Impact of dose reduction and treatment delay of neoadjuvant chemotherapy in gastric and esophageal adenocarcinoma

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Research article

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Abstract

Background Neoadjuvant chemotherapy in resectable gastric and esophageal adenocarcinoma is often hampered by toxicities and fragile patients resulting in dose reductions and/or treatment delays. The aim of this study was to assess how these treatment modifications affect outcome. Methods A series of 63 consecutive patients treated 2008-2014 with neoadjuvant EOX (epirubicin, oxaliplatin and capecitabine) and surgical resection, with or without adjuvant treatment, were reviewed. Chemotherapy dose index (DI), i.e. the ratio of actual to planned cumulative dose, and time index (TI), i.e. the ratio of planned to actual total duration, were calculated. Associations of neoadjuvant EOX DI and TI with histopathologic response were analysed with binary logistic regression. Time to recurrence (TTR) and overall survival (OS) were estimated using Kaplan-Meier analyses. Results Statistically significant associations were found between neoadjuvant EOX TI >= 0.95 and a major histopathologic response (0-10% residual cancer cells) and between neoadjuvant EOX DI >= 0.95 and a response with 0-50% residual cancer cells. Significantly improved TTR and OS were seen in patients with a major histopathologic response. Conclusions Our results suggest that treatment delays of neoadjuvant chemotherapy in gastric or esophageal adenocarcinoma should be avoided in order to achieve a major response.

Background

For patients with resectable gastric or esophageal adenocarcinoma perioperative (i.e. neoadjuvant + adjuvant) chemotherapy is standard of care in many countries, particularly in Europe. This approach is based on the MAGIC trial [1] and the FFCD 9703 trial [2], where the addition of chemotherapy resulted in a 13-14% improved 5-year survival compared to surgery alone. In the MAGIC trial the ECF regimen (epirubicin, cisplatin and fluorouracil) was used and the FFCD 9703 trial had a similar regimen but without epirubicin. Since the REAL-2 trial [3] in advanced gastric and esophageal cancer demonstrated that the more convenient EOX regimen (epirubicin, oxaliplatin and capecitabine) yielded a longer survival compared to ECF, most centers in Sweden chose to use EOX also in the perioperative setting, with three cycles before and three cycles after surgery.

Delivering triplet chemotherapy in gastric and esophageal cancer is a major challenge due to toxicities and fragile patients, commonly leading to dose reductions and treatment delays or even premature discontinuation, but little is known about how these treatment modifications affect outcome.

A widely used method to describe treatment delivery is the Hryniuk model [4] of relative dose intensity (RDI), which is the ratio of actual to planned dose intensity, where dose intensity is the cumulative dose divided by the total treatment duration. There are several publications on the relationship between RDI and survival in various malignancies but few have assessed the differential contribution of the individual components of RDI.

In gastric cancer a few studies have investigated the relationship between RDI and survival in palliative [5] and adjuvant [6] settings, but to our knowledge there are no previous reports on associations between RDI (or its individual components) of neoadjuvant chemotherapy and outcome.

The primary aim of this study was to assess whether dose reductions and/or treatment delays affect histopathologic response, in a consecutive cohort of patients treated with neoadjuvant EOX for resectable gastric or esophageal adenocarcinoma.

Materials And Methods

Study design and participants

From a cohort previously used in studies on prognostic and predictive biomarkers in resectable gastric and esophageal adenocarcinoma [7, 8], we identified 99 patients who started neoadjuvant EOX at the Skåne University Hospital in Lund and Malmö between January 1, 2008 and December 31, 2014. Out of these there were 63 patients who after neoadjuvant EOX proceeded to surgical resection, and where detailed chemotherapy data was available. See Figure 1 for an overview of the cohort and Table 1 for a detailed description. Classification of tumor stage was done according to the 7th edition of the UICC/AJCC TNM classification, in which tumors in the gastroesophageal junction Siewert type I–III are classified as esophageal cancer. Surgical radicality was classified as: R0 = no residual tumor (free resection margins according to the pathology report), R1 = possible microscopic residual tumor (narrow or compromised resection margins according to the pathology report), R2 = macroscopic residual tumor (according to the operative report). Last follow-up date was December 31, 2017.

Relative dose intensity, dose index and time index of EOX

The EOX regimen