Definitive CRT (organ preservation) in Esophageal cancer

Is it possible and what's new?

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Introduction:

Esophageal cancer (EC) is an aggressive disease.

The two most common types of EC are adenocarcinoma (AC) and squamous cell carcinoma (SCC).

AC and SCC differ with regard to etiology, geographic distribution, response to chemotherapy/ radiotherapy, prognosis and possibly need for surgical resection.

Neoadjuvant chemoradiotherapy followed by radical esophagectomy is a standard treatment.

Morbidity after esophagectomy however is still considerable and has an impact on patients‘ quality of life.

Given a pathologic complete response rate of approximately 30% in the CROSS trial in patients after neoadjuvant chemoradiation followed by surgery, active surveillance has been introduced as a new alternative approach.

The CROSS trial

This study randomized 366 patients(T2 ,T3 or N+) with squamous cell carcinoma(25%) or adenocarcinoma(75%) of the esophagus or GEJ to treatment with

(1) preoperative carboplatin (AUC 2 mg/mL/minute) and paclitaxel 50 mg/m$_2$once weekly for 5 weeks, and concurrent radiotherapy (1.8 Gy daily to 41.4 Gy in 23 fractions), followed by surgery, or

(2) immediate surgery.

Result:

The CROSS study showed Significantly improved OS and DFS

on the chemoradiotherapy arm in both SCC and AC

Furthermore, the CROSS study showed that nearly one third of the patients had a pCR:

49% in SCC and 23% in AC

Benefits of an active surveillance:

- Theoretically, patients with a cCR may have been cured (i.e. have a true pCR) and could potentially be spared an esophagectomy.
- Identification of the group of patients is that, despite surgery, early systemic recurrence will occur (within 1 year) and surgery for local disease control is not needed; therefore, patients are put at risk for morbidity and mortality of an operation without changing prognosis.

(In other words, avoiding unnecessary major surgery at a time when distant metastases are present but cannot be detected)

Published trials comparing neoadjuvant chemoradiation followed by surgery to definitive chemoradiotherapy

- German trial (Stahl et al. JCO 2005)
- French FFCD 9102 (Bedenne et al. JCO 2007)

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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.

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

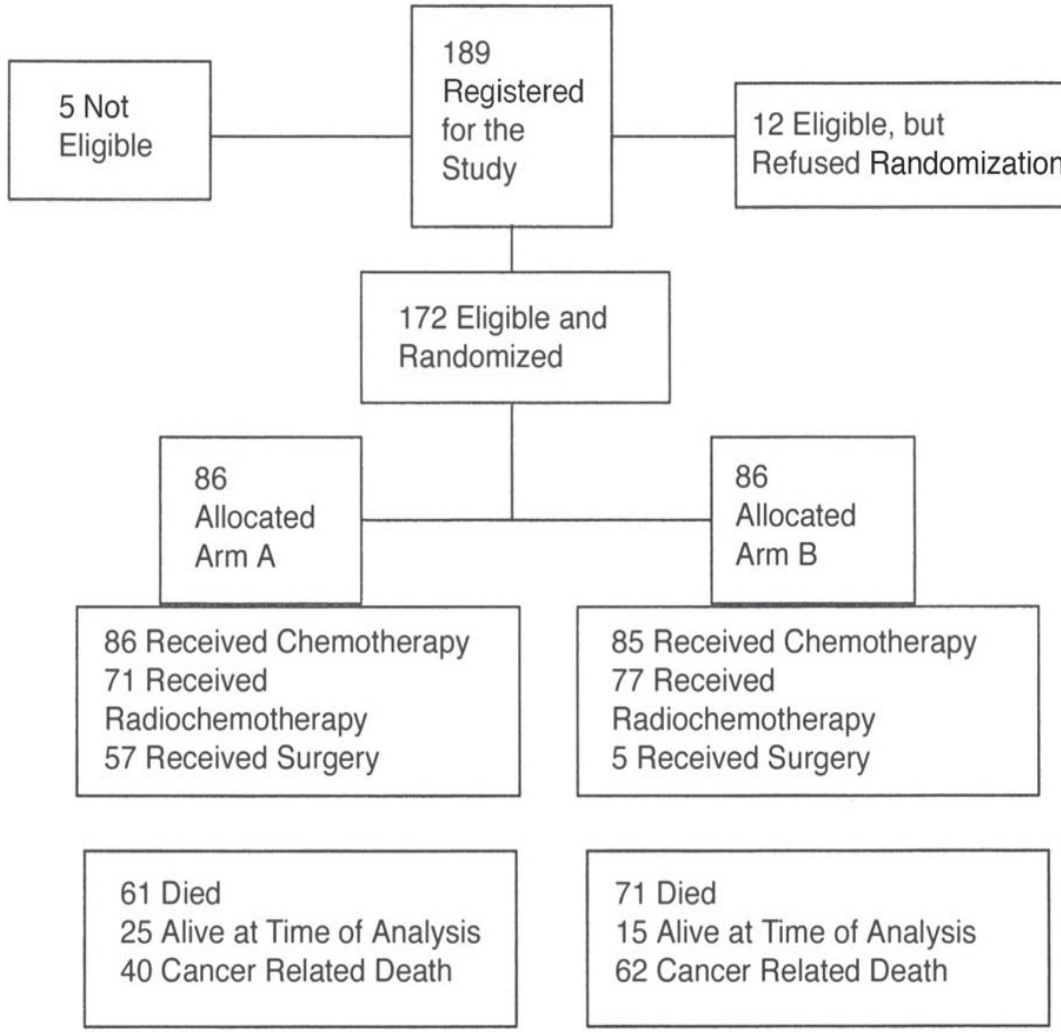
Phase 3 equality RCT
nCRT fallowed by surgery(arm A) vs dCRT (arm B)

