Individual patient data meta-analysis of neoadjuvant chemotherapy followed by surgery versus upfront surgery for carcinoma of the esophagus or the gastroesophageal junction

Matthieu FARON (MD, MSc)[1,2], Armel Maurice CHEUGOUA-ZANETSIE (MSc)[1,3], Pierre THIRION (MD, PhD)[4], Matthew NANKIVELL (PhD)[5], Kathryn WINTER(MSc)[6], David CUNNINGHAM (MD, PhD)[7], Ate VAN DER GAAST(MD, PhD)[8], Simon LAW(MD, PhD)[9], Ruth LANGLEY (MD, PhD)[5], Florent de VATHAIRE[10] (PhD), Michele Valmasoni (MD, PhD)[11], Muriel MAUER (PhD)[12], Jack ROTH (MD, FACS)[13], Val GEBSKI (BA, MStat, honorary FRANZCR)[14], Bryan H BURMEISTER (MD, PhD)[15], Xavier PAOLETTI (PhD)[16], Johanna VAN SANDICK (MD, PhD)[17], Jianhua FU (MD, PhD)[18], Michel DUCREUX (MD, PhD)[19], Pierre Blanchard (MD, PhD)[1, 20], Jayne TIERNEY[5](PhD), Jean-Pierre PIGNON (MD, PhD)[1,3], Stefan MICHIELS (PhD) [1,3] on behalf of the MANATEC-02 collaborative group[21]

1. Oncostat U1018, Inserm, Université Paris-Saclay, Équipe Labellisée Ligue Contre le Cancer, Villejuif, France
2. Service de Chirurgie Viscérale Oncologique, Gustave Roussy Cancer Campus, Villejuif, France
3. Bureau de Biostatistiques et Epidémiologie , Gustave Roussy Cancer Campus, Villejuif, France
4. St. Luke's Hospital, Dublin, Ireland
5. MRC Clinical Trial Unit at UCL, London, UK
6. NRG Oncology Statistics and Data Management Center, Philadelphia, PA, United States
7. National Institute for Health Research, Biomedical Research Centres, Royal Marsden, London, UK
8. Department of Medical Oncology, Erasmus MC, Rotterdam, The Netherlands
9. Department of Surgery, The University of Hong Kong, Hong Kong SAR, China
10. Epidémiologie des radiations U1018, Inserm, Université Paris-Saclay, Villejuif, France
11. Padova University Hospital, Center for Esophageal Diseases, Department of Surgery, Oncology and Gastroenterology, Padova, Italy
12. EORTC Headquarters, Brussels, Belgium
13. Department of Thoracic and Cardiovascular Surgery, Division of Surgery, MD Anderson, Houston, United States
14. National Health and Medical Research Council Clinical Trials Centre , University of Sydney, Sydney, Australia
15. Princess Alexandra Hospital, Woolloongabba, Australia
16. Département de biostatistiques, Institut Curie, Paris
17. Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands
18. Sun Yat-Sen University Cancer Center, Guangzhou, China
19. Département de médecine oncologique, Gustave Roussy Cancer Campus, Paris-Saclay University, Villejuif France, France
20. Département de radiothérapie, Gustave Roussy Cancer Campus, France
21. MANATEC-02 collaborative group see appendix for full list of members and affiliations

Corresponding author: Matthieu FARON

- 114 rue Edouard Vaillant 94805, Villejuif CEDEX, France
- Matthieu.faron@gustaveroussy.fr
- +33.1.42.11.65.79

This study was presented as a Poster at the ASCO 2021 Annual Meeting

Funding: This study was funded by the French Programme Hospitalier de Recherche Clinique en Cancérologie (PHRC-K)

Abstract:

Introduction: Which neoadjuvant treatment for locally advanced thoracic esophagus (TE) or gastroesophageal junction (GEJ) carcinoma is best remains an open question. Randomized controlled trials variously accrued patients with adenocarcinoma (ADK) and squamous cell carcinoma (SCC), making strong conclusions hard to obtain. The primary objective of this Individual Participant Data meta-analysis was to investigate the effect of neoadjuvant chemotherapy on overall survival (OS).

Patients and methods: Eligible trials should have closed to accrual before 2016 and compared neoadjuvant chemotherapy (CS) and surgery to surgery alone (S). All relevant published and unpublished trials were identified via searches of electronic databases, conference proceedings and clinical trial registers. The main endpoint was OS. Investigators were contacted to obtain the IPD which was recoded, harmonized, and checked. A random effects Cox model, stratified by trial, was used for meta-analysis and subgroup analyses were pre-planned.

Results: 16 trials were identified as eligible. IPD were obtained from 12 trial and 2,478 patients. CS was associated with an improved OS vs S, HR=0.83[0.72-0.96], p<0.0001, translating to an absolute benefit of 5.7% at 5-years from 16.8% to 22.5%. Treatment effects did not vary substantially between ADK (HR=0.73[0.62-0.87]) and SCC (HR=0.91[0.76-1.08] interaction p=0.26). A somewhat more pronounced effect was observed in GEJ (HR=0.68[0.50-0.93]) vs TE (HR=0.87[0.75-1.00], interaction p=0.07). CS was also associated with a greater DFS (HR=0.74[0.64-0.85], p<0.001).

Conclusions: Neoadjuvant chemotherapy conferred a better OS than surgery alone and should be considered in all anatomical location and histological subtypes.

Keyword: preoperative, chemotherapy, esophageal cancer, gastroesophageal junction, individual patient data, meta-analysis

Introduction

With 456,000 new cases each year, esophageal cancer is the 8th most frequent cancer in the world and remains a therapeutic challenge illustrated by annual 400,000 cancer related deaths.[1] In non-metastatic patients, surgery (S) has long been the main therapeutic option and remains the cornerstone of the treatment. Upfront surgery was associated with poor oncological results, especially in locally advanced disease it provided rational for multi-modal treatment. Among them, the therapeutic sequence of neoadjuvant chemotherapy followed by surgery (CS) has been extensively studied and became one of the standards of care in patients with advanced stage, defined as T2 or more, any N or any T with N1 or more, M0. However, carcinoma is a heterogeneous entity due to the combination of two predominant histological subtypes: adenocarcinoma (AC) and squamous cell carcinoma (SCC) and two anatomical locations: thoracic esophagus (TE) and gastro-esophageal junction (GEJ). Randomized controlled trials have seldom separated these entities resulting in difficulties in clinical daily practice to propose a personalized strategy based on tumor pathological and anatomical characteristics. Both European and American guidelines acknowledge this fact.[2,3] Still, different histological subtypes may not be equally sensitive to chemotherapy. Non individual patients' data (IPD) meta-analyses do not have the ability to perform proper pathological or anatomical site specific subgroup analysis.[4] Our group has previously reported at the ASCO annual meeting 2007 the results of a first IPD-based MA and demonstrated significant benefits for neoadjuvant chemotherapy.[5] Since then new trials or updated follow-up may have become available and newer trials may provide additional information on efficacy and toxicity and allow to explore the impact of pathology ad tumor site on therapeutic outcome.

