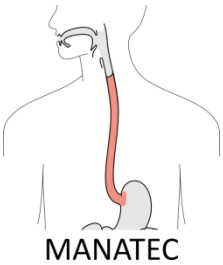

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MANATEC-02: individual patient data Meta-Analysis of chemotherapy or chemo radiotherapy as NeoAdjuvant Treatment of Esophageal or gastro esophageal junction Carcinoma

Appendix: Network-Meta-Analysis Methodology

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Registered in Prospero: CRD42018107158

Pre-Planned analysis (October 2018)

This Network Meta-Analysis (NMA) will be using individual Participant Data (IPD) either in one or two step under the frequentist paradigm.

The primary endpoint will be overall survival. Secondary endpoints using time-to-event methods will be: disease-free survival, pattern of recurrence (as competing events), and cancer death / non cancer death. All these endpoints will be analyzed with a 6-months landmark. Secondary endpoints based on binomial outcomes will be: R0 resection rate, postoperative mortality and postoperative morbidity. See main protocol for full definitions of endpoints.

Principle statistical model

The principal analysis will use a one-step IPD-based model based on a mixed effect Cox model. The same model will be used for time to event secondary endpoints. A mixed-effect generalized linear model with logarithmic link function and binomial distribution of the residuals will be used for binary secondary endpoints. The three treatment option will be coded with two parameters and the third one ("functional parameter") will be deduced by contrast.[1] To allow a better estimation of the variance, the treatment will be coded as -0.5/+0.5. [2] Patients will be nested inside trial and each trial will have its baseline risk (random intercept). The correlation matrix of the random effect will be set so that a null correlation between the intercept and the slopes will be assumed. The provisional search identified only one, small multi-arm trial. If the definitive search identifies other multi-arm trials, the variance-covariance matrix of the random effects will be set to take this into account.

Table 1: Coding of the treatment indicator used in the network

Type of trial	Randomisation Arm	Treatment indicator 1	Treatment indicator 2
S vs. CS	CS	+0.5	0
	S	-0.5	0
S vs. CRS	CRS	0	+0.5
	S	0	-0.5
CS vs. CRS	CRS	-0.5	+0.5
	CS	+0.5	-0.5

S: Surgery , CS: Chemotherapy surgery, CRS: Chemoradiotherapy surgery

Analysis of interaction

As in the pairwise model, interaction will be tested by introducing in the model a treatment indicator * covariable term for both indicators. No random effects will be used for the interaction term.

The following variable will be tested: histological subtype, tumor location, age (continuous) and sex.

Sensitivity analysis

A frequentist two step model will be used as a sensitivity analysis. Trial specific (Hazard Ratio (contrasts) along with their standard deviation will be calculated by a Cox model. Then the contrasts will be combined by the model based on the analogy with electrical network proposed by Rücker.[3] In absence of heterogeneity the fixed effect model will be used, otherwise the random effect model will be.

Consistency hypotheses

The consistency hypotheses in the one-step model will be tested by introducing in the model a supplementary parameter. [4,5] The functional parameter has been chosen to be in the CRS vs CS contrast. So this parameter will have value +0.5 if a patient has been assigned to the CRS arm of a CRS-CS trial, -0.5 if assigned to the CS arm of a CRS vs CS trial and 0 otherwise. If the confidence interval of this parameter does not include 0, this will indicate an inconsistency issue.

The Netmeta package also provide a measure of inconsistency (within design part of the Q statistics).[3]

Amendment to the NMA protocol for the one-step model (December 2020)

Adjustment for confounders

Recent results demonstrated that in a NMA, interaction with modifier unbalanced between comparison may create bias.[6,7] Besides, this unbalance can lead to transitivity [8–10] or unconsistency [11] issues.

Therefore, the principle model will be adjusted for major potential confounders: age, sex, histological subtypes and anatomical location. The choice of the confounders will be based on Akaike's Information Criteria.

Missing values

In case of missing values for important confounders a multiple imputation will be used. The imputation model will be Multiple imputation by Chained Equation (MICE).[12] All imputation models will take into account the trial as a grouping factor. Quantitative variables will be imputed by predictive mean matching. Qualitative variable will be imputed by Generalized Linear Mixed-effects Models. At least 20 iterations of the algorithm will be used and trace plots will be examined to ensure that convergence has been obtained. Twenty imputed data frames will be generated. They will be combined according to Rubin's rule.[13]

Sensitivity analyses

The unadjusted, not imputed model will be also used a sensitivity analysis to ensure that the modification did not lead to major change in estimations (consistency, values of the random effects).

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