SCC only ,locally advanced ,non-metastatic

Intervention:
_nCRT :induction(5fu +leucov+etoposide +cisplatin) +
cocomitant chemotherapy (cis + etop)
+ RT (40 Gy) falowed br surgery
_ dCRT: same chemo +60 to 65 Gy +/- brachy

primary endpoint : OS at **2 years**

N:172



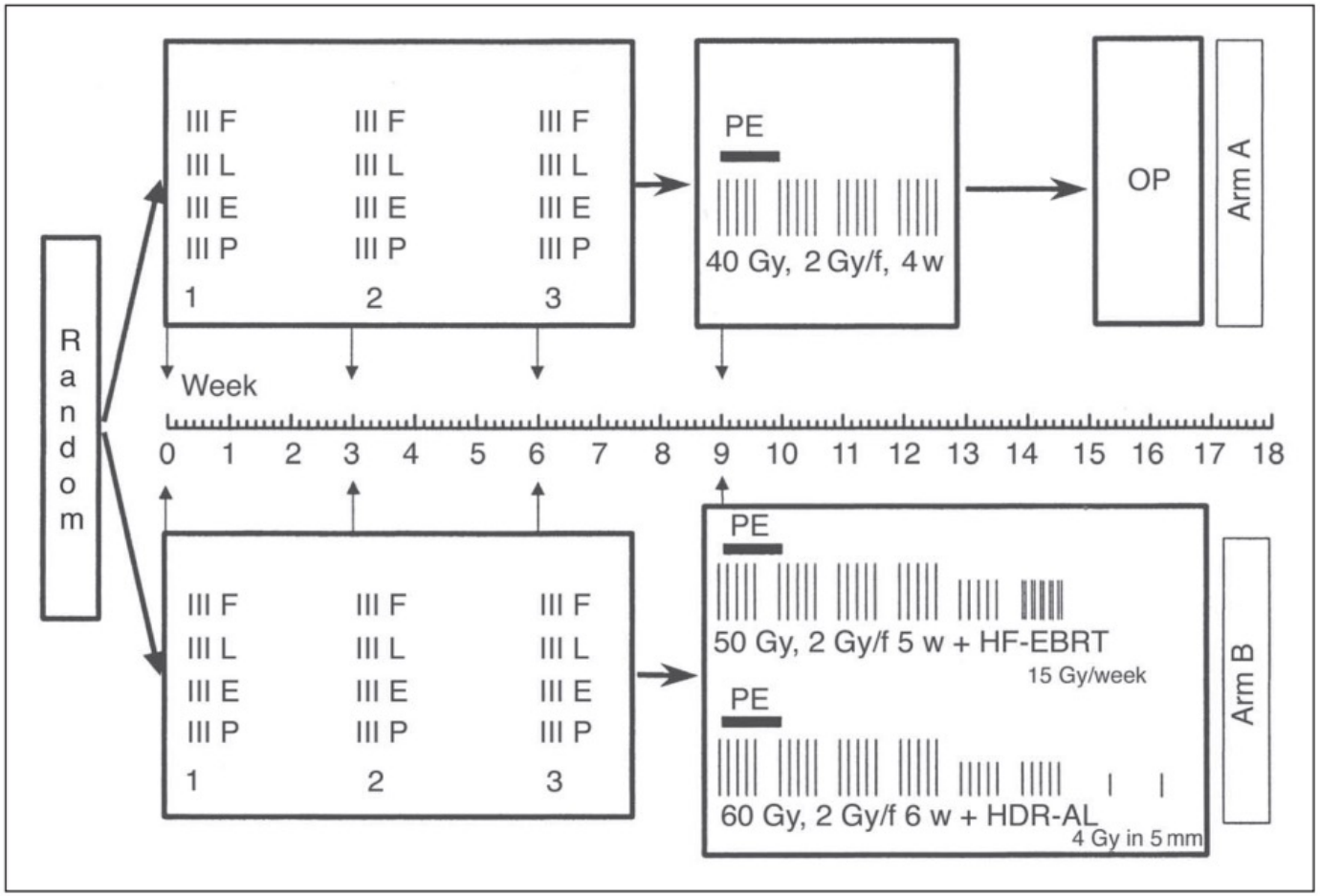


Fig 1. Treatment schedule of preoperative chemoradiotherapy (arm A) and dose-escalated chemoradiotherapy without surgery (arm B). FLEP, bolus fluorouracil 500 mg/m^2, leucovorin 300 mg/m^2, etoposide 100 mg/m^2, and cisplatin 30 mg/m^2 on days 1 to 3 every 3 weeks; PE, cisplatin 50 mg/m^2 on days 2 to 8 and etoposide 80 mg/m^2 on days 3 to 5 concomitant with radiotherapy; f, fraction; HF-EBRT, hyperfractionated external-beam radiotherapy with 2 × 1.5 Gy/d; HDR-AL, high dose–rate afterloading therapy (4 Gy in a depth of 5 mm) if tumors could be traversed by a 10- to 14-mm bougie applicator. Smaller tick marks during radiotherapy represent treatment of a reduced volume.

- Patients were seen for the first follow-up 8 to 12 weeks after the end of treatment and, thereafter, every 3 months up to 2 years. Afterwards, follow-up was planned every 6 months up to 5 years.