The goal of this study was to update the previous IPD meta-analysis with new information to evaluate the benefits and risk associated with neo-adjuvant chemotherapy in patients with locally advanced carcinomas of the esophagus or the GEJ with an emphasis on histological subtypes and anatomical location.

Patients and Methods

A protocol for this study was made a priori and is available on Gustave Roussy's website (https://www.gustaveroussy.fr/sites/default/files/meta-analysis-protocole-ma-f.pdf). The meta-analysis was registered in Prospero with number CRD42018107158. The study was approved by the French National Commission of Informatics and Liberty.

Eligibility criteria

Published and unpublished clinical trials without language restrictions were eligible if they were randomized in a way which precludes prior knowledge of the treatment assigned and were closed to patient accrual on or before December 31st, 2015. The eligible trials should have randomized patients with esophageal carcinoma s (either squamous cell carcinoma or adenocarcinoma) with resectable disease without distant metastasis. They must have compared treatment strategies of upfront surgery versus

and either thoracic esophagus (TE) and gastro-esophageal junction (GEJ) with non-metastatic resectable disease. They must have compared treatment strategies of surgery alone versus neoadjuvant chemotherapy followed by surgery as first line therapy.

New identified trials (i.e., not included in the previous IPD meta-analysis) including less than 60 patients (30 patients by arm) or trials that compared different neoadjuvant chemotherapy protocols only were excluded from the present meta-analysis.

In trials which have included patients with esophageal carcinoma as well as other tumor sites (e.g., study including both GEJ and gastric carcinomas) only patients with esophageal carcinoma were included in the present meta-analysis.

Study identification strategy

Three electronic databases were queried for published trials: Pubmed, Web of science and Scopus. Additionally, two trials registers (Clinicaltrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL)) and four conference proceedings (American Society of Clinical Oncology, American Society of Therapeutic Radiation Oncology, European Society of Medical Oncology and Proceedings of the European Cancer Conference Organization) were searched to identity trials unpublished or only presented as an abstract. Finally, bibliographies of identified trials were manually searched, and all members of the international advisory board were asked for additional references. Full search equations for the electronic databases are given in the **appendix B**.

Identified records were first screened based on the title, then abstract. The full article of potentially eligible studies was then assessed to verify that they met the inclusion criteria. In case of uncertainty about the eligibility of a trial, this was discussed within the project management group was held until a consensus was reached.

Data collection process

Trial investigators were principally reached by e-mails (see **Appendix C1** for full methods). Available data were checked and reanalyzed in order to identify potential errors or discrepancies between the received data and the published one according to a standardized protocol which follows the recommendations of the Cochrane Individual Participant Data Meta-analysis Methods Group and PRISMA IPD [6], and if required queries were made to the investigators.

Studied items and endpoints

Overall survival (OS) was the primary endpoint and defined as the time from randomization until death due to any cause; patients remaining alive and those lost to follow-up were censored on the date of last follow-up. Secondary survival endpoints were disease-free survival (DFS) and its decomposition pattern of failure in competing risks (see below), defined as the time from 6 months after randomization (landmark) until death due to any cause or any recurrence and cause specific (cancer, non-cancer) deaths, to consider the difference in duration of treatment in the comparative arms.

The secondary endpoints were R0 resection rate , chemotherapy related acute toxicities according to NCI-CTCAE 3 [7], when applicable , and severe postoperative complications defined as life threatening or requiring a re-intervention as well as 30 days postoperative mortality.

Statistical analyses

All analyses were conducted on an intent-to-treat basis (i.e., all randomized patients were included in the analyses according to the allocated treatment). Median follow-up was estimated with the reverse Kaplan-Meier method.

For time-to-event outcomes, both fixed **(Appendix C2)** and random effects model were used, but here we report mainly random effects models. The overall HRs were calculated using an IPD based Cox

random effect model with a trial-specific random baseline risk ("random intercept") and a trial specific random treatment effect ("random slope").[8]. Chi–square heterogeneity tests were used to test for statistical heterogeneity among trials, as well as the I^2 index[9] with a value below 25% considered as low heterogeneity. Survival curves were estimated for both treatment groups according to Kaplan-Meier method. Restricted Mean Survival Time (RMST) differences were calculated according to pooled Kaplan-Meier method[10] **(Appendix C3).** Similar analyses were performed for disease-free survival, but because of the different timing of surgery between the two arms a 6-months landmark method was prespecified.[11]

A stratified Fine and Gray competing risk model was used for the analysis of the pattern of failure, based on three events : local recurrence, distant recurrence including combined local and distant and death without recurrence.[12] **(Appendix C4)** Treatment effect on cancer related and non-cancer related deaths were calculated according to the Peto's method.[13]

For binary outcomes (R0 resection rate, morbidity, and postoperative mortality rates) trial specific risk ratios (RR) were calculated along with their 95% CI and combined with an IPD-based mixed effect generalized linear model. **(Appendix C5)**

Prespecified subgroup analyses were planned according to the histological subtype (AC vs. SCC), the tumor location (TE vs. GEJ), age (considered as continuous or categorized), sex, baseline T and N from the TNM. (**Appendix C6**). They were done by including in the Cox model a covariate x treatment interaction term. Sensitivity analyses with exclusion of clear outliers, small trials (< 60 patients) and a subset analysis according to the type of chemotherapy used (5FU-Cisplatin based versus others) were planned. An unplanned sensitivity analysis was also done for the interaction between treatment effect and tumor location or histology. As all trials did not include both location and histology this analysis was necessary to confirm that interaction were not due to between trial variation in treatment effect only but also to within trial variation.

As there are no chemotherapy related toxicities in the upfront surgery group, results on toxicities were descriptive only and presented as count (percentage).

Analyses were either stratified by trial or trial was used as grouping variable on random effects models. All p-values were two-sided. Analyses were done with SAS 9.4 and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria 2018) along with the lme4, coxme and meta packages.

Data sharing statement

The MANATEC-02 collaborative group supports data sharing and can be approached by email for new collaborations. However, specific agreements will need to be set up between the individual sponsors of the trials to ensure data recipients comply with the required level of data integrity and legal and ethical considerations.

