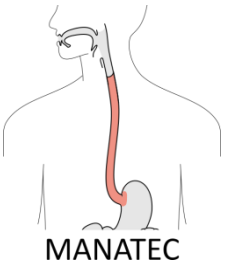

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

MANATEC-02: individual patient data Meta-Analysis of chemotherapy or chemo radiotherapy as NeoAdjuvant Treatment of Esophageal or gastro esophageal junction Carcinoma

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CONTENTS

RATIONALE AND OBJECTIVE

Rationale

According to WHO, esophageal cancer is the 8th most frequent cancer in the World with 456 000 new cases each year. Despite several therapeutic improvements, cancer related mortality remains high with 400 000 deaths per year corresponding to the 6th most lethal cancer.[1] In the locally advanced, non-metastatic, stages (UICC II and III), multimodality treatment still includes surgery (S) as a standard but the best neo-adjuvant treatment remains to be determined. Two neoadjuvant treatments have been mainly studied: neoadjuvant chemotherapy followed by surgery (CS) and neoadjuvant chemoradiotherapy followed by surgery (CRS). Most of the trials have compared one of these neo-adjuvant treatments versus upfront surgery using various protocols, with discordant results. Only a few trials of moderate trial size have compared CS versus CRS. Given the low level of evidence for the direct comparison, both American and European guidelines consider them as alternatives.[2,3] Moreover, esophageal cancers are heterogeneous entities with two histological types: squamous cell carcinoma and adenocarcinoma and two different anatomical locations: thoracic esophagus and gastro-esophageal junction (not taking into count cervical esophagus for which treatment strategy is different). There may be variation in the effects of neoadjuvant treatment by these subgroups but trials sometimes restricted inclusion to one histology or one location and sometimes not.

Our group has previously reported as abstract (ASCO 2007: abstract 4512 and ASTRO 2008: Abstract 158) two individual patient data meta-analyses both showing a significant benefit of neoadjuvant chemotherapy (hazard ratio (HR) = 0.87; 95% confidence interval = 0.79-0.95) and of neoadjuvant radio-chemotherapy (HR = 0.82; 95% confidence interval = 0.72-0.93,) on overall survival, translating to potential absolute benefits of 4.3% and 6.5%, respectively at 5 years. Although based on 9 neoadjuvant chemotherapy trials (including 2 102 patients) and on 9 chemoradiotherapy trials (including 1 210 patients), in both cases, the treatment effect was heterogeneous between trials. Since then, many new trials have been reported, and some older trials have been updated advocating for new meta-analyses. On the other hand, few trials are already available for the comparison of the neoadjuvant protocols. A network meta-analysis would allow combining the information coming from both the direct and indirect comparison. Several trials are currently recruiting worldwide (Appendix D), but observing a sufficient amount of overall survival event is long and the final data won't be available before several years. The identification of a surrogate for overall survival might permit to obtain these results faster.

Objectives

The mains aims are to evaluate individually the effects on *overall survival* of the three modality using standard pairwise meta-analysis strategies and then indirectly compare their effects, via:

1. An update of the prior meta-analysis on neoadjuvant chemotherapy followed by surgery versus upfront surgery for which 78% of the data are currently already available (MA#1)
2. An update of the prior meta-analysis on neoadjuvant chemo-radiotherapy followed by surgery versus upfront surgery (MA#2)
3. A new meta-analysis of neoadjuvant chemotherapy followed by surgery versus neoadjuvant chemoradiotherapy followed by surgery (MA#3).
4. A network meta-analysis of all the treatments combining the data of MA #1, #2 and #3.

In addition, we will also compare the effect of these treatments on disease-free survival, pattern of failure, cancer/non cancer mortality, R0 resection rate and postoperative mortality/complications.

Lastly, the value of disease-free survival as surrogate of overall survival will be studied.

GENERAL METHODS

Systematic reviews and quantitative meta-analyses based on updated *individual patient data* (IPD) will be carried out. The IPD approach involves the central collection, validation and analysis of data from all patients from all relevant randomized trials. This has been described as the "gold standard" method for meta-analysis, particularly when the expected benefit of the experimental therapy is small and when results of clinical trials are not consistent, as in this setting. This method allows the inclusion of all randomized trials (published or not published), thorough checking of trial and data quality, updating of follow-up and analyses by intent-to-treat. These meta-analyses will provide the most reliable estimate of efficacy and toxicity of the addition of neoadjuvant chemotherapy or chemoradiotherapy to surgery.[4]

TRIAL ELIGIBILITY CRITERIA

Published and unpublished trials without language restriction are eligible.

Eligible Trials must

- be randomized in a way which precludes prior knowledge of the treatment assigned
- be closed to patient accrual on or before December 31st 2015 (more recent and ongoing trials will be listed but no data collected)
- have aimed to randomize **patients**
  - with carcinoma of the esophagus (either squamous cell carcinoma or adenocarcinoma)
  - with locally advanced resectable disease without distant metastasis
  - receiving first line therapy
- have compared treatment strategies of :
  - upfront surgery versus neoadjuvant chemotherapy followed by surgery
  - upfront surgery versus neoadjuvant chemoradiotherapy followed by surgery
  - neoadjuvant chemotherapy versus chemoradiotherapy both followed by surgery

Exclusion criteria

- New trials (i.e. not included in the previous meta-analysis) including less than 60 patients (30 patients by arm
- Trials that compared radiotherapy without concurrent chemotherapy were not eligible
- Trials that compared different chemotherapy protocols only or different chemoradiotherapy protocols only were not eligible

IDENTIFICATION OF TRIALS

In order to avoid publication bias, both published and unpublished trials are eligible. To identify as many relevant trials as possible, systematic searches of a number of trial sources will be carried out and updated during the course of the project, ensuring a comprehensive and up-to-date database of trials. The search strategy is described in appendix A. In case of uncertainty about the eligibility of a trial, discussion within the project management group and the advisory board will be held until a consensus is reached.

Electronic Databases

Trials published are sought by searching electronic databases, without language restrictions, using the Cochrane Collaboration optimal search strategy for identifying randomized controlled trials, plus MeSH and free-text term terms relating to gastro esophageal cancer and the treatments :

- Pubmed
- Web of Science
- Scopus

The detailed search strategy used during this search is presented in Appendix A.

Trial Registers

Trial registers will be searched to identify trials that may or may not (yet) be published or are still recruiting patients:

- ClinicalTrials.gov
- Cochrane Central Register of Controlled Trials (CENTRAL)

Conference Proceedings

In addition, conference proceedings will be searched:

- Proceedings of the American Society of Clinical Oncology (ASCO)
- Proceedings of the European and American Society of Therapeutic Radiation Oncology (ESTRO, ASTRO)
- Proceedings of the European Society of Medical Oncology (ESMO)
- Proceedings of the European Cancer Conference Organization (ECCO)

with the aim of identifying trials that may have only been reported as abstracts

Additional hand searches

Bibliographies of identified trial publications and review articles will be screened for further trials.

