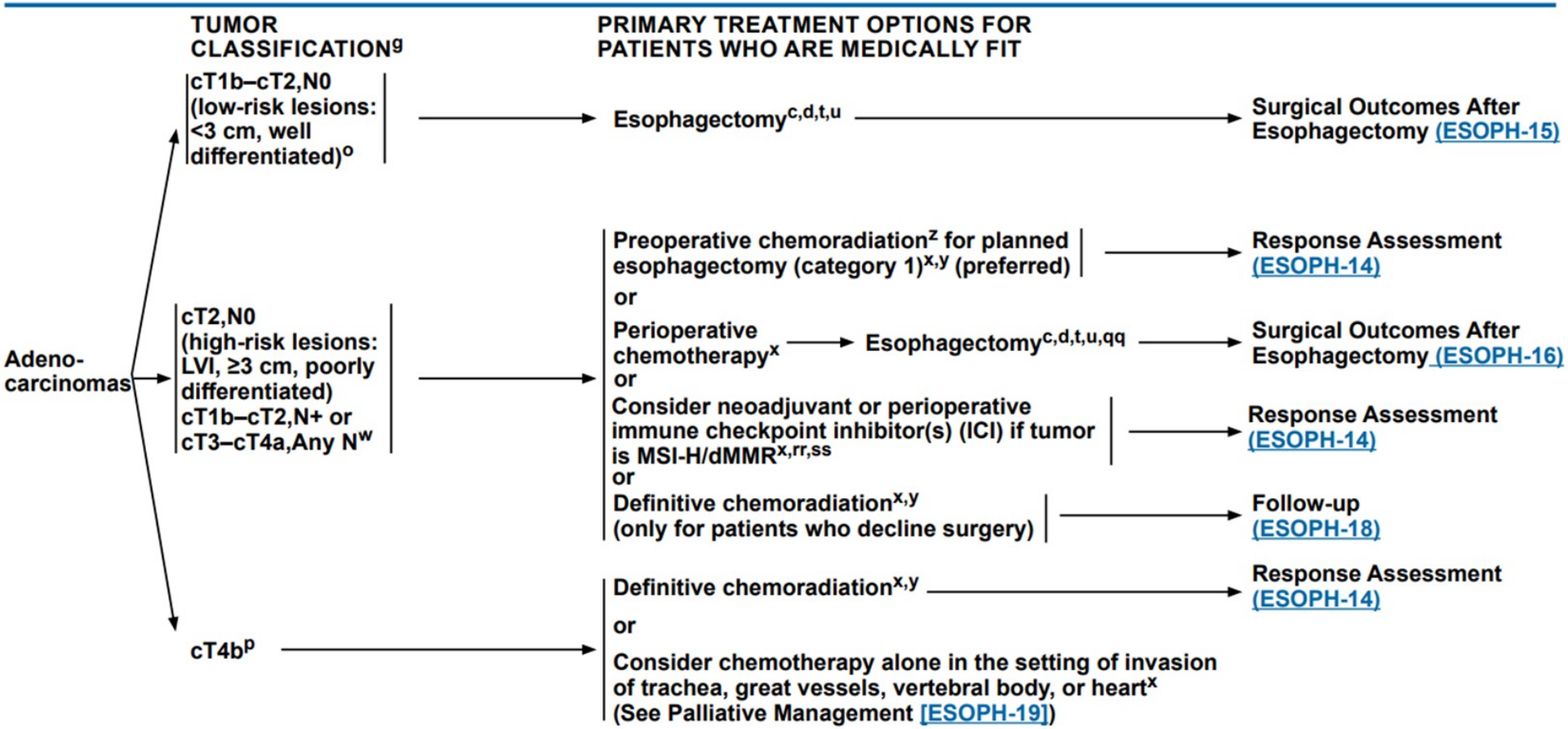

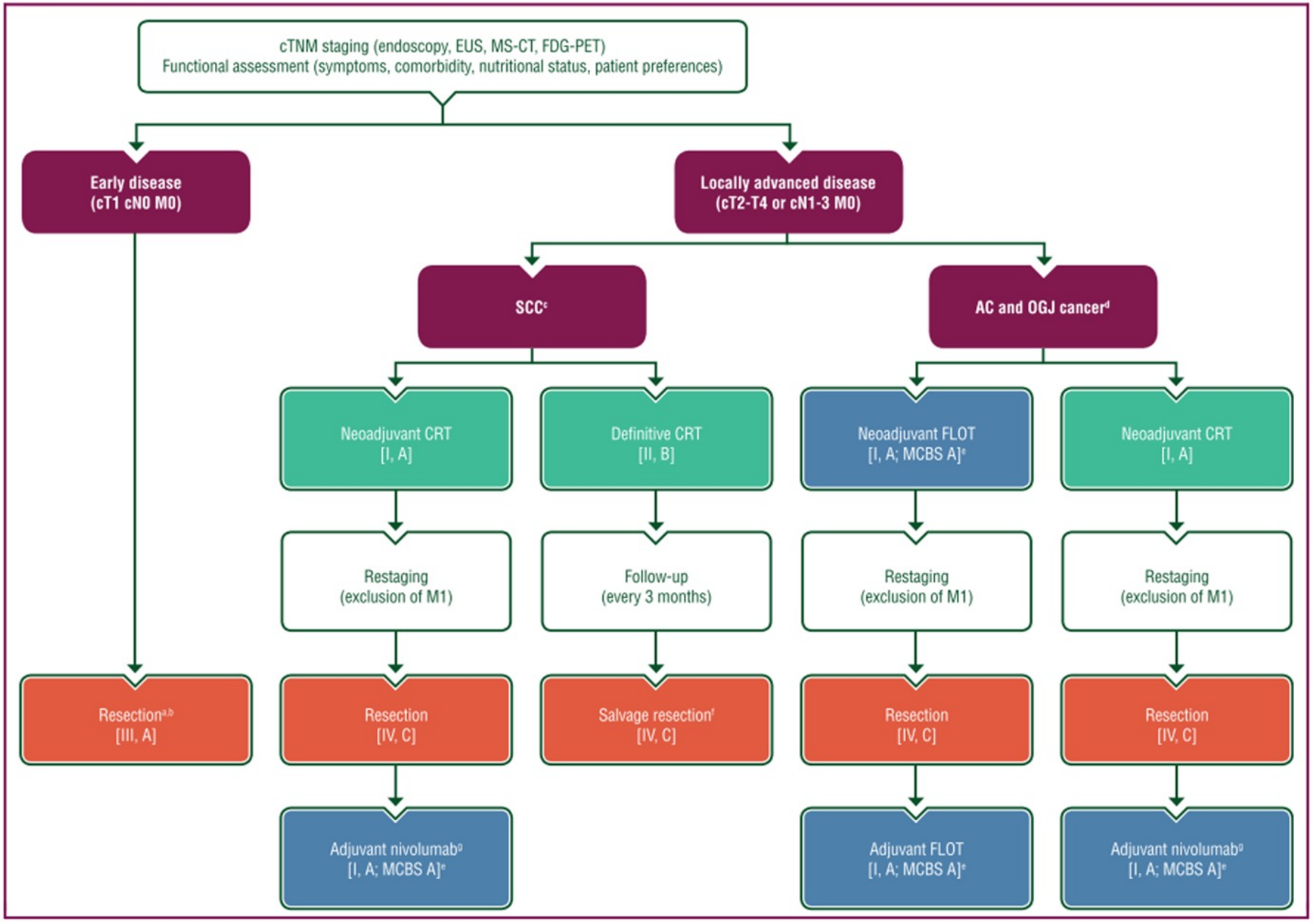
cTNM staging (endoscopy, EUS, MS-CT, FDG-PET)
Functional assessment (symptoms, comorbidity, nutritional status, patient preferences)
Early disease (cT1 cN0 M0)
Locally advanced disease (cT2-T4 or cN1-3 M0)
SCC[c]
AC and OGJ cancer[d]
Neoadjuvant CRT [I, A]
Definitive CRT [II, B]
Neoadjuvant FLOT [I, A; MCBS A][e]
Neoadjuvant CRT [I, A]
Restaging (exclusion of M1)
Follow-up (every 3 months)
Restaging (exclusion of M1)
Restaging (exclusion of M1)
Resection[a,b] [III, A]
Resection [IV, C]
Salvage resection[f] [IV, C]
Resection [IV, C]
Resection [IV, C]
Adjuvant nivolumab[g] [I, A; MCBS A][e]
Adjuvant FLOT [I, A; MCBS A][e]
Adjuvant nivolumab[g] [I, A; MCBS A][e]


Thank you