Results

Available studies

The study flow chart is presented in **Figure 1**. After extensive review of the literature sixteen trials were identified as eligible.[14–30] and are described in **table 1**. The data from four trials, all completed before 195 and representing a total of 262 pts or 9.6% of the overall identified patient population, were not made available. The 12 remain trials included 2478 patients, representing 96% of all those

randomized. One of the 12 available trials (Scandinavia) had a four-arm design allowing two comparisons (CS vs S and Chemoradiotherapy vs radiotherapy surgery) were included leading to 13 comparisons in the present meta-analysis.

For the 12 available trials, the median follow-up times for overall survival were 5.6 years, but with major variation, from 2.6 to 26 years, between individual trials (See **table 1**). No major design or data-related issue was identified during checking, and all 12 available trials, representing a total of 2478 patients, could be included in the present meta-analysis.

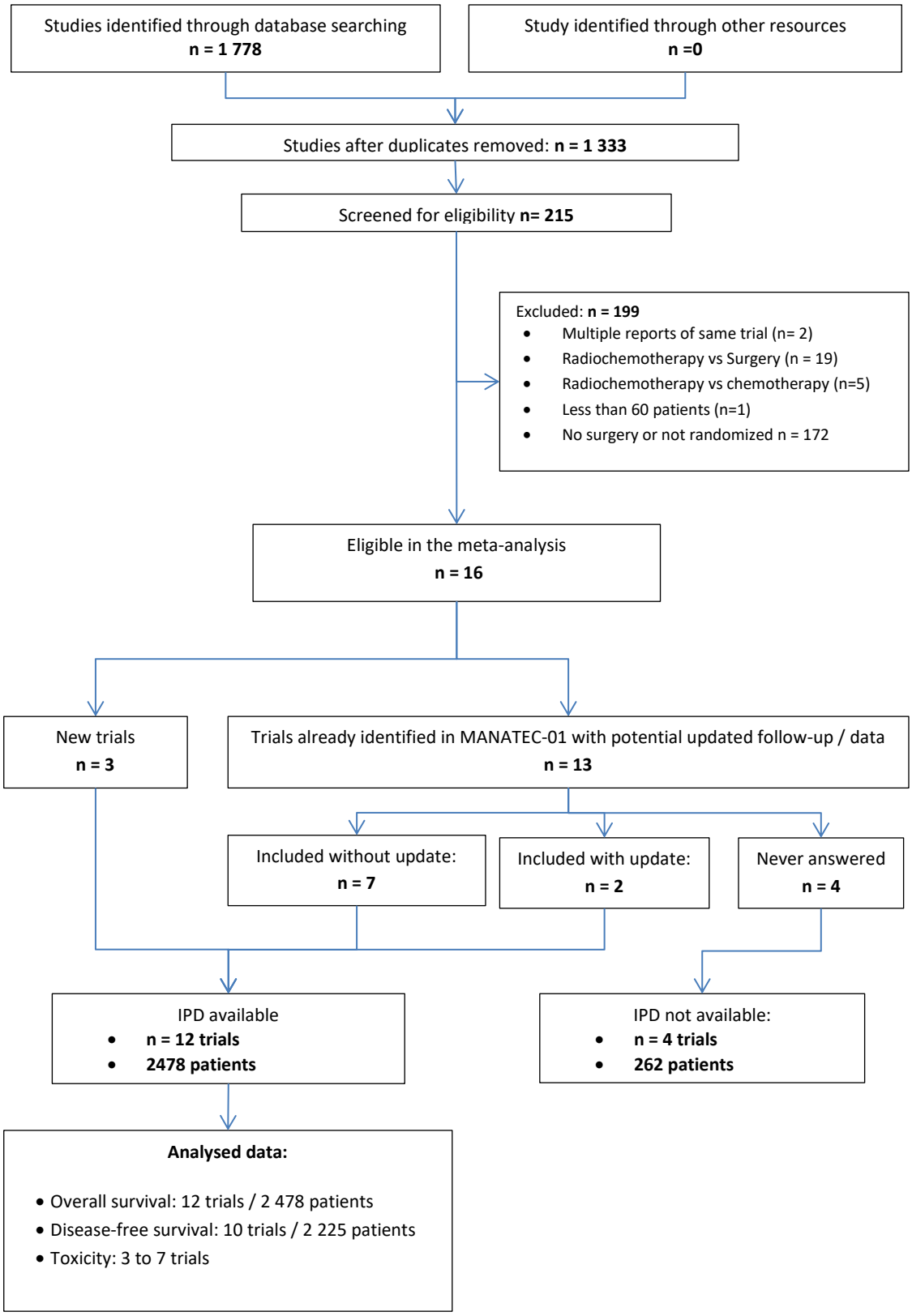

Figure 1: PRISMA-Individual Patients' Data (IPD) Flow diagram

Table 1: Description of the 16 eligible trials

Trial **Short name** (First author Year)	**Accrual period**	**N Cycles**	**Neoadjuvant chemotherapy protocol**	**Median follow-up (years [95% CI])[£]**	**N***	**Thoracic Esophagus / Gastro-Esophageal junction***	**Squamous cell carcinoma / Adenocarcinoma***
IPD available							
MD Anderson (Roth 1988) [†] [14]	1982-1986	2	Cisplatin 120 mg/m²/d; day 1 Bleomycin 10 UI/m²/d; days 3 to 6 Vindesine 3 mg/m²/d; days 1, 8, 15, 22	2.6[1.4-NR]	36	36/0	36/0
Scandinavia (Nygaard 1992) [†§] [15]	1983-1988	2	Cisplatin 20 mg/m²/d; days 1 to 5 Bleomycin 5 mg/m²/d; days 1 to 5				
- ***Scandinavia 1*** (CS vs S)				11[7.4-NR]	106	104/0	106/0
- ***Scandinavia with radiotherapy*** (CRS vs RS)			+ 35 Gy / 20 fractions	11[7.9-NR]	111	104/0	111/0
Oeso 2 (Giuli) [†] (Unpublished)	1985-1989	2	Cisplatin 120 mg/m²/d, day 1. Bleomycin 10 mg/m²/d, days 3 to 6 Vinblastine 3 mg/m²/d, days 1, 8, 15 & 22.	4.2[4.2-5.0]	122	0/0	122/0
Songkla (Maipang 1994) [†] [16]	1988-1990	2	Cisplatin 100 mg/m²; day 1 Bleomycin 10 mg/m² then 10mg/m²/d; days 4 to 7 Vinblastin 3 mg/m² days 1, 18, 15, 22	4.5[2.9-NR]	46	46/0	46/0
Queen Mary (Law 1997) [‡] [17]	1989-1995	2	Cisplatin 100 mg/m²; day 1 Fluorouracil 500 mg/m²/d; days 1 to 5	26 [23, NR]	147	144/0	147/0
Rotterdam (Boonstra 2011) [†] [18]	1989-1996	2-4	Cisplatin 80 mg/m²; day 1 Etoposide (IV) 100 mg/m²; day 1-2 Etoposide (PO) 200 mg/m²; day 3-5	4.6[4.1-6.5]	169	150/0	169/0
RTOG 8911 (Kelsen 1998) [†] [19,20]	1990-1995	3	Cisplatin 100 mg/m²; day 1 Fluorouracil 1000 mg/m²/d; days 1 to 5	9.2[8.8-10]	467	308/151	216/244
Italy (Ancona 2001) [†] [21]	1992-1997	2	Cisplatin 100 mg/m²; day 1 Fluorouracil 1000 mg/m²/d; days 1 to 5	6.9[6.6-7.8]	96	96/0	96/0