All participating trialists will be asked to review and when possible supplement the list of eligible trials.

Trials identified

A provisional search identified:

- 16 trials, representing 2 573 patients for the S versus CS comparison
- 16 trials, representing 2 455 patients for the S versus CRS comparison
- 4 trials, representing 484 patients for the CS versus CRS comparison

As one trial is included in the three comparisons a total number of 34 trials and 5 512 patients are available. The full list of these trials along with summary information is presented in appendix B.

ENDPOINTS

Primary endpoint

- Overall survival defined as the time from randomization until death due to any cause; patients remaining alive and those lost to follow-up will be censored on the date of last follow-up.

Secondary endpoints

- Disease-free survival defined as the time from randomization plus a 6 months landmark until first event including local, distant recurrence/progression (failure) or death from any cause; patients alive without progression will be censored on the date of last follow-up;
- Pattern of recurrence/progression: local recurrence-free survival and distant recurrence-free survival and if enough data available, cumulative loco-regional recurrence/progression rate and cumulative distant recurrence/progression rate; patients who experienced a distant recurrence/progression and loco-regional recurrence/progression on the same date will be counted in distant progression;
- Cancer and non-cancer mortality, if data on recurrence and cause of death available;
- Acute toxicity during neoadjuvant treatment, for descriptive purpose only for MA#1 and MA#2;
- Compliance with neoadjuvant treatment, for descriptive purpose only for MA#1 and MA#2;
- Rate of patients untreated by surgery after neoadjuvant treatment;
- Tumor resectability : rate of R0 resection (according to trial definition);
- Rate and severity of severe postoperative complications (NCI-CTC, Clavien-Dindo[5] ≥ 3);
- 30 days postoperative mortality.

DATA COLLECTION

Data on baseline characteristics and all outcomes will be sought for all patients randomized into each trial. Up to date follow-up will be requested in order to report on longer-term outcomes. Data on compliance and toxicity will be collected as in our meta-analysis.[6]

- Baseline characteristics
  - Patient identifier (de-identified)
  - Date of birth (or de-identified date* derived from this date) or age at randomization
  - Sex
  - Performance status
  - Tumor stage (TNM, version to be specified)
  - Location of tumor (thoracic esophagus versus gastro esophageal junction)
  - Histology (squamous cell carcinoma or adenocarcinoma)
  - Date of randomization (or de-identified date derived from this date)
- Treatments characteristics
  - Treatment allocated as planned in the protocol
  - Date of the first day and the last day of neoadjuvant treatment
  - Number of cycles (or injections) received during neoadjuvant chemotherapy
  - Dates of radiotherapy start and end
  - Total dose and number of fractions of radiotherapy received
  - Ability to perform the planned surgery
  - Date of surgery
  - Type of surgery (trans-hiatal vs. trans thoracic)
- Toxicity/postoperative complication
  - Toxicity scale
  - Acute toxicity of neoadjuvant treatment (mucositis, diarrhea, nausea & vomiting, anemia, platelets, leucocytes, neutrophils, creatinine, pulmonary, skin, hand and foot syndrome, oesophagus, upper GI, Heart…)
  - Postoperative (within 30 days) complication (anastomotic fistula, postoperative death…)
  - Long term toxicity
- Outcomes
  - Preoperative clinical response
  - R0 resection rate
  - Complete pathological response rate
  - Survival status

* A random number of days can be added to the true dates for each patient

  - Date of death or last follow-up
  - Cause of death
  - Loco-regional failure status
  - Date of loco-regional failure
  - Distant failure status
  - Date of distant failure
- Other
  - Whether excluded from trial analysis
  - Reason for exclusion

Suggested coding conventions for these data are provided in order to facilitate data merging (Appendix E). However, data will be accepted in whatever format is most convenient for the individual trial investigator or data center.

A limited amount of information on trial design as well as the original trial protocol and associated publications will be requested on a separate form (Appendix F).

DATA CHECKING

All data will be checked by standard procedure using SAS program which follows the recommendations of the Cochrane Individual Participant Data Meta-analysis Methods Group[7] on and PRISMA IPD.[8]

Data will be checked for missing values as well as data validity and consistency across variables, and compared with published results if any. To assess randomization integrity, we will look for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. Follow-up of patients will also be assessed to ensure that it was well balanced between treatment arms and as updated as possible. Any queries will be solved with the responsible trial investigator or statistician. In case of quality questions raised by checking, the eligibility of the trial for the meta-analysis will be assessed by the Project management group and the Advisory board.

Each trial will be re-analysed and the analyses sent to trial investigator for validation.

The data collection and checking will be done by the Gustave Roussy Meta-analysis Unit. Copies of the final agreed database of all trials included in all comparisons will be held by Gustave Roussy. All trial data will be held securely and will not be used, circulated or distributed in any way that allows access to individual trial data, without first seeking permission from trial investigators.

ANALYSIS

All analyses will be conducted on an *intent-to-treat* basis (i.e. all randomized patients will be included in the analyses according to the allocated treatment). Three standard meta-analyses will be performed (neoadjuvant chemotherapy followed by surgery (CS) vs. upfront surgery (S), neoadjuvant chemoradiotherapy followed by surgery (CRS) vs. upfront surgery (S), CS vs. CRS and then a network meta-analysis combining the results of these 3 meta-analyses.

Median follow-up will be estimated with the use of the reverse Kaplan-Meier method.[9]

Analyses will be *stratified by trial* and all p-values will be two-sided. Analyses will be done with the R 3.5 (R Foundation for Statistical Computing, Vienna, Austria 2018) software.

Pairwise meta-analyses

EFFICACY ANALYSES

MAIN ANALYSIS OF TIME TO EVENT OUCTOME

For time-to-event outcomes, the individual times to event will be used in the stratified (by trial) logrank test. The log-rank expected number of events and variances of the observed minus expected number of events will be used to produce hazard ratio (HR) estimates and their 95% confidence intervals (95%CI) of the effect of treatment for individual trials. Chi–square heterogeneity tests will be used to test for statistical heterogeneity among trials as well as the I^2 index that expresses in percentage the proportion of variability of the results related to heterogeneity rather than to the sampling error[10] I^2 value below 25% is considered as low heterogeneity. In case of low heterogeneity, the overall pooled HR (and 95% CI) will be estimated by the fixed effects model,[11] whereas it will be estimated by a random effects models in case of explained heterogeneity. The R package "coxme" will be used for the random effects model.