RESULT:

- The pCR rate was 33% among patients who went to surgery.

- there was no significant difference in 3-year survival

(31% vs 24%) for those who were randomized to preoperative chemoradiation followed by surgery versus chemoradiation alone.

- treatment-related mortality was significantly increased in the surgery arm (12.8% vs 3.5%, *P* <.05)

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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 Recherche Clinique, and the Association pour la Recherche Contre le Cancer.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology, May 18-21, 2002, Orlando, FL, and the 27th Annual

ABSTRACT

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

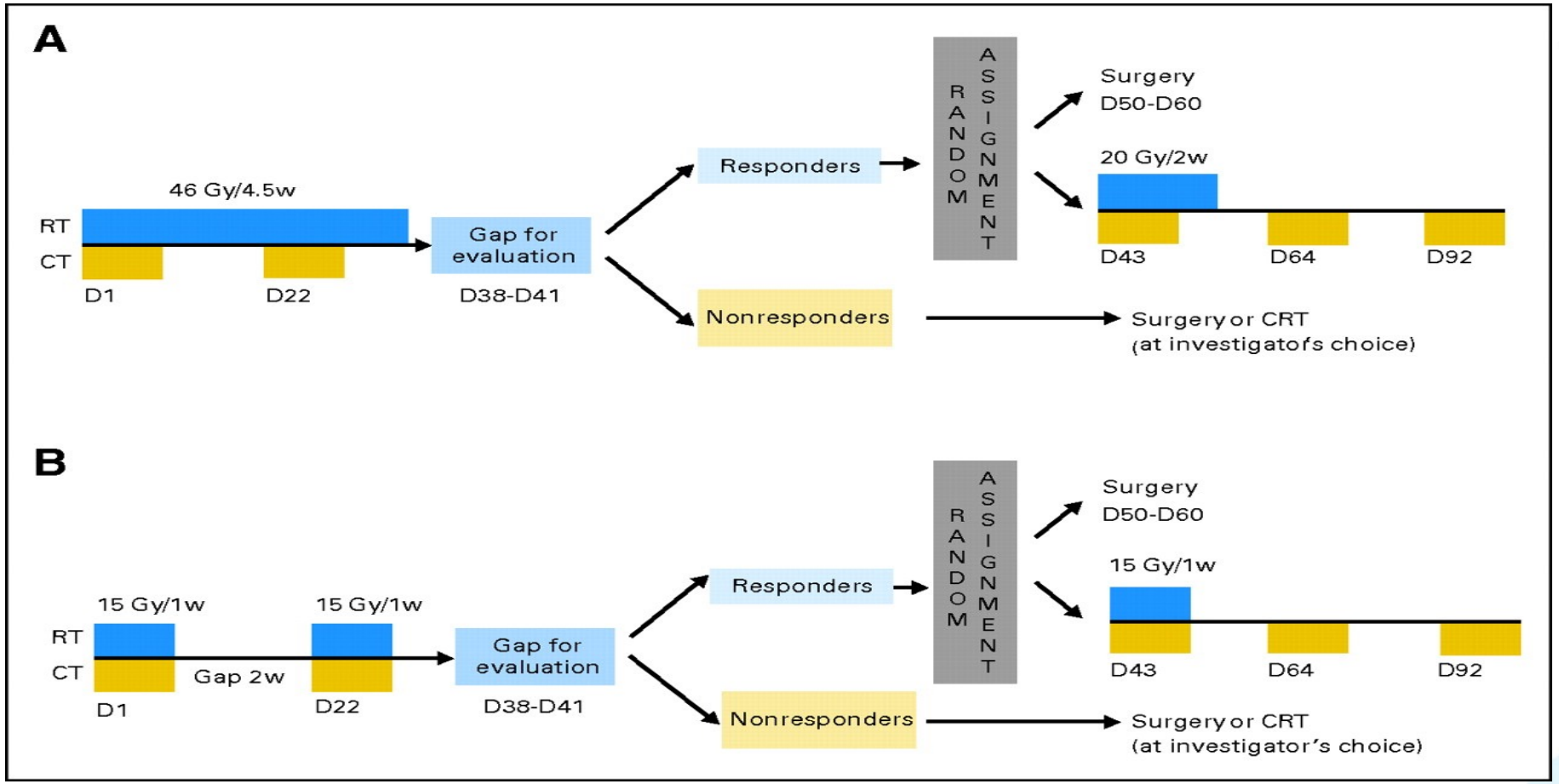
Eligible patients had operable T3N0-1M0 thoracic esophageal cancer. Patients received two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. Patients with response 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%.