MRC EO-02 (Medical Research Council 2002) ‡ [22,23]	1992-1998	2	Cisplatin 80 mg/m²; day 1 Fluorouracil 1000 mg/m²/d; days 1 to 4	4.0[3.8-4.5]	802	720/82	247/533
MAGIC (Cunningham 2006) μ [24]	1994-2002	3	Cisplatin 60 mg/m²; day 1 Fluorouracil 200 mg/m²/d; days 1 to 21 Epirubicin 50 mg/m²; day 1	3.3[2.9-4.0]	131	73/58	0/131
ACCORD7 (Ychou 2011**)**μ [25]	1995-2003	2-3	Cisplatin 100 mg/m²; day 1 Fluorouracil 800 mg/m²/d; days 1 to 5	6.2[5.2-8.7]	169	25/144	0/167
EORTC 40954 (Schuhmacher 2010) μ [26]	1999-2004	2	Cisplatin 50 mg/m² day; days: 1-15-29 Fluorouracil 2000 mg/m²/d; days: 1-8-15-22-36	4.4[3.9-5.4]	76	0/76	0/56
IPD not available							
CAO (Schlag 1992) [27]	NA	3	Cisplatin 20 mg/m²/day; days 1 to 5 Fluorouracil 1000 mg/m²/day; days 1 to 5		46	46/0	46/0
China 01 (Wang 2000) [28]	1987-1988	1	FPLC¶ 2x20 mL/day x 12.5 days		60	0/60	0/60
China 02 (Wang 2001) [29]	1991-1994	NA	Cisplatin 30 mg days 1 to 5		100	100/0	97/3
Kagoshima (Baba 2000) [30]	1993-1995	2	Cisplatin 70 mg/m²; day 1 Fluorouracil 700 mg/m²/day; days 1 to 5		56	56/0	56/0
Total: 16 trials					**2 740 (100%)**	**2 008/571**	**1 495/1 194**
Available: 12 trials					2 478 (90.4%)	1 806/511	1 296/1 131
Not available: 4 trials					262 (9.6%)	202/60	199/63

IV: intra-venous, PO: per os, NA: Not available

RTOG: Radiation Therapy Oncology Group, ACCORD; EORTC: European Organization for the Research and Treatment of Cancer, ACCORD: Actions Concertées dans les Cancers Colorectaux et Digestifs

* Subgroups may not sum to total because of unknown values or undifferentiated tumors (see supplementary table 1 for detail on missing data)

£ No trial had significant differences of follow-up across arms

† Included in the previous meta-analysis, no updated follow-up available

‡ Included in the previous meta-analysis, updated follow-up available

§ A 2x2-arm trial: Surgery only (S), Chemotherapy Surgery (CS), Radiotherapy Surgery (RS), Chemoradiotherapy Surgery (CRS); as in the previous meta-analysis on pre-operative chemotherapy, both the comparison of CS vs. S (n=106) and CRS vs RS (n=111) were included.

μ Trials including also gastric cancer. The overall numbers of patients randomized in these trials are respectively: 503 (MAGIC), 224 (ACCORD7) and 144 (EORTC40954).

¶ fluorouracili polyphase liposome composita pro orale (~ 2000 mg fluorouracil)

Characteristics of the included patients

The characteristics of the 2 478 patients are presented in **table 2** and patients' characteristics by trial are reported in **appendix D**. The main demographic and tumor related characteristics were well balanced between the two comparative arms It should be noted that because of the extensive period during which the trials were conducted the pretreatment clinical T and N stage were rarely reported. s. The median age was 62 and most of the patients were male. Due to the period of accrual and individual trial design, more than 50% of patient were diagnosed with squamous cell carcinoma and more than ¾ of tumor were located in the thoracic esophagus

Table 2: Characteristics of the included patients

	Surgery alone (S) N = 1,243[1]	**Neoadjuvant chemotherapy and Surgery (CS)** N = 1,235[1]	**All** N = 2,478[1]
Age in years (median (IQR))	62 (55, 68)	62 (54, 68)	62 (54, 68)
Sex			
Male	985 (79%)	996 (81%)	1981 (80%)
Female	257 (21%)	239 (19%)	496 (20%)
Unknown	1	0	1
Performance status			
0	621 (65%)	611 (64%)	1,232 (65%)
1	314 (33%)	321 (34%)	635 (33%)
2-3-4	19 (2.0%)	21 (2.2%)	40 (2.1%)
Unknown	289	282	571
Tumor location			
Thoracic esophagus	895 (77%)	911 (79%)	1,806 (78%)
Gastro-esophageal junction	264 (23%)	247 (21%)	511 (22%)
Unknown	84	77	161
Histology			
Squamous cell carcinoma	647 (53%)	649 (54%)	1,296 (53%)
Adenocarcinoma	573 (47%)	558 (46%)	1,131 (47%)
Undifferentiated or Unknown	23	28	51
Clinical (Baseline) T from TNM			
T1-T2	276 (60%)	291 (63%)	567 (62%)
T3-T4	182 (40%)	171 (37%)	353 (38%)
Unknown	785	773	1,558
Clinical (Baseline) N from TNM			
N0	224 (69%)	235 (71%)	459 (70%)
N+	101 (31%)	95 (29%)	196 (30%)
Unknown	918	905	1,823

[1] Data are N (percent of non-missing values) unless otherwise stated.

Effects of preoperative chemotherapy on overall survival

Overall effect

OS is based on IPD from all 2,478 patients and 2,010 deaths. The addition of neoadjuvant chemotherapy to surgery was associated with a statistically significant improved OS when compared to surgery alone, with a random effects HR_{random}=0.83 [95%CI:0.72-0.96], p=0.008 **(Figure 2)**. There was heterogeneity which persisted even after exclusion of the Songkla trial (outlying treatment see sensitivity analysis).