The proportional hazards assumption will be checked at the 5 % significance level according to the methodology described by Wei et al., in which trial-specific p-values from Grambsch-Therneau test are pooled.[12]

Survival curves will be estimated for both treatment groups using annual mortality rates and hazard ratio.[13] They are used to calculate absolute differences in the survival rates every year. The same analyses will be performed for disease-free survival. Because of the different timing of surgery between the two arms and its high sensitivity compared to radiology to identify small intra-abdominal metastasis, a 6-month land mark method will be used with a modified log rank test[14] as in the RTOG 8911 trial.[15]

The Fine and Gray competing risk model will be used for local progression and distant progression.[16] For each of these endpoints, the studied type of progression will be analyzed as the main event. The other types of progression and death without progression will be

analyzed as competing events. Alive patients without progression will be censored. Sub-distribution hazard ratios will be estimated in each trial with the "cmprsk" R package and global sub-distribution hazard ratios will be estimated with the "crrSC" R package. Cumulative incidences will also be computed using the same packages.

For cause specific survival, analyses will be performed using the Peto's log-rank subtraction method[11] as the main analysis and cause specific hazard test[17] as a sensitivity analysis.

ADDITIONAL ANALYSIS OF TIME TO EVENT OUTCOME

The restricted mean survival time (RMST) estimates the life expectancy for one treatment arm up to a certain time horizon t*.[18,19] The difference in restricted mean survival time (rmstD) can thus quantify the treatment effect expressed in terms of life years gained. The rmstD is an appealing absolute outcome measure as it is valid even in case of non-proportional hazards. To take into account the trial effect, we will estimate, as secondary analysis, the overall rmstD as follows. First, we will estimate rmstD in each trial as the area between trial-specific Kaplan-Meier curves. Second, we will pool the rmstDs using a DerSimonian-Laird random effects meta-analysis model. This method has already been used by Wei and colleagues (as "Integrated difference of survival functions" but with fixed effects[12]) and Lueza and colleagues[20] (as "Pooled Kaplan-Meier"). The overall rmstD will be estimated at t* = 3 years and t* = 5 years and a graphic displaying rmstD varing time horizon t* will also be computed. Ninety-five percent CI and Wald tests will also be provided for the estimation of rmstD.

INFORMATION CONTENT ("POWER")

Based on the results of our previous work, a minimal difference of 4% in the overall survival rates at 5 years (16% to 20% in the S versus CS comparison and 18% to 25% in S versus CRS comparison) is expected. The 2 500 patients (2 069 events) expected in each comparison in MA#1 and MA#2 would yield a power of 85% to detect a difference of at least 6.5% (HR = 0.875) with a bilateral log-rank test and an alpha risk of 5%.[21]

For MA#3 the 500 patients in the direct comparison would give a power of 31% to detect a 5% differences in overall survival at 5 years (20% to 25%, 384 events, two sided test) but the addition of the 5 000 patients in the indirect comparison (4 138 "indirect events" $\approx$ 1 034 "direct events") may raise this power to nearly 80% as the precision of the estimates is divided by four for the indirect comparisons.[22]

TOXICITY AND RESECTION ANALYSES

For dichotomous outcomes such as toxicity (grade 3-4 versus grade 0-2) in the CS vs. CRS meta-analysis, the number of events and numbers of patients will be used to calculate risk ratio estimates of treatment effect. These risk ratios will be generated for individual trials and pooled across trials, using the fixed effects model. In case of heterogeneity, random effects models will be used.

ANALYSIS BY TRIAL LEVEL

Providing that there are sufficient data available, analyses are planned whereby trials, or arms within trials, will be grouped according to:

- planned dose of radiotherapy (<40 Gy, >= 40 Gy),
- type of chemotherapy (cisplatin + 5FU vs. other),
- similarity or not of the chemotherapy in the two arms for the comparison CS vs CRS.

ANALYSES BY PATIENT LEVEL

Providing there are sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups:

Age (years)	<60, 60-64, 65-69, 70+
Sex	Male, female
Histology	Squamous cell carcinoma, Adenocarcinoma
Tumor location	Thoracic esophagus, Gastroesophageal junction
T stage from the TNM	T1-T2, T3-T4
N stage from the TNM	N0, N+

To test whether there is any evidence that particular types of patients benefit more or less from investigated treatment, we will estimate interaction between treatment effect and patient subgroups in Cox model stratified by trial and containing treatment effect, covariate effect, and treatment-covariate interaction (one-stage model method).[23]

Sensitivity analysis

Sensitivity analyses will be done by exclusion of small trials (<60 patients), exclusion of trial using sequential chemoradiotherapy and exclusion of any trials that are clear outliers.

Network meta-analysis

The network meta-analysis will use all the trials identified for all comparisons. International recommendation on network meta-analysis will be followed.[24] A frequentist approach will be used with the R-package "Netmeta". Heterogeneity will be evaluated by the I^2,[10] and the consistency by Q statistics.[25] In case of heterogeneity a "random effect" model will be used or the trial(s) responsible for it identified. In case of inconsistency the responsible closed loop will be identified. Treatments will be ranked by the P-Score.[26] A specific supplement to the protocol will be prepared for the network meta-analysis.

Surrogate end-point identification and validation

Clinicians and researchers are in need of earlier markers of treatment efficacy than overall survival at 5 years. The possibility to use disease-free survival (DFS) as a surrogate for overall survival (OS) will be analyzed using the correlation method both at the patient's and the trial's levels. Two steps will be undertaken. Firstly, we will assess the correlation between

OS and DFS at the patient level with a bivariate model taking censoring into account.[27] Secondly, at the trial's level, we will evaluate the correlation between the treatment effect on OS and the treatment effect on DFS by either a linear regression model weighted by trial's size[28], or the Poisson model proposed by Rotolo et al.[29] Finally, The surrogate threshold effect[30] (i.e. the minimal treatment effect to observe on the surrogate (DFS) to predict a non-null effect of the treatment on the true endpoint (OS)) will be estimated by the trial's level linear regression. A specific supplement to the protocol will be prepared for the surrogate analysis.

WORKING PARTIES IN THE META-ANALYSIS

In order to complete the meta-analysis successfully, three groups with specific functions have been created: 1) the *Project management group* 2) the *Advisory board* 3) the *MANATEC Trialists' Collaborative Group*.

The *Project management group* is in charge of the coordination of the meta-analysis. It is responsible for collating the list of eligible trials and for inviting investigators to provide data available on patients. The *Project management group* is also in charge of checking, processing and analyzing the data. Finally, the *Project management group* is responsible for preparing reports, publications and works in close collaboration with the *Advisory Board*.

The *Advisory board* will include international experts in the field of medical oncology, radiotherapy and surgery involved in esophageal cancer, and experts in meta-analysis. The list of its members is given on the page 3. The *Advisory board* will support the *Project management group* with medical and methodological expertise, help determine trials relevant to the overview, promote contact between investigators and all the collaborators, determine trial quality if necessary, discuss the results before communication to the trialists, and review the manuscript before submission for publication.

Trial investigators will be responsible for providing the *Project management group* with data on patients and for discussing the reports prepared by the Advisory board and the Project management group.

The *MANATEC Trialists' Collaborative Group* will comprise the *Project management group*, the *Advisory Board* and *trial investigators*.