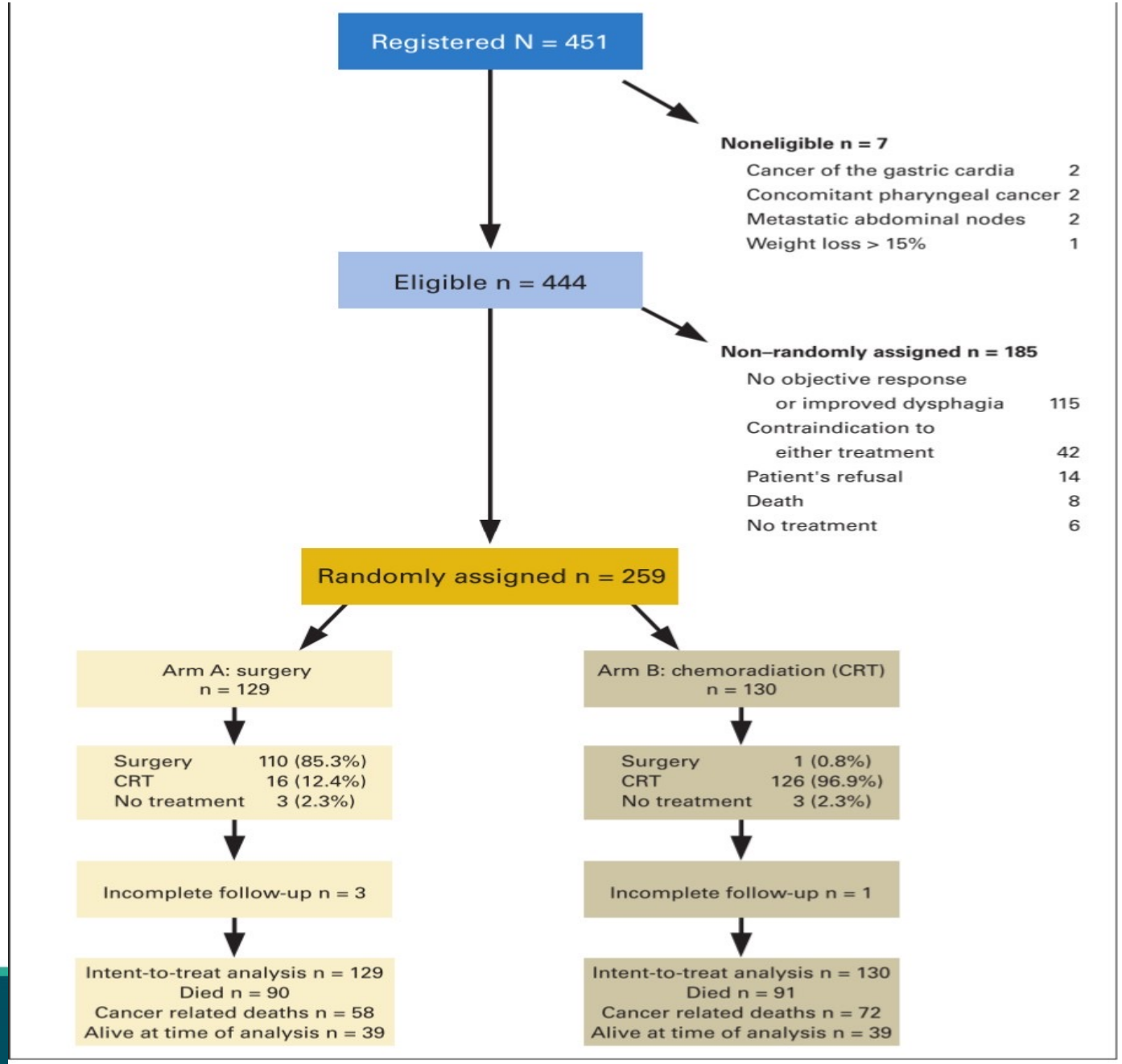
Results

Of 444 eligible patients, 259 were randomly assigned; 230 patients (88.8%) had epidermoid cancer, and 29 (11.2%) had glandular carcinoma. Two-year survival rate was 34% in arm A versus 40% in arm B (hazard ratio for arm B *v* arm A = 0.90; adjusted $P = .44$). Median survival time was 17.7 months in arm A compared with 19.3 months in arm B. Two-year local control rate was 66.4% in arm A compared with 57.0% in arm B, and stents were less required in the surgery arm (5% in arm A *v* 32% in arm B; $P < .001$). The 3-month mortality rate was 9.3% in arm A compared with 0.8% in arm B ($P = .002$). Cumulative hospital stay was 68 days in arm A compared with 52 days

- eligible patients with clinically resectable T3 N0 to 1 M0 squamous cell carcinoma (89%) or adenocarcinoma (11%) of the esophagus were enrolled.

- Work-up included: **clinical examination**
  gastroscopy with biopsies
  esophagogram, bronchoscopy
  supraclavicular ultrasonography,
  thoracoabdominal CT scan
  endoscopic ultrasonography when available.


A
46 Gy/4.5w
RT
CT
D1
D22
Gap for evaluation
D38-D41
Responders
Nonresponders
RANDOM ASSIGNMENT
Surgery
D50-D60
20 Gy/2w
D43
D64
D92
Surgery or CRT
(at investigator's choice)
B
15 Gy/1w
15 Gy/1w
RT
CT
Gap 2w
D1
D22
Gap for evaluation
D38-D41
Responders
Nonresponders
RANDOM ASSIGNMENT
Surgery
D50-D60
15 Gy/1w
D43
D64
D92
Surgery or CRT
(at investigator's choice)


Registered N = 451
Noneligible n = 7
Cancer of the gastric cardia 2
Concomitant pharyngeal cancer 2
Metastatic abdominal nodes 2
Weight loss > 15% 1
Eligible n = 444
Non–randomly assigned n = 185
No objective response or improved dysphagia 115
Contraindication to either treatment 42
Patient's refusal 14
Death 8
No treatment 6
Randomly assigned n = 259
Arm A: surgery n = 129
Surgery 110 (85.3%)
CRT 16 (12.4%)
No treatment 3 (2.3%)
Incomplete follow-up n = 3
Intent-to-treat analysis n = 129
Died n = 90
Cancer related deaths n = 58
Alive at time of analysis n = 39
Arm B: chemoradiation (CRT) n = 130
Surgery 1 (0.8%)
CRT 126 (96.9%)
No treatment 3 (2.3%)
Incomplete follow-up n = 1
Intent-to-treat analysis n = 130
Died n = 91
Cancer related deaths n = 72
Alive at time of analysis n = 39

- 444 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.
- The 259 patients who had at least a partial response were then randomized to surgery versus additional chemoradiation, which included three cycles of 5-FU, cisplatin, and concurrent radiation (either 20 Gy at 2 Gy per day or split course 15 Gy).