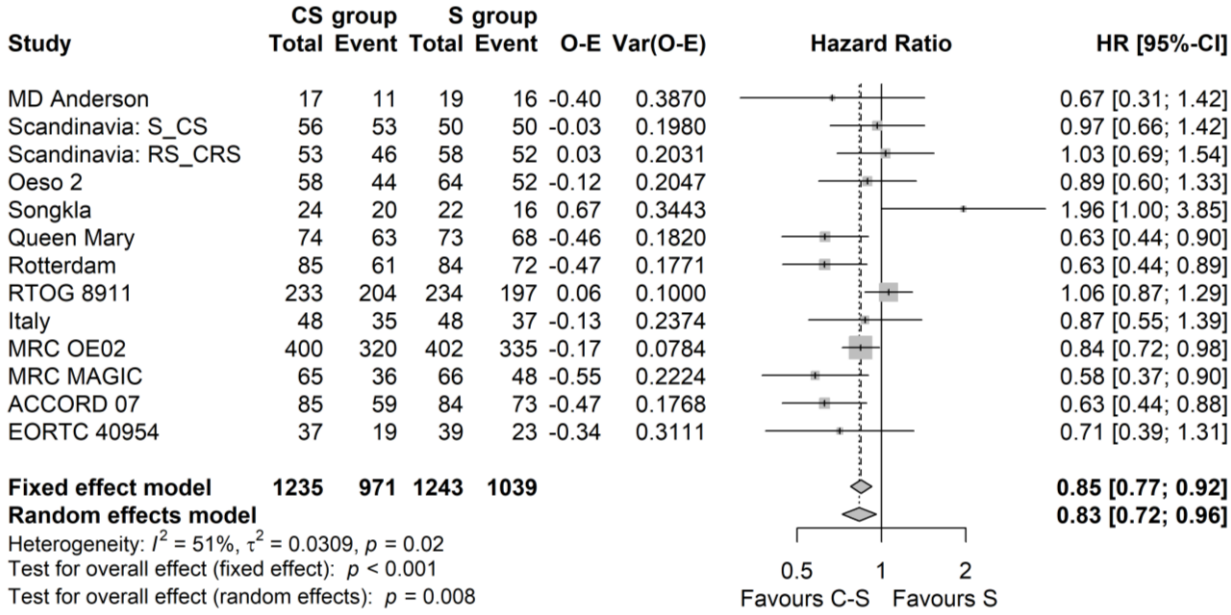

Figure 2: Forest plot of the preoperative chemotherapy effect on overall survival in the overall population

C-S: Chemotherapy followed by surgery, S: Surgery, Random effects Hazard ratio calculated by One-step Random Effects Cox model

These results translate to a preoperative chemotherapy 5.5% absolute benefit in 3-year overall survival at 3 years from 23.9% to29.4% and 6.1% at five years from 14.8% to 20.9% **(Figure 3)**. Differnences in restricted mean survival times (RMST) by treatment are reported in **table 3**, demonstrating a positive OS effect of neoadjuvant chemotherapy for both studied anatomical sites and pathological subtypes.

Table 3: RMST at five years for overall and disease-free survival

	RMST in CS arm (months)	RMST in S arm (months)	RMST differences* (months (95% CI))
Overall survival			
Overall population	25.1	21.7	+3.3 (+0.8;+5.9)
Thoracic Esophagus	20.9	22.7	+2.0 (-0.7;+4.8)
Gastro-esophageal junction	33.0	25.8	+6.9 (+2.4;+11.3)
Squamous cell carcinoma	22.1	20.3	+1.8 (-1.5;+5.0)
Adenocarcinoma	28.0	23.7	+4.5 (+1.8;+7.1)
Disease-free survival			
Overall population	25.0	19.6	+5.5 (+2.4;+8.7)

Thoracic Esophagus	22.6	19.2	+3.8 (+0.7;+6.9)
Gastro-esophageal junction	30.2	20.2	+9.8 (+4.0;+15.5)
Squamous cell carcinoma	22.2	19.2	+3.4 (-0.6;+7.45)
Adenocarcinoma	26.4	19.4	+6.9 (+3.5;+10.3)

* Because of the pooled variance used and the random effects, RMST differences may not be the exact subtraction of the two arms