An investigator meeting will be organized by the *Project management group* to discuss the preliminary results of the meta-analysis and to plan additional analyses.

PRACTICAL CONSIDERATIONS

The Project management group, located in the Biostatistics and Epidemiology unit at Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Project management group. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for these meta-analyses or methodological work in the field of meta-analysis. An investigator meeting will be organized to discuss the preliminary results.

PUBLICATION POLICY

Any publication arising from this project will be made on behalf of the MANATEC Collaborative Group and include a list of all collaborators. All manuscripts will be sent for review to all the collaborators before submission.

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APPENDIX

A: Trial search strategy

PUBMED

(((((("Esophagogastric Junction"[MeSH] OR "Cardia"[MeSH] OR oesophago-gastric junction OR gastroesophageal junction) AND (neoplasms OR cancer OR tumor OR adenocarcinoma OR carcinoma OR epidermoid OR squamous cell)) OR ("Esophageal Neoplasms"[MeSH] AND "Stomach Neoplasms"[MeSH]) OR ("Esophageal Neoplasms"[MeSH] OR (esophag* AND (neoplasms OR cancer OR tumor OR adenocarcinoma OR carcinoma OR squamous cell)))) AND (((chemotherapy OR drug therapy OR cisplatinum OR carboplatin OR oxaliplatin OR bleomycin OR mytomicin c OR methotrexate OR 5-fluorouracil OR hydroxyurea OR vindesine OR vinblastine OR vinorelbine OR vincristine OR taxane* OR paclitaxel OR docetaxel OR gemcitabine OR vepesid OR VP-16 OR VP16 OR irinotecan OR FOLFOX OR T-FOX) OR (radio-chemotherapy OR chemoradiotherapy OR chemo-radiotherapy OR chemoradiotherapy OR radiotherapy)) AND (neoadjuvant OR neo-adjuvant OR induction OR preoperative OR perioperative))) AND (esophag*[Title] OR oesophag*[Title] OR junction[Title] OR cardia[Title]) AND ((((randomized controlled trial[Publication Type] OR clinical trial, phase iii[Publication Type] OR clinical trial, phase iv[Publication Type]) OR clinicaltrials.gov[Secondary Source ID] OR isrctn[Secondary Source ID]) OR randomized controlled trials as topic[MeSH Terms]) AND ((random OR randomised OR randomized) AND (trial* OR study OR studies)) OR (rct OR rcts)) AND ("1990"[Date - Publication] : "2017"[Date - Publication]))

WEB OF SCIENCE

#6 #5 AND #4 AND #3 AND #2 AND #1
DocType=All document types; Language=All languages;

#5 (TS=(random*))
DocType=All document types; Language=All languages;

#4 (TS=(neoadjuvant OR (neo adjuvant) OR preoperative OR pre operative OR perioperative OR (peri operative) OR induction))
DocType=All document types; Language=All languages;

#3 (TS=(chemotherapy OR (drug therapy) OR chemoradiation OR chemoradiotherapy OR chemoradiotherapy OR radio-chemotherapy OR pharmacotherapy))
DocType=All document types; Language=All languages;

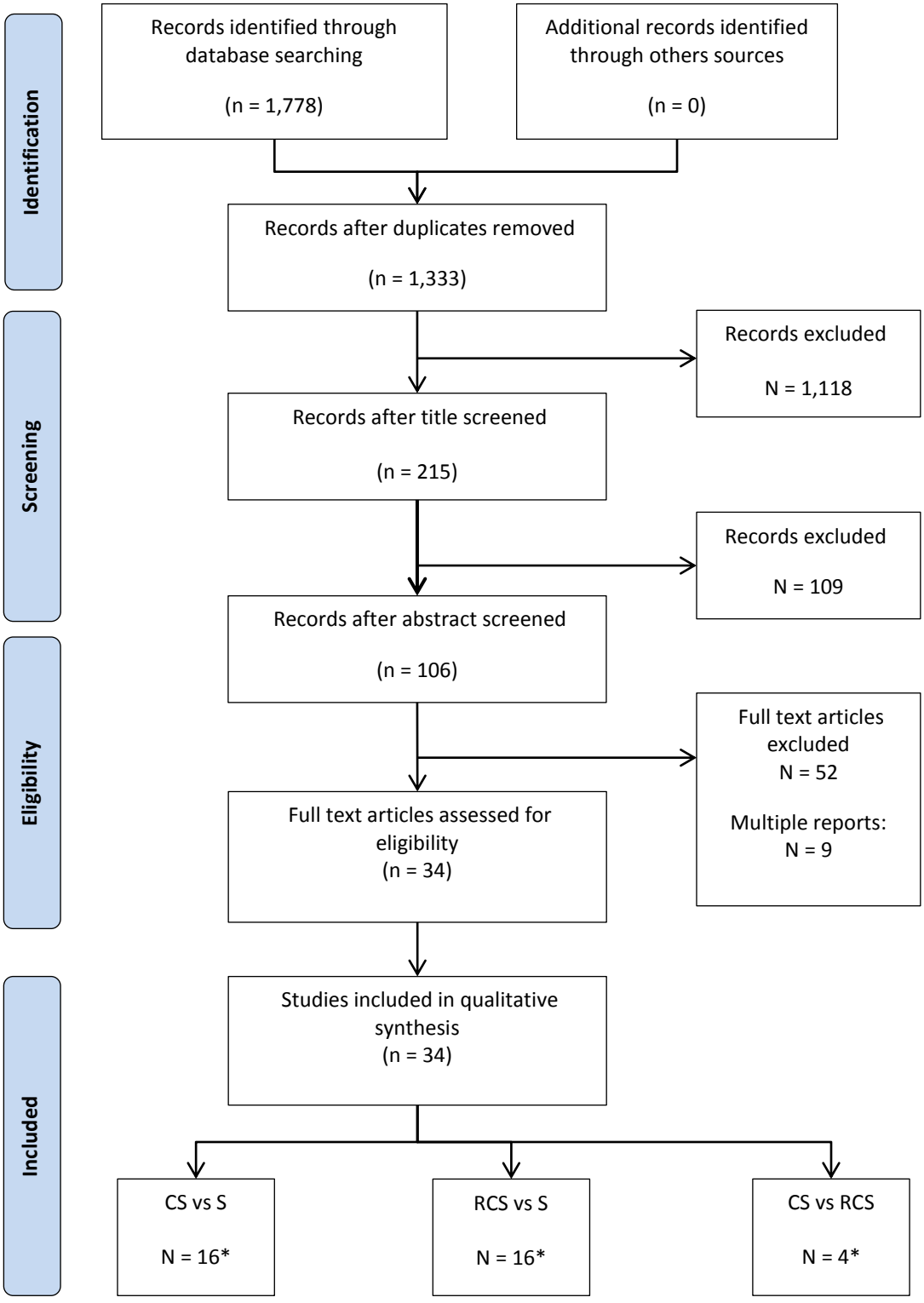
#2 (TS=(cancer* OR carcinoma* OR adenocarinoma* OR malignan* OR tumor* OR tumour* OR neoplasm OR (squamous)))
DocType=All document types; Language=All languages;