- A clinical complete response was defined by the absence of dysphagia and of visible tumor on esophagogram.
- A partial response was defined as a decrease of more than 30% of the tumor length on esophagogram and improvement of dysphagia.

Follow up:

- endoscopy with biopsies
- esophagogram
- thoracoabdominal CT scan
- if available, endoscopic ultrasonography
- Follow-up was carried out every 3 months for 2 years and then
- every 6 months thereafter.

Result:

- There was no significant difference in:

  2-year survival (34% vs 40%, *P* = .44)

or

  median survival (17.7 vs 19.3 months)

in patients who underwent surgery versus additional chemoradiation.

- For the 259 randomly assigned patients, median survival time was 18.6 months.
- there was a significantly higher rate of treatment-related mortality in patients who underwent surgery.

our main concern???

Tumor recurrence…

after organ preservation

What is the role of salvage surgery?

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.59.9092

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

Sheraz Markar, Caroline Gronnier, Alain Duhamel, Arnaud Pasquer, Jérémie Théreaux, Mael Chalret du Rieu, Jérémie H. Lefevre, Kathleen Turner, Guillaume Luc, and Christophe Mariette

Sheraz Markar, Imperial College, London, United Kingdom; Caroline Gronnier, Christophe Mariette, and Alain Duhamel, Site de Recherche Intégrée sur le Cancer OncoLille; North of France University; University Hospital of Lille; Caroline Gronnier and Christophe

ABSTRACT

Purpose
The aim of this large multicenter study was to assess the impact of salvage esophagectomy after definitive chemoradiotherapy (SALV) on clinical outcome.

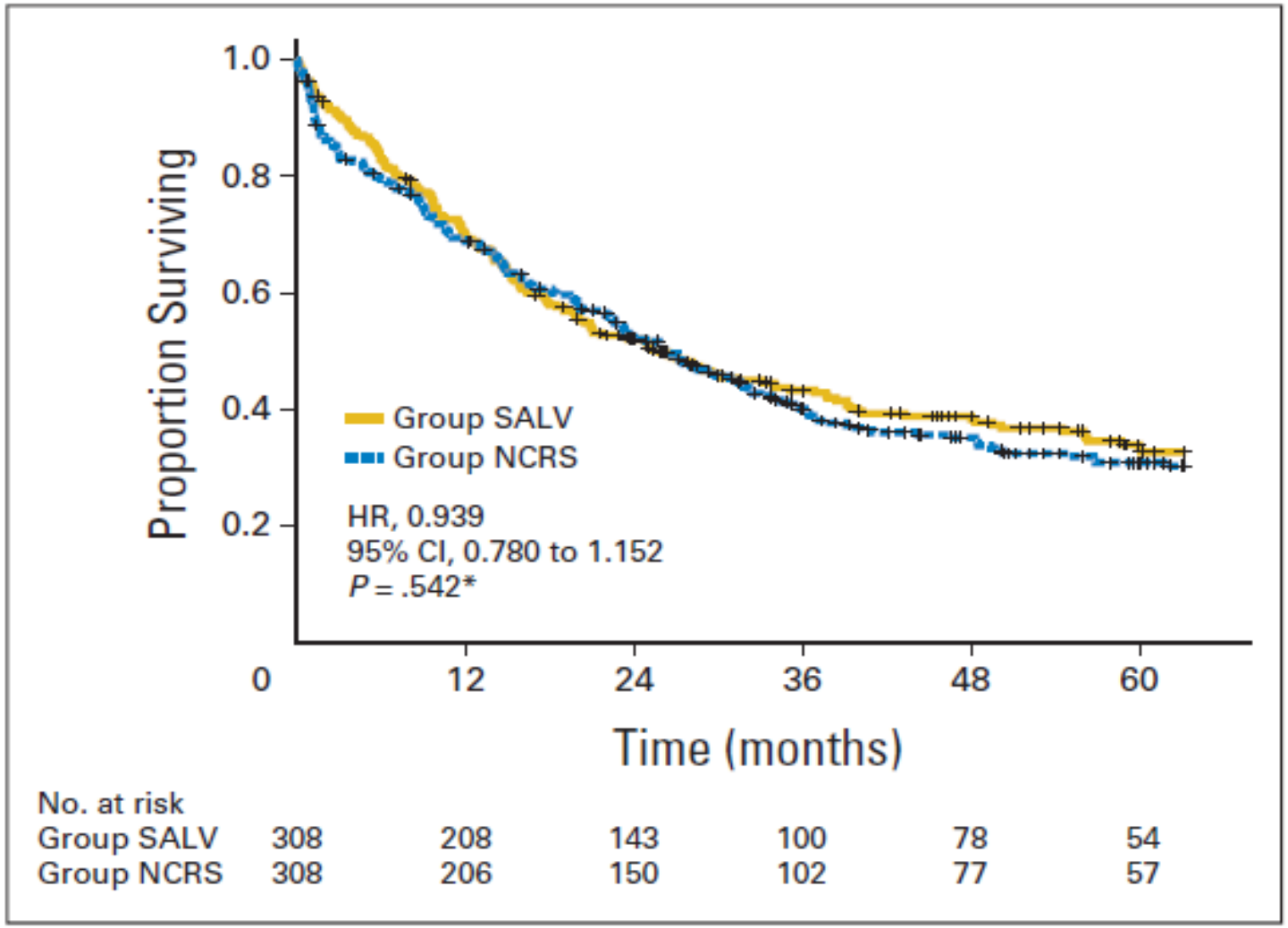
- A total of 848 patients were included in the study:
- 308 in the SALV group (for persistent, recurrent disease) and
- 540 in the nCRT + palnned surgey group.
- Of the 308 patients who underwent SALV, 234 had persistent and 74 had recurrent disease.
- The primary aim: to assess the impact of SALV after dCRT on clinical outcome in comparison with NCRS.