RMST: Restricted mean survival time, CS: Chemotherapy-Surgery, S: Surgery

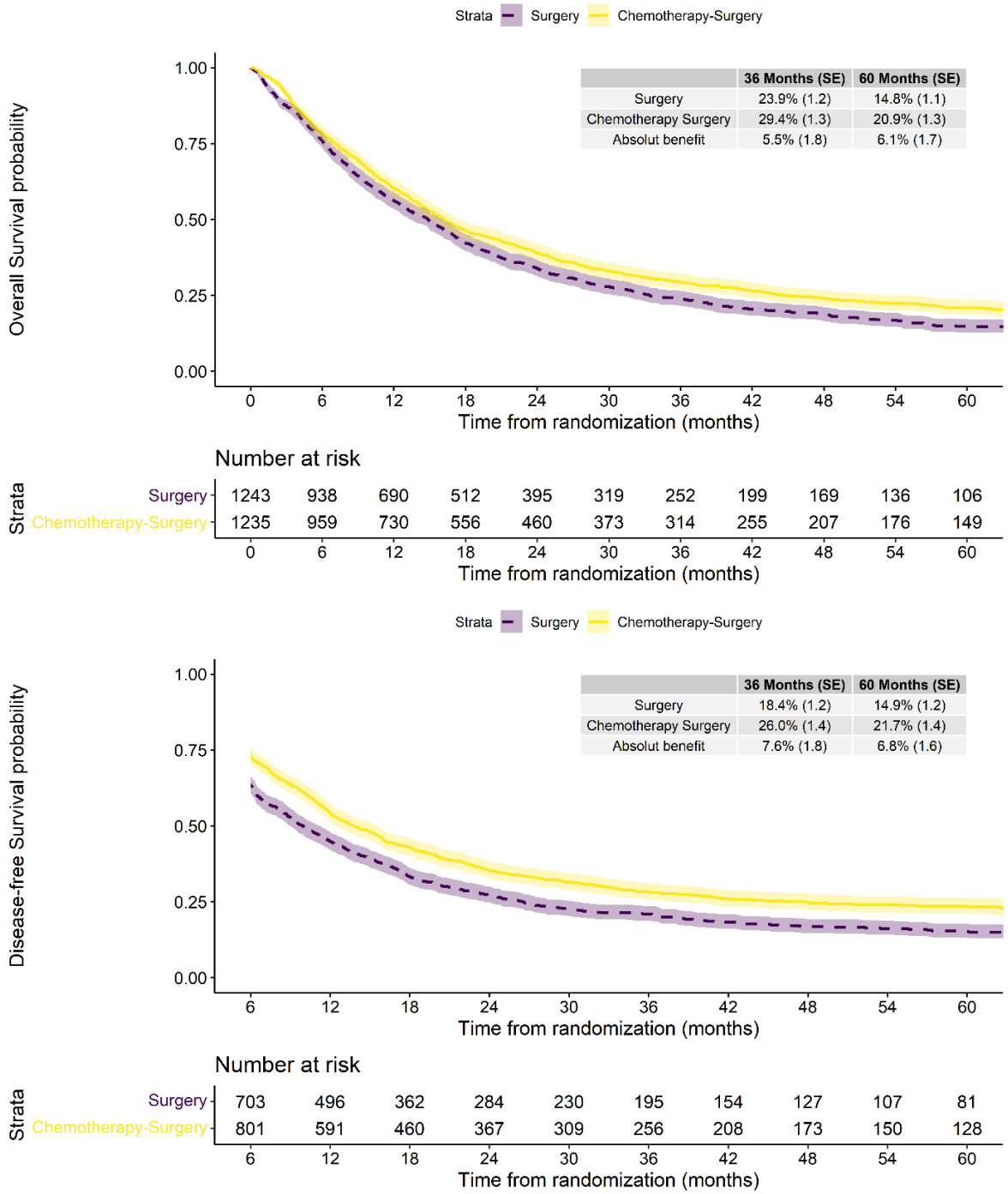

Figure 3: Survival curves for (top) overall survival and (bottom) disease-free survival (with a 6-month landmark) on the overall population.

Effects by participant subgroup

Subgroup analyses suggested a potential difference in effect by tumor location ($p_{interaction}$=0.07) with a HR_{random}=0.87 [0.75-1.00] in the thoracic esophagus group vs HR_{random}=0.68 [0.50-0.93] in the gastroesophageal junction group. (**Appendix E.1.1**). However, only 511 patients (22%) had a tumor located in the gastroesophageal junction.

Subgroup analyses by histology subtype revealed no significant interaction between the histological subtype and the treatment effect ($p_{interaction}$=0.26) with HR=0.91 [0.76-1.08] in the SCC group and HR=0.73 [0.62-0.87] in the AC group. (**Appendix E.1.2**) suggesting similar magnitude of benefit of neoadjuvant chemotherapy in both pathological subtypes.

No significant interactions were found with age either as categorical (p=0.21) (**Appendix E.1.3**) or continuous (p=0.98), and sex (p=0.43) (**Appendix E.1.4**).

Effects of preoperative chemotherapy on other endpoints

Disease-free survival

Disease-free survival data were available for 10 trials (2,225 patients). During follow-up 1, 783 DFS events (**Appendix F.1**) occurred, with 705 of them occurring before the 6-months landmark. The addition of neoadjuvant chemotherapy to surgery was associated with a statistically significant improved DFS compared to surgery alone, with a, HR_{random}=0.74 [0.64-0.85], p<0.001. **(Figure 4)** There was some degree of heterogeneity persisting even after the exclusion of the Songkla trial **(**See sensitivity analyses**)**

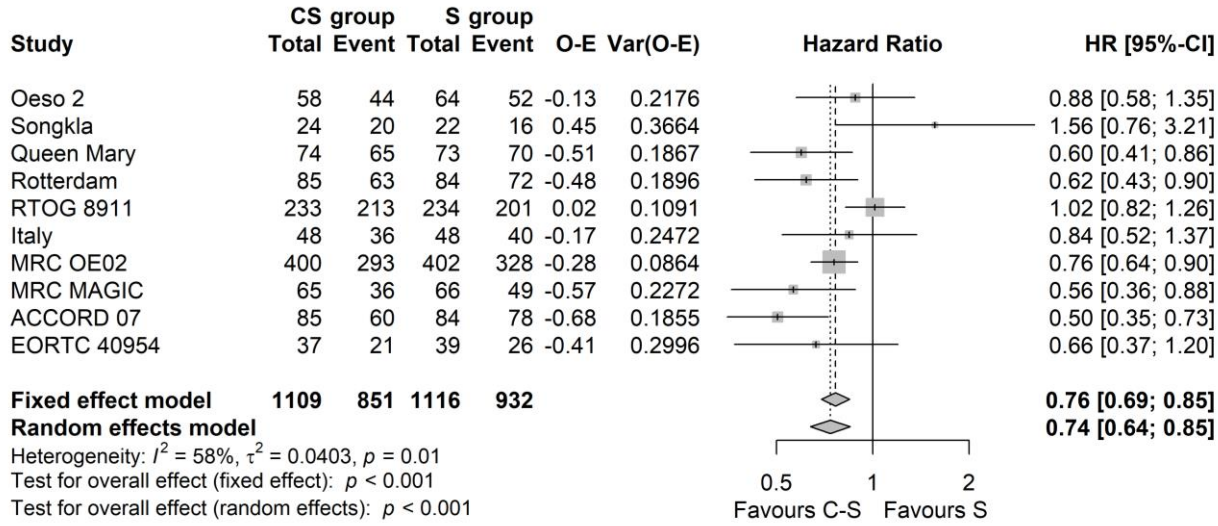

Figure 4: Forest plot of the preoperative chemotherapy effect on disease-free survival in the overall population

C-S: Chemotherapy followed by surgery, S: Surgery, Random effects Hazard ratio calculated by One-step Random Effects Cox model

The relative treatment effect translated into 7.6% absolute benefit in disease-free survival at 3 years, from 18.4 to 26.0% and 6.8% at 5 years from 14.9 to 21.7% **(Figure 3)**.