#1 (TS= (oesophag* OR esophagi* OR cardia OR (gastro-oesophag* junction) OR (gastro-esophag* junction) OR (gastrooesophag* junction) OR (gastroesophag* junction) OR (Esophagogastric Junction) OR (oesophago-gastric junction)))
DocType=All document types; Language=All languages;

SCOPUS

(TITLE-ABS-KEY (oesophag* OR esophag* OR cardia OR "gastro-oesophag* junction" OR "gastro-esophag* junction" OR "gastrooesophag* junction" OR "gastroesophag* junction" OR "Esophagogastric Junction" OR "oesophago-gastric junction") AND TITLE-ABS-KEY (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*) AND TITLE-ABS-KEY (squamous OR epidermoid OR "undifferentiated carcinoma" OR adenocarcinoma* OR carcinoma*) AND TITLE-ABS-KEY (chemotherapy OR chemoradiation OR "drug therapy" OR chemoradiotherapy OR chemoradiotherapy OR radio-chemotherapy OR pharmacotherapy) AND TITLE-ABS-KEY (neoadjuvant OR "neo adjuvant" OR preoperative OR "pre operative" OR perioperative OR "peri operative" OR induction) AND TITLE-ABS-KEY (random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts) AND TITLE-ABS-KEY (trial OR trials OR study OR studies)) AND PUBYEAR > 1989

FLOW CHART



S: Surgery, CS neoadjuvant chemotherapy followed by surgery, RCS: neoadjuvant chemoradiotherapy followed by surgery

* One trial with four arms is included in the three comparisons

B: Provisional list of eligible trials

META-ANALYSIS OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY VERSUS UPFRONT SURGERY (MA#1)

Trial First author /short name	Accrual period	N Cycles	Neoadjuvant chemotherapy protocol	N Analyzed/ Randomized**	TE/GEJ	SCC / ADC among TE/GEJ
Roth 1988/MD Anderson [*] (J Thorac Cardiovasc Surg)[31]	1982-1986	2	Cisplatin 120 mg/m²/day ; day 1 Bleomycin 10 UI/m²/day ; days 3 to 6 Vindesine 3 mg/m²/day ; days 1, 8, 15, 22	36/39	39/0	39/0
Schlag 1992[$] (Arch Surg, 1992)[32]	NA	3	Cisplatin 20 mg/m²/day; days 1 to 5 Fluorouracil 1000 mg/m²/day; days 1 to 5	46/46	46/0	46/0
Nygaard 1992/ Scandinavia [§*] (World J Surg, 1992)[33]	1983-1988	2	Cisplatin 20 mg/m²/day ; days 1 to 5 Bleomycin 5 mg/m²/day ; days 1 to 5	106/217	106/0	106/0
Giuli/Oeso 2[*] (Unpublished)	1985-1989	2	Cisplatin 120 mg/m²/d, day 1. Bleomycin 10 mg/m²/d, days 3 to 6 Vinblastine 3 mg/m²/d, days 1, 8, 15 & 22.	122/122	122/0	122/0
Wang 2000[$] (Oncology reports 2000)[34]	1987-1988	1	FPLC[%%] 2x20 mL/day x 12.5 days (~ 2000 mg fluorouracil)	60/60	0/60	0/60
Maipang 1994/Songkla[*] (J Surg Oncol 1994)[35]	1988-1990	2	Cisplatin 100 mg/m²; day 1 Bleomycin 10 mg/m² then 10mg/m²/day; days 4 to 7 Vinblastin 3 mg/m² days 1, 18, 15, 22	46/46	46/0	46/0
Law 1997/Quen Mary[*] (J Thoracic Cardiovasc Surg 1997)[36]	1989-1995	2	Cisplatin 100 mg/m²; day 1 Fluorouracil 500 mg/m²/day; days 1 to 5	147/147	147/0	147/0
Boonstra 2011/Rotterdam[£] (BMC Cancer 2011)[37]	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	169/169	169/0	169/0
Kelsen 1998/RTOG 8911[£] (NEJM 1998)[15] (J Clin Oncol 2007)[38]	1990-1995	3	Cisplatin 100 mg/m²; day 1 Fluorouracil 1000 mg/m²/day; days 1 to 5	443/467	467/0	220/247
Wang 2001[$] (Chinese Journal of	1991-1994	NA	Cisplatin 30 mg days 1 to 5	100	100/0	97/3

Oncology, 2001)[39]						
Ancona 2001/Italy* (Cancer, 2001)[40]	1992-1997	2	Cisplatin 100 mg/m²; day 1 Fluorouracil 1000 mg/m²/day; days 1 to 5	94/96	94/0	94/0
Medical Research Council 2002/MRC EO-02* (Lancet 2002)[41] (J Clin Oncol, 2009)[42]	1992-1998	2	Cisplatin 80 mg/m²; day 1 Fluorouracil 1000 mg/m²/day; days 1 to 4	802/802	720/82	247/533
Baba 2000$ (Dis Esophagus, 2000)[43]	1993-1995	2	Cisplatin 70 mg/m²; day 1 Fluorouracil 700 mg/m²/day; days 1 to 5	56	56/0	56/0
Cunningham 2006μ (New England J Med 2006)[44]	1994-2002	3	Cisplatin 60 mg/m²; day 1 Fluorouracil 200 mg/m²/day; days 1 to 21 Epirubicin 50 mg/m²; day 1	131	73/58	0/131
Ychou 2011* μ (J Clin Oncol, 2011)[45]	1995-2003	2-3	Cisplatin 100 mg/m²; day 1 Fluorouracil 800 mg/m²/day; days 1 to 5	139	25/114	0/139
Schuhmacher 2010 μ (J Clin Oncol 2010)[46]	1999-2004	2	Cisplatin 50 mg/m² day; days: 1-15-29 Fluorouracil 2000 mg/m²/day; days : 1-8-15-22-36	76	0/76	0/76
16 trials				**2573**	2194/401	1382/1704

TE: Thoracic Esophagus, GEJ: Gastro-Esophageal Junction, SCC: Squamous Cell Carcinoma, ADC: Adenocarcinoma, IV: intra-venous, PO: per-os, NA: Not Available

% number of eligible patients (i.e. patient with other localization than TE/GEJ excluded) analyzed in the previous meta-analysis or in the publication for the new trials.

§ Four-arm trial: S only, CTS, CTRS, preoperative RT; in the previous meta-analysis on pre-operative chemotherapy, both the comparison of CS vs. S (n=106) and CRS vs preoperative radiotherapy + surgery (n=111) were included.