- SALV was defined as removal of the esophagus for persistent or recurrent disease within the tumor and/or locoregional lymph nodes after dCRT.
- PERS was defined as presence of cancer on endoscopic or radiologic investigation with histologic confirmation within 3 months of dCRT. REC was defined as presence of cancer within the tumor or locoregional nodes after 3 months of dCRT.

RESULT:

- After a median follow-up of 54.4 months, there was no significant difference between the SALV and NCRS groups in 3-year overall (43.3% *v* 40.1%; *P*.542) or disease-free survival (39.2% *v* 32.8%; *P*.232).

- there were no significant differences between SALV and NCRS groups in in-hospital mortality or morbidity, (17.2% *v* 10.7%)


1.0
0.8
0.6
0.4
0.2
Proportion Surviving
Group SALV
Group NCRS
HR, 0.939
95% CI, 0.780 to 1.152
P = .542*
0
12
24
36
48
60
Time (months)
No. at risk
Group SALV 308 208 143 100 78 54
Group NCRS 308 206 150 102 77 57

- Importantly, there were no differences in oncologic safety of surgery, including extent of nodal dissection, between the SALV and NCRS groups, indicating that standard surgery can be performed safely in patients undergoing SALV

- In conclusion, these results suggest that SALV after dCRT can be performed in experienced esophageal cancer centers with low mortality and morbidity rates and result in good survival.

New trials

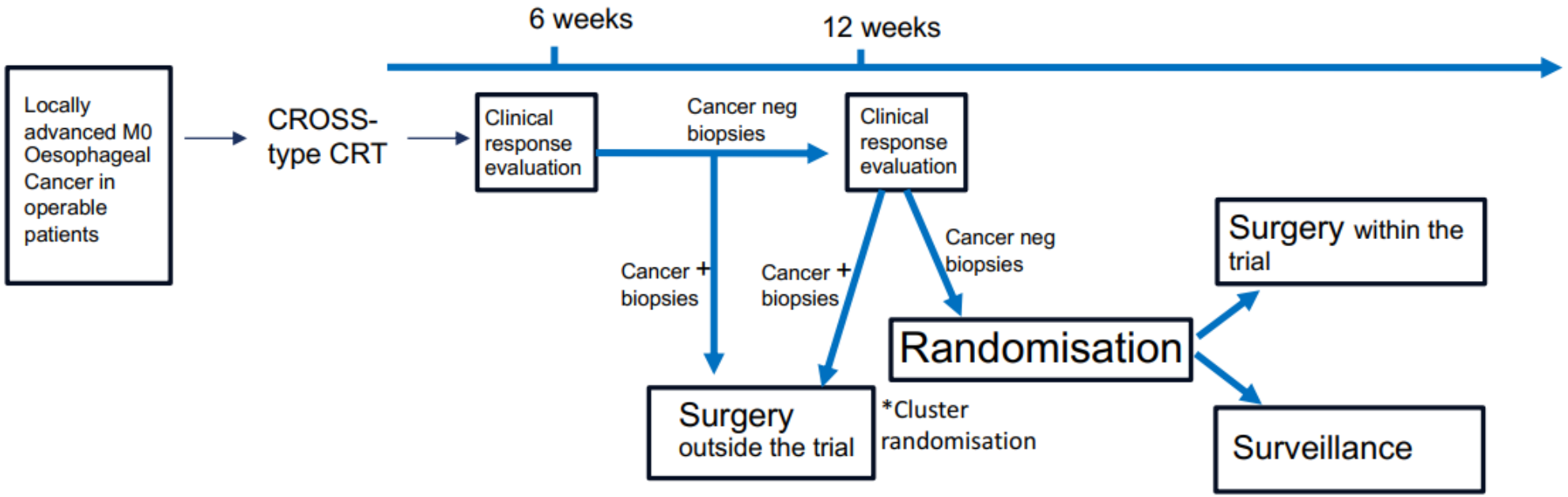
- SANO
- Esostrate- Prodige 32

- In the SANO trial and previous trials, both histological oesophageal cancer types have been assessed together – squamous cell carcinoma and adenocarcinoma

The SANO trial

Is surgery really needed in **clinical complete responders** after CROSS type nCRT?