The differences in RMST between arms per anatomical sites and pathological subtype are reported in **table 3,** demonstrating a positive DFS effect of neoadjuvant chemotherapy for both studied anatomical sites and pathological subtypes

Subgroup analysis by tumor location indicated a significant difference ($p_{interaction}$=0.05) with an HR_{random}=0.78 [0.68-0.89] for tumor located in the TE and an HR_{random}=0.61 [0.42-0.89] for tumor located at the GEJ. Subgroup analysis on histological subtype showed an HR_{random}=0.83 [0.68-1.00] for SCC and HR_{random}=0.69 [0.57-0.83] for the AC ($p_{interaction}$=0.31). (**Appendix E.2.1 and E.2.2**). There were no significant interactions with age (p=0.10 as categorical and 0.96 as continuous) or sex (p=0.54). (**Appendix E.2.3 and E.2.4**)

Competing risks / pattern of failure analysis

Local recurrences were statistically significantly less frequent in patients treated with neoadjuvant chemotherapy with a subdistribution sHR=0.73 [0.60-0.88], p=0.001, without significant interaction (variation) according to histological subtypes (p=0.97) or tumor location (p=0.87). **(Appendix Figures F.3.1, F.3.2 and F.3.3)**

Distant recurrences were also statistically significantly less frequent in patients treated with neoadjuvant chemotherapy (sHR=0.82 [0.71-0.95], p = 0.01) without significant interaction (variation) according to histological subtypes (p=0.22) or anatomical location (p=0.55). **(Appendix Figures F.4.1, F.4.2 and F.4.3)**

No statistically significant increase in Death without recurrence was observed with the addition of neoadjuvant chemotherapy (sHR=1.12 [0.96-1.29], p=0.17). A significant interaction was found with the histological subtype (p=0.006) with a greater risk of death without relapse in the neoadjuvant chemotherapy group for patient with SCC 1.38 [1.12-170] versus 0.90 [0.73-1.12] for ADK. Another significant interaction was identified with the anatomical location (p=0.009) with a greater risk of death without relapse in the neoadjuvant chemotherapy group for patient with TE 1.23 [1.03-1.46] versus 0.68 [0.46-1.02] for GEJ. **(Appendix Figures F.5.1, F.5.2 and F.5.3)**

Cancer and non-cancer related mortality

Data for cancer and non-cancer related death analysis were available were available for 10 trials including 2 225 patients.

During follow-up 1 690 (69%) cancer and 92 (3.8%) non-cancer related death were reported. In the Surgery alone group (S) 891 (80%) cancer and 30 (2.8%) non cancer related deaths were reported (**Appendix table G.1**). In the neoadjuvant chemotherapy and surgery (CS) arm 799 (76%) cancer and 62 (5.5%) non cancer related deaths were reported. For non-cancer death, only eight trials had at least one event.

Cause-specific survival analysis revealed that preoperative chemotherapy was associated with a lower risk of cancer death HR=0.76 [0.65-0.90], p=0.004 (**Appendix figure G.2**). For non-cancer death, only eight trials had at least one event and no significant difference was found HR=1.45 [0.76-2.76], p=0.37 (**Appendix figure G.3**). Absolut differences in mortality rates at five years were -7.1% (±1.8) % for cancer deaths and +1.4 (±1.7) % for non-cancer deaths. (**Appendix figure G.4).**

Other outcomes

Administration of preoperative chemotherapy had no clear effect on R0 resection rates, p=0.26 (**Appendix H**); postoperative mortality, p=0.50 (**Appendix I**) or postoperative morbidity, p=0.57 (**Appendix J**).

Toxicities

Information on toxicities was seldom available and often not graded, for example with three trials having data on esophageal toxicity, seven trials on leucocyte toxicity or and one trial on platelets toxicity. Descriptive information on toxicities is given in **table 4.** Based on the limited data available, the most frequent toxicities were of white blood cells and mucositis all other toxicities were observed in less than 10% of the patients.

Table 4: Toxicities observed in the preoperative chemotherapy arms of the trials

Toxicities	Number of trials (patients)*	N with toxicity/N total in the chemotherapy arm[$]	Percent
Neutrophils	5 (909)	104/451	23.1%
Leucocytes	7 (1107)	73/533	13.7%
Mucositis	6 (976)	65/476	13.7%
Nausea	6 (985)	47/487	9.7%
Upper Gastrointestinal	2 (142)	4/72	5.6%
Platelet	7 (1107)	28/533	5.3%
Anemia	6 (938)	22/444	5.0%
Esophagus	3 (609)	11/305	3.6%
Diarrhea	6 (985)	17/486	3.5%
Heart	5 (854)	10/426	2.3%
Creatinine	4 (387)	4/193	2.1%
Pulmonary	4 (340)	2/159	1.3%
Skin	5 (518)	1/255	0.4%
Hand-foot syndrome	2 (122)	0/60	0.0%

* Number of trials and corresponding number of patients included in the meta-analysis with reported information and less than 20% missing data on this toxicity.

[$] Total of patient with non-missing value for this toxicity

Sensitivity and subset analyses

Planned sensitivity and subset on chemotherapy modalities analyses revealed no substantial modification of the results (**Appendix K**). Sensitivity analyses on interaction revealed no substantial modification either.

Discussion

In the present IPD meta-analysis we confirm the benefits of preoperative chemotherapy and surgery when compared to surgery alone on OS and DFS with absolute benefits of 6 and 7% respectively at 5 years. Preoperative chemotherapy also lowered both the risk of local and distant recurrences and cancer deaths but was not associated with greater postoperative mortality or morbidities. The IPD allowed us to perform subgroup analysis on two pre-specified factors: histological subtypes and tumor locations. We found no strong argument for a different efficacy according to histological subtypes. A slightly more pronounced efficacy of preoperative chemotherapy for tumors located at the GEJ than TE for both OS and DFS was observed but relied on few patients with tumor located at the GEJ. Several strengths of this study must be highlighted. This is a large-scale IPD meta-analysis, including 96% of the patients from eligible trials, included updated follow-up, and allowed us the ability to perform subgroup analyses. The final sample size (2, 478 patients) is large, giving power to detect variation in treatment effects.

Some weaknesses of the current study may be acknowledged. We were not able to retrieve IPD for all the identified trials. Nevertheless, these trials represent only a small fraction of all the available evidence and are unlikely to substantially change the results given the large number of deaths and local or distant recurrences. The inclusion period is large, therefore, variation in baseline risk, supportive care and surgical techniques across the study period is likely. All trial started accrual before 2000 and half of them before 1990. Moreover, while all chemotherapies protocols were platinum based, they were not all identical. Yet, the use of a random effect model allowing trial-specific variations for the baseline risk and trial-specific treatment effect may have lowered the importance of this issue. Moreover, no trend for a greater treatment effect over time was seen. Despite the random effect's models and the exclusion of on outlier trial, some degree of heterogeneity remained. Also, no important interaction was seen between treatment effect and the type of chemotherapy and no clear trend of greater benefits across time was seen. While new class of drugs (targeted therapies and immunotherapy) may confer a greater benefits in the future, the current standard [2] is still a combination of a platinum and a fluoropyrimidine. The analysis of toxicities is limited because several of the included trials were undertaken at a time where toxicities were not recorded as thoroughly as they are nowadays. Therefore, readers should interpret these data with caution. The same phenomenon most likely also applies to postoperative morbidities. As illustrated by the limited information on pre-operative TNM stage, reported in only seven trials, the pre-operative investigation and assessment of the resectability of tumors have dramatically evolved, with the advent of endoscopic ultrasound and new imaging modality, but end up being identical between treatment arms for individual trials.