* Data available for the previous meta-analysis or database hosted at Gustave Roussy

£ Data available for the previous meta-analysis but updated data may be available

$ Data were not available for the previous meta-analysis

μ Trials including also gastric cancer. The overall numbers of patients randomized in these trials are respectively: 503 (Cunningham 2006), 224 (Ychou 2011) and 144 (Schuhmacher 2010).

** for the trials included in the previous meta-analysis, number of eligible patients corresponds to the number of patients include in the meta-analysis.

%% fluorouracili polyphase liposome composita pro orale

NETWORK META-ANALYSIS OF NEOADJUVANT TREATMENTS (CHEMOTHERAPY VERSUS CHEMORADIOTHERAPY) FOLLOWED BY SURGERY VERSUS UPFRONT SURGERY (STEP#2)

TRIALS COMPARING NEOADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGERY VERSUS SURGERY ALONE (MA#2)

Trial	Accrual period	Radiotherapy protocol	Chemotherapy protocol	N	TE/GEJ	SCC / ADC
Nygaard 1992[§*] (World J Surg, 1992)[33]	1983-1988	35 Gy 20 fractions	Cisplatin 20 mg/m²/day ; days 1 to 5 Bleomycin 5 mg/m²/day ; days 1 to 5 RT 3 weeks after chemo completion	103/103	103/0	103/0
Apinop 1994 (Hepatogastroenterology, 1994)[47]	1986-1992	40 Gy 20 fractions	Cisplatin 100 mg/m²; days 1 and 29 Fluorouracil 600 mg/m²; days 1 to 4 and 29 to 32 RT concomitant	69	69/0	69/0
Le Prise, 1994[*] (Cancer, 1994)[48]	1988 - 1991	20 Gy 10 fractions	Cisplatin 100 mg/m²; days 1 and 21 Fluorouracil 600 mg/m²; days 2 to 5 and 22 to 25 RT concomitant	91/104	104/0	104/0
Urba 2001[*] (J Clin Oncol, 2001)[49]	1989-1994	45 Gy	Cisplatin 20 mg/m²; days 1 to 5 and 17-21 Fluorouracil 300 mg/m²/day; days 1 to 21 Vinblastine 1 mg/m²/day : days 1 to 4 and 17 to 21 RT concomitant	100/100	50/0	25/75
Bosset, 1997[*] (New England J Med, 1997)[50]	1989-1995	37 Gy	Cisplatin 85 mg/m² RT concomitant	294/297	297/0	297/0
Bass 2014[*] (New England J Med, 1996)[51] (Dis Oesophagus, 2002)[52] (Eur J Cancer, 2014)[53]	1990-1997	40 Gy 15 fractions	Cisplatin 75 mg/m²; days 7 and 49 Fluorouracil 15 mg/kg; days 1 to 5 and 42 to 47 RT concomitant	210/211	211/0	98/113
Burmeister 2005[*] (Lancet Oncol, 2005)[54]	1994-2000	35 Gy 15 fractions	Cisplatin 80 mg/m²; day 1 Fluorouracil 800 mg/m²; days 1 to 4 RT concomitant	256/257	256/0	95/158

An 2003 (Chinese J Oncol, 2003)[55]	1996-1997	36 Gy 12 fractions	Cisplatin Fluorouracil RT concomitant	97	97/0	NA
Tepper 2008* (J Clin Oncol, 2008)[56]	1997-2000	50.4 Gy 28 fractions	Cisplatin 100 mg/m²; days 1 and 29 Fluorouracil 1000 mg/m²; days 1 to 4 and 29 to 32 RT concomitant	56	56/0	14/42
Lv 2010 (World J Gastro Enterol, 2010)[57]	1997-2004	40 Gy 20 fractions	Paclitaxel 135 mg/m² ; days 1 and 22 Cisplatin 20 mg/m²/day ; days 1 to 3 and 22 to 24 RT concomitant	238	238/0	238/0
Lee 2004* (Ann Oncol, 2004)[58]	1999-2002	45,6 Gy 38 fractions	Cisplatin 60 mg/m²; days 1 and 21 Fluorouracil 1000 mg/m²; days 2 to 5 and 22 to 26 RT concomitant	101	101/0	101/0
Peng 2008 (Tumor, 2008)[59]	2000-2002	40 Gy NA	Cisplatin 70 mg/m² Fluorouracil 500 mg/m² Rx concomitant	80	80/0	80/0
Mariette, 2014 (J Clin Oncol, 2014)[60]	2000-2009	45 Gy 25 fractions	Cisplatin 750 mg/m²; days 1 and 29 Fluorouracil 800 mg/m²; days 1 to 4 and 29 to 32 RT concomitant	195	195/0	137/57
van Hagen 2012 (New England J Med, 2012)[61] (Lancet Oncol, 2015)[62]	2004-2008	41,4 Gy 23 fractions	Paclitaxel 50 mg/m² Carboblatin (AUC 2 mg/mL/min) RT concomitant	366	268/88	84/275
Yang, 2012 (Zhonghua yi xue za zhi, 2012)[63]	2007-2011	40 Gy 20 fractions	Vinorelbin 25mg/m² ; days 1-8-22-29 Cisplatin 75 mg/m² ; days 1-22 Rx concomitant	123	123/0	123/0
Zhao 2015 (American J Med Science, 2015)[64]	2012-2013	45 Gy 25 fractions	Capecitabin 2000 mg/m²/day ; days 1 to 14 Oxaliplatin 130 mg/m2 ; day 1 RT concomitant	76	0/76	0/76
16 trials				**2455**	**2301/164**	**1621/796**

TE: thoracic esophagus, GEJ: gastro-esophageal junction, SCC: Squamous Cell Carcinoma, ADC: Adenocarcinoma RT: radiotherapy

§ Four-arm trial, all arms are not included in the analysis

* Data available from the previous meta-analysis or database hosted at Gustave Roussy

TRIALS COMPARING NEOADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGERY TO NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY (MA#2)

Trial	Accrual period	Chemotherapy protocol	Chemoradiotherapy protocol	N	TE/GEJ	SCC / ADC
Nygaard 1992§$ (World J Surg, 1992)[33]	1983-1988	2 cycles of : Cisplatin 20 mg/m²/day ; days 1 to 5 Bleomycin 5 mg/m²/day ; days 1 to 5	35 Gy 20 fractions CT same as CT group Started 3 weeks after chemo	109	109/0	109/0
Stahl 2009 (J Clin Oncol, 2009)[65] (Eur J Cancer, 2017)[66]	2000-2005	2.5 cycles of : Cisplatin 50 mg/m²/day : biweekly Fluorouracil 2000 mg/m² ; days 1-8-15-22-29-36	30 Gy 15 fractions CT same as CT group Followed by CRT with Cisplatin 50 mg/m²/day : days 1-8 Etoposide 80 mg/m²/day ; days 3 to 5	119	0/119	0/119
Burmeister 2011 (Eur J Cancer, 2011)[67]	2000-2006	2 cycles of : Cisplatin 80 mg/m² ; day 1 Fluorouracil 1000 mg/m²/day ; days 1to 4	35 Gy 15 fractions Same as CT group with reduced 5-FU to 800 mg/m² Starting at day 22	75	75/0	0/75
Klevebro 2016 (Ann Oncol, 2016)[68]	2006-2013	3 cycles of : Cisplatin 100 mg/m² ; day 1 Fluorouracil 750 mg/m²/day ; days 1to 5	40 Gy 20 fractions CT same as CT group Concomitant with cycle 2 and 3	181	150/31	50/131
4 Trials				**484**	**334/150**	**159/325**

TE: thoracic esophagus, GEJ: gastro-esophageal junction, SCC: Squamous Cell Carcinoma, ADC: Adenocarcinoma, CT: chemotherapy

§ Four-arm trial, all arms are not included in the analysis

$ Included in the previous meta-analysis

C: Excluded trials

Trial	Accrual period	Group	Treatments	Reason for exclusion
Basi 2013 (Int J Hemato Onco and Stem Cell Research 2013)[69]	2011	CS vs S	3 cycles of : • Cisplatin 75mg/m²; day 1 • Docetaxel 75mg/m²; day 1 • Fluorouracil 750 mg/m²; day 1	54 patients only
Natsugoe 2006 (Dis Oeso, 2006)[70]	1997-2001	RCS vs S	RT concomitant • 40 Gy in 20 fractions • Cisplatin 7 mg/day • Fluorouracil 350 mg/day	53 patients only

D: Ongoing trials

Trial	Country	Location Histology	Treatment arms	Primary Endpoint	N	Status
Re-Evaluation (NCT02442440)	China	TE SCC	**A:** Surgery alone **B:** 3 cycles of Paclitaxel and Cisplatin followed by surgery	OS 5 years	528	Recruiting since June 2015 2.5 years enrolment 5 years follow-up
TOPGEAR (ACTRN12609000035224) [71]	World	GEJ ADC	**A:** Perioperative ECF (3+3) **B:** Perioperative ECF (3+3) plus chemoradiation (45 Gy / 25 fr)	OS 5 years	720	318 patients recruited in November 2016
CMISG1701 (NCT03001596)[72]	China	TE SCC	**A:** 2 cycles of Cisplatin / Paclitaxel **B:** 4 weeks of chemoradiation (40 Gy/ 20 fr) paclitaxel + cisplatin	OS 3 years	364	40 patients in March 2017
ESOPEC (NCT02509286)[73]	Germany	TO / EGJ ADC	**A:** Perioperative chemotherapy and surgery (FLOT protocol: 5-FU/leucovorin/ oxaliplatin/docetaxel) **B:** Neoadjuvant chemoradiation (CROSS protocol: 41.4Gy plus carboplatin/ paclitaxel) followed by surgery	OS 3 years	550	Recruiting
Neo-AEGIS (NCT01726452)[74]	European	TO / EGJ ADC	**A:** Modified perioperative MAGIC (Epirubicin Cisplatin/Oxaliplatin 5-FU/Capecitabine) **B:** CROSS (Carboplatin and Paclitaxel with concurrent radiotherapy, 41.4Gy/23 fr, over 5 weeks) followed by surgery	OS 3 years	594	Recruiting
NExtT (JCOG 1109) (UMIN000009482)	Japan	TO SCC	**A:** Two cycles of Cisplatin / 5FU **B:** Three Docetaxel/Cisplatin/5FU **C:** Chemoradiotherapy (41.4 Gy/23 fr) (Cisplatin / 5FU)	OS 5 years	483	Recruiting since 2013

TE: thoracic esophagus, GEJ: gastro-esophageal junction, SCC: Squamous Cell Carcinoma, ADC: Adenocarcinoma, OS: overall survival, CT: chemotherapy

E: Suggested coding and ways of sending data

Please provide data on all patients randomized.

It is important when trying to achieve a synthesis of the results of many different trials to include all patients randomized, whether or not they were included in the trial analysis, received their allocated treatment, or were properly followed up. Please try to include all patients randomized according to their original treatment allocation, or indicate where post randomization exclusions or losses have occurred. If this will cause a delay, please send us what you can now, and extra information later. To ensure the data are completely anonymised, participants name and original ID should not be included but rather a new identifier generated by the trial team.

WAYS OF SENDING THE DATA

You may supply your data on CD/DVD sent by post or by secure email or via a secure platform. If sending data via email or post, please encrypt the data and let us know how it has been encrypted in a separate mail. Our email addresses are matthieu.faron@gustaveroussy.fr and jean-pierre.pignon@gustaveroussy.fr. We should be able to read any standard CD/DVD, if you let us know its specification. Please accompany disk with a printout of its contents.

Data can be sent in almost any format (ASCII, Excel, Access, SAS datasets, Rdata or RDS, etc.), but please indicate which format has been used.

FORMAT FOR THE DATA

The preferred format for the information is described on the following pages. However, if a different format is more convenient for you, this should cause no great difficulty as long as it is clearly specified.

Label	Coding
Identity and initial characteristics	
Patient identifier	characters
Sex	1=Male, 2=Female, 9=Unknown
Date of Birth* or age	DD-MM-YYYY 2 digits, 99=Unknown
Performance status	For Karnofsky index use 3 digits, for WHO or ECOG 1, digit, 9=Unknown
Preoperative Workup	
Tumor location	1=Cervical esophagus (less than 15 cm from incisors), 2=Upper thoracic esophagus (15-25 cm from incisors), 3=Mid thoracic esophagus (25-38 cm from incisors), 4=Lower thoracic esophagus (38-40 cm from incisors), 5=Gastro-esophageal junction, 9=Unknown
Tumor type on biopsy	1=Squamous cell carcinoma, 2=Adenocarcinoma, 3=Other, 9=Unknown, if Other specify,
T stage on CT or US at patient entry$	0=T0, 1=T1, 2=T2, 3=T3, 4=T4, 5=TX, 6=Tis, 9=Unknown

Label	Coding
N stage on CT or US at patient entry[$]	0=N0, 1=N+, 2=NX, 9=Unknown
Metastasis at patient entry[$]	0=M0, 1=M1, 2=MX, 9=Unknown
If TNM not available stage at entry[$]	1= Stage I, 2= Stage II, 3= Stage III, 4= Stage IV
Treatment	
Date of randomization*	DD-MM-YYYY
Treatment allocated	1=Surgery, 2=Pre-operative chemotherapy, 3= Pre-operative chemo-radiotherapy
Date of first chemo cycle (or injection)*	DD-MM-YYYY
Date of last chemo cycle (or injection)*	DD-MM-YYYY
Number of cycles (or injection)	2 digits, 99=Unknown
Date of radiotherapy start*	DD-MM-YYYY
Date of radiotherapy end*	DD-MM-YYYY
Radiotherapy dose	2 digits + 1 digit separated by a decimal point, 99=Unknown
Radiotherapy number of fraction	2 digits, 99=Unknown
Pre-operative clinical response status	1= Clinical complete response 2= Partial response 3= Stable disease (including minor response), 4=Progressive disease, 5= Not assessable for response 9=Unknown
Surgery and Pathology	
Surgery	0=No, 1=Yes
Date of surgery*	DD-MM-YYYY
Type of surgery	Text
Surgical margin	0=R0, 1=R1, 2=R2
Response to preoperative treatment (if available)	1= Clinical complete response 2= Partial response 3= Stable disease (including minor response), 4=Progressive disease, 5= Not assessable for response 9=Unknown
Acute toxicity (pre-operative treatment): Grade 3, 4 or 5 (death), specify toxicity criteria used	
Mucositis	0=No, 1=Yes, 9=Unknown
Diarrhoea	0=No, 1=Yes, 9=Unknown
Nausea & vomiting	0=No, 1=Yes, 9=Unknown
Anaemia	0=No, 1=Yes, 9=Unknown
Platelet	0=No, 1=Yes, 9=Unknown
Leucocytes	0=No, 1=Yes, 9=Unknown
Neutrophils	0=No, 1=Yes, 9=Unknown
Creatinine	0=No, 1=Yes, 9=Unknown
Pulmonary (acute)	0=No, 1=Yes, 9=Unknown
Skin	0=No, 1=Yes, 9=Unknown
Oesophagus	0=No, 1=Yes, 9=Unknown
Upper GI	0=No, 1=Yes, 9=Unknown
Heart	0=No, 1=Yes, 9=Unknown
Hand and foot syndrome	0=No, 1=Yes, 9=Unknown
Other (indicate the type of toxicity)	0=No, 1=Yes, 9=Unknown
Long term toxicity, specify toxicity criteria used	
Long term toxicity	0=No, 1=Yes
Worst late toxicity grade	1 digit, 0 to 5 according to EORTC-RTOG
If yes, please describe	text

Label	Coding
Postoperative complications	
Postoperative complication (within 30 days)	0=No, 1=Yes
If yes, worst postoperative complication grade (within 30 days)	1=1-2 (not severe), 2=3-4 (severe) , 9=unknown
If yes, specify	text
Postoperative death (within 30 days and/or in hospital death)	0=No, 1=Yes, 9=unknown
Follow-up	
Date of last follow-up or death*	DD-MM-YYYY
Vital status	0=Alive, 1=Dead
Cause of death	1=Clearly malignant, 2= Clearly related to treatment, 3= Non-malignant and not related to toxicity, 9= Unknown *If related to treatment, specify: related to surgery, radiotherapy or chemotherapy*
Loco-regional recurrence	0=No, 1=Yes, 9=Unknown
Date of first loco-regional recurrence*	DD-MM-YYYY
Distant recurrence	0=No, 1=Yes, 9=Unknown
Date of first distant recurrence*	DD-MM-YYYY
Excluded from trial analysis	0=No, 1=Yes
Reason for exclusion	Text

* Or de-identified date derived from this date (i.e. a random number of days, the same for all dates and all patients, added to the true dates). Delay (i.e. time between two dates) may also be provided,

$ Specify tumor staging used.

F: Participation Form

TRIAL DETAIL AND CONTACT

Trial Name / Clincialtrials.gov number/ references: Click-here to enter text

Name of coordinator / investigator: Click-here to enter text
Address: Click-here to enter text
Telephone: Click-here to enter text Fax: Click-here to enter text
Email: Click-here to enter text

DATA MANAGER / STATISTICIAN

Name: Click-here to enter text
Address: Click-here to enter text
Telephone: Click-here to enter text Fax: Click-here to enter text
Email: Click-here to enter text

PARTICIPATION

Are you willing to take part in the meta-analysis? Choose
Are the details of your trial correct? Choose
Is the most recent publication cited in the publication list? Choose
If no, please give correct details:
Click-here to enter text

For the collection of trial data, if different from above, please give details of the appropriate contact:
Name: Click-here to enter text
Address: Click-here to enter text
Telephone: Click-here to enter text Fax: Click-here to enter text
Email: Click-here to enter text

OTHER STUDY

Do you know any other relevant trial not listed in the protocol? Choose

If yes, please provide details: Click-here to enter text

TRIAL DETAILS

Did the trial have a target for patient accrual? Choose Target : Click-here to enter text
Did the trial reach its target accrual? Choose
If not reason : Click-here to enter text

Date trial opened Click-here to enter date
Date trial closed Click-here to enter date

What method was used to conceal randomisation? Choose one

What method of randomisation was used in this trial? Choose one

What, if any, stratification factors were used? Click-here to enter text

What proportions in each arm? (e.g.1:1) Click-here to enter text

Can you provide the trial protocol: Choose

Please list treatments used in the arms of your trial* (including drugs given):

Arm 1: Click-here to enter text
Arm 2: Click-here to enter text
Arm 3: Click-here to enter text
Arm 4: Click-here to enter text

Which TNM or other staging classification was used? Click-here to enter text

Which performance status was used? Click-here to enter text

Which classifications were used for toxicity?

Acute: Choose one If other, specify: Click here to enter text
Late: Choose one If other, specify: Click here to enter text

Will some of the data requested be never available? Choose
If yes, please specify: Click-here to enter text

USE OF THE INDIVIDUAL PATIENTS' DATA FOR METHODOLOGICAL RESEARCH

I agree that an anonymised version of the trial data that I supplied for the meta-analysis can be used in methodological research to explore and improve trial and meta-analysis design and conduct:

☐ Yes ☐ No

FINAL CONSENT

Any data supplied will remain the property of the trialist(s) who supplied it. These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data.

Date: Signature:

Please return to: matthieu.faron@gustaveroussy.fr / jean-pierre.pignon@gustaveroussy.fr

G: Update Form

TRIAL DETAIL AND CONTACT

Trial Name / Clincialtrials.gov number/ references: Click-here to enter text

PARTICIPATION

Are you willing to take part in the meta-analysis update? Choose
Is the most recent publication cited in the publication list? Choose
If no, please give correct details:
Click-here to enter text

For the collection of trial data, <u>if different from previous version</u>, please give details of the appropriate contact:

Name: Click-here to enter text
Address: Click-here to enter text
Telephone: Click-here to enter text Fax: Click-here to enter text
Email: Click-here to enter text

OTHER STUDY

Do you know any other relevant trial not listed in the protocol? Choose

If yes, please provide details: Click-here to enter text

NEW DATA

Will updated survival data will be available? Choose
Are you willing to send data regarding endpoints not studied in the previous meta-analysis? Choose

FINAL CONSENT

Any data supplied will remain the property of the trialist(s) who supplied it. These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data.

Date: Signature:

Please return to: matthieu.faron@gustaveroussy.fr / jean-pierre.pignon@gustaveroussy.fr