Trial design:



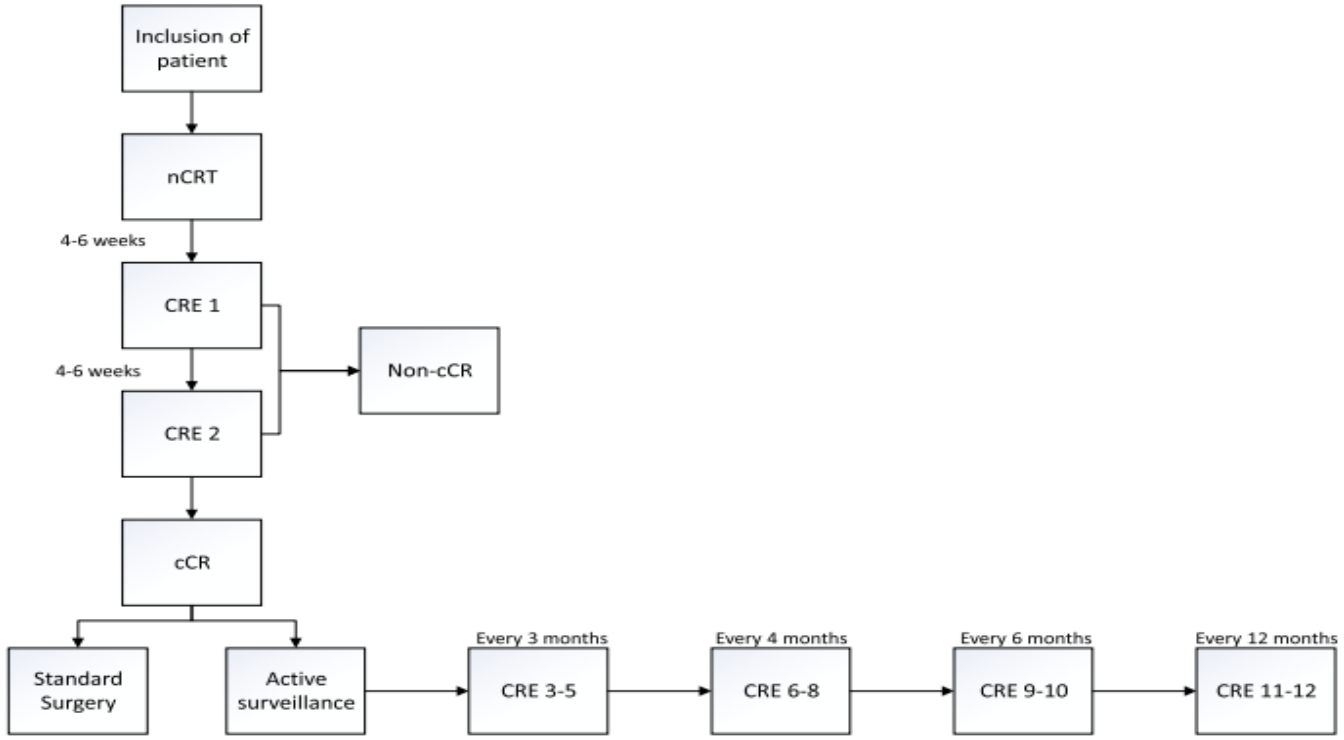
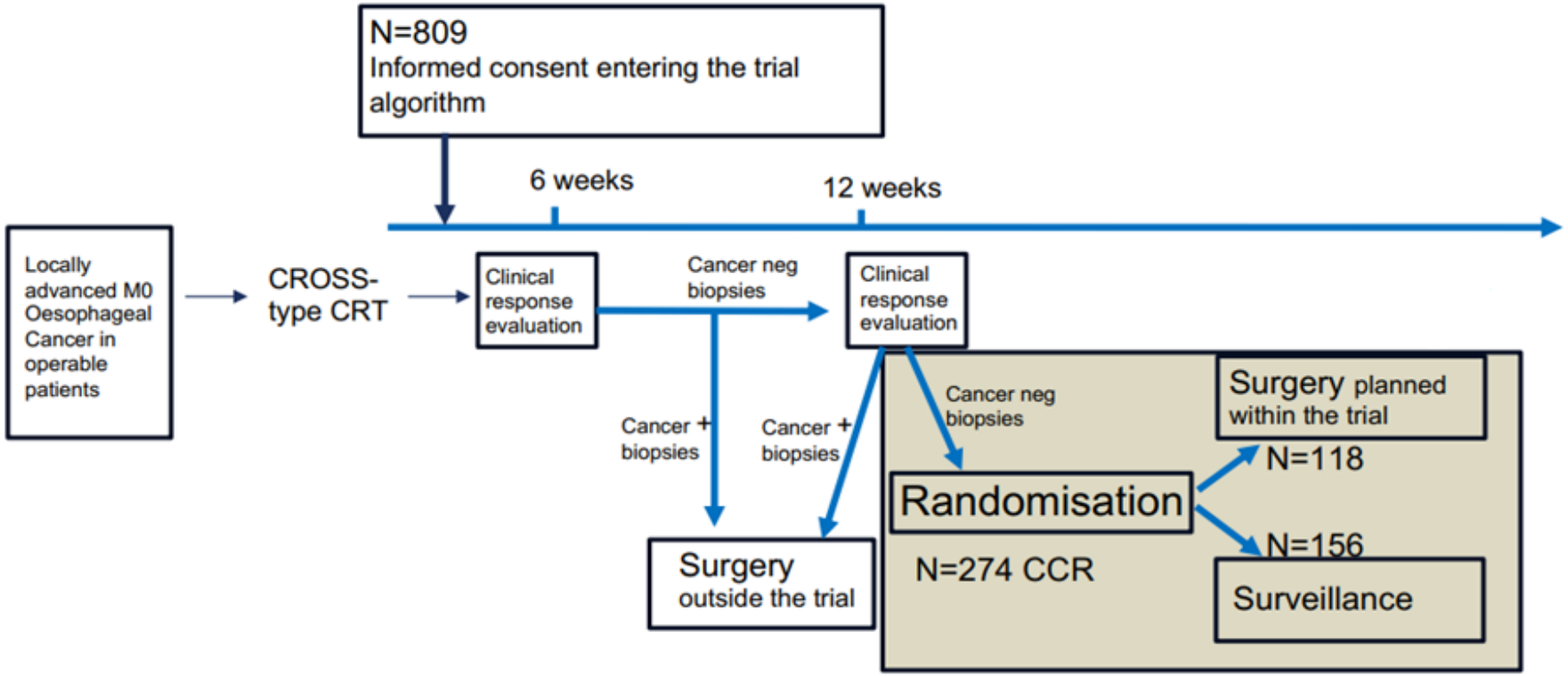


Fig. 1 Schematic overview of the SANO trial, comparing active surveillance with standard oesophagectomy in patients with oesophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy. Patients in whom no residual tumour is detected at two clinical response evaluations after 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

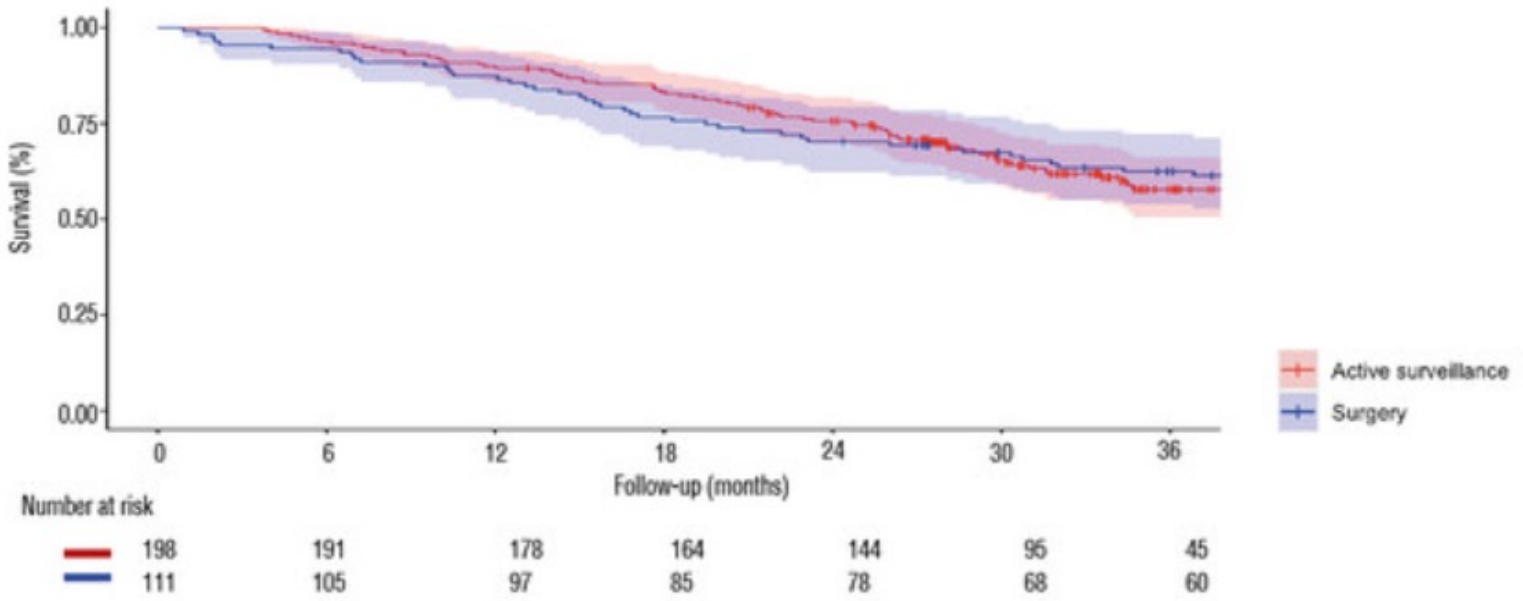


- Findings revealed that overall survival (OS) from the day of clinically complete response (CCR) – the primary endpoint – was not inferior to surgery at 2 years in patients with oesophageal cancer who underwent active surveillance (hazard ratio [HR] 1.14, 95% confidence interval [CI] 0.74–1.78; p=0.55)

- In addition, global health-related quality of life (HRQoL) using the EORTC QLQ-C30 was significantly better at 6 and 9 months in patients who received active surveillance than surgery

Overall Survival

HR 1.14, 95% CI 0.74 – 1.78, p = 0.55
Noninferiority testing at 2 years 95% upper boundary < 15% difference (p<0.01)



- A similar study is ongoing in France, the Esostrate- Prodige 32 study (NCT02551458) that randomizes patients with a complete clinical response (cCR) to systematic surgery versus surveillance and rescue surgery after chemoradiation.
- The investigators will also attempt to identify prognostic and predictive markers of cCR and pCR using blood samples and diagnostic biopsies to aid in determining which patients can ultimately avoid surgery.

Summery:

- No OS benefit in surgery
- Improvement of QOL
- reducing surgical mortality
- Safety of salvage surgery
- More evidence for SCC
- Waiting for new trials
- Promising data about ct-DNA in CCR assessment


THANK
YOU
FOR
YOUR
ATTENTION