The study has two major implications: (i) it confirms that preoperative chemotherapy should be considered as standard in this population (ii) and does not suggest that adenocarcinomas are more sensitive to chemotherapy than squamous cell carcinomas. The other potential preoperative treatment is preoperative chemo-radiotherapy and is the real competitor. The comparison of its efficacy as compared to with chemotherapy relies on few data. Several trials are ongoing to compare these two treatments: Re-Evaluation (NCT02442440), TOPGEAR[31] (ACTRN12609000035224), CMISG1701[32] (NCT03001596), ESOPEC[33] (NCT02509286), Neo-AEGIS[34] (NCT01726452), NExtT (JCOG 1109, UMIN000009482), but the final results will not be available before several years. The current study will be completed soon by a wider IPD network meta-analysis including trials comparing

preoperative chemo-radiotherapy to surgery and trials comparing preoperative chemotherapy and preoperative chemo-radiotherapy when the data of all the network will be available, they might give new insights on the best neoadjuvant treatment and the potential interactions.

Conclusion

Neoadjuvant chemotherapy rather than upfront surgery should be considered for both locally advanced squamous cell carcinoma or adenocarcinoma of the thoracic esophagus or GEJ. The slightly more pronounced effect seen for the few tumor located at the GEJ need to be confirmed in subsequent works.

References

[1] World Health Organisation. GLOBOCAN 2008. http://globocan.iarc.fr/.

[2] Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2016;27:v50–7. https://doi.org/10.1093/annonc/mdw329.

[3] National Comprehensive Cancer Network N. NCCN Clinical Practice Guidelines in Oncology. NCCN Clinical Practice Guidelines in Oncology n.d. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed June 18, 2017).

[4] Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev 2015:CD001556. https://doi.org/10.1002/14651858.CD001556.pub3.

[5] Thirion PG, Michiels S, Le Maître A, Tierney J. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma. JCO 2007;25:4512–4512. https://doi.org/10.1200/jco.2007.25.18_suppl.4512.

[6] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data: The PRISMA-IPD Statement. JAMA 2015;313:1657. https://doi.org/10.1001/jama.2015.3656.

[7] Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP n.d. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed October 26, 2020).

[8] Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011;64:949–67. https://doi.org/10.1016/j.jclinepi.2010.11.016.

[9] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58. https://doi.org/10.1002/sim.1186.

[10] Lueza B, Rotolo F, Bonastre J, Pignon J-P, Michiels S. Bias and precision of methods for estimating the difference in restricted mean survival time from an individual patient data meta-analysis. BMC Med Res Methodol 2016;16. https://doi.org/10.1186/s12874-016-0137-z.

[11] Sposto R, Stablein D, Carter-Campbell S. A partially grouped logrank test. Stat Med 1997;16:695–704.

[12] Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999;94:496–509. https://doi.org/10.1080/01621459.1999.10474144.

[13] Rotolo F, Michiels S. Testing the treatment effect on competing causes of death in oncology clinical trials. BMC Med Res Methodol 2014;14:72. https://doi.org/10.1186/1471-2288-14-72.

[14] Roth JA, Pass HI, Flanagan MM, Graeber GM, Rosenberg JC, Steinberg S. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg 1988;96:242–8.

[15] Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992;16:1104–9; discussion 1110.

[16] Maipang T, Vasinanukorn P, Petpichetchian C, Chamroonkul S, Geater A, Chansawwaang S, et al. Induction chemotherapy in the treatment of patients with carcinoma of the esophagus. J Surg Oncol 1994;56:191–7.

[17] Law S, Fok M, Chow S, Chu KM, Wong J. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 1997;114:210–7. https://doi.org/10.1016/S0022-5223(97)70147-8.

[18] Boonstra JJ, Kok TC, Wijnhoven BP, van Heijl M, van Berge Henegouwen MI, Ten Kate FJ, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal

squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer 2011;11:181. https://doi.org/10.1186/1471-2407-11-181.
[19] Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–84. https://doi.org/10.1056/NEJM199812313392704.
[20] Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol 2007;25:3719–25. https://doi.org/10.1200/JCO.2006.10.4760.
[21] Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer 2001;91:2165–74.
[22] Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727–33. https://doi.org/10.1016/S0140-6736(02)08651-8.
[23] Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–7. https://doi.org/10.1200/JCO.2009.22.2083.
[24] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20. https://doi.org/10.1056/NEJMoa055531.
[25] Ychou M, Boige V, Pignon J-P, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715–21. https://doi.org/10.1200/JCO.2010.33.0597.
[26] Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210–8. https://doi.org/10.1200/JCO.2009.26.6114.
[27] Schlag PM. Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Fuer Onkologie der Deutschen Gesellschaft Fuer Chirurgie Study Group. Arch Surg 1992;127:1446–50.
[28] Wang XL, Wu GX, Zhang MD, Guo M, Zhang H, Sun XF. A favorable impact of preoperative FPLC chemotherapy on patients with gastric cardia cancer. Oncol Rep 2000;7:241–4.
[29] Wang C, Ding T, Chang L. [A randomized clinical study of preoperative chemotherapy for esophageal carcinoma]. Chin J Oncol 2001;23:254–5.
[30] Baba M, Natsugoe S, Shimada M, Nakano S, Kusano C, Fukumoto T, et al. Prospective evaluation of preoperative chemotherapy in resectable squamous cell carcinoma of the thoracic esophagus. Dis Esophagus 2000;13:136–41.
[31] Leong T, Smithers BM, Haustermans K, Michael M, Gebski V, Miller D, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. ANNALS OF SURGICAL ONCOLOGY 2017;24:2252–8. https://doi.org/10.1245/s10434-017-5830-6.
[32] Tang H, Tan L, Shen Y, Wang H, Lin M, Feng M, et al. CMISG1701: A multicenter prospective randomized phase III clinical trial comparing neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy followed by minimally invasive esophagectomy in patients with locally advanced resectable esophageal squamous cell. BMC Cancer 2017;17. https://doi.org/10.1186/s12885-017-3446-7.
[33] Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Rothling N, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT

protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer 2016;16:503–503. https://doi.org/10.1186/s12885-016-2564-y.

[34] Reynolds JV, Preston SR, O'Neill B, Baeksgaard L, Griffin SM, Mariette C, et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC CANCER 2017;17. https://doi.org/10.1186/s12885-017-3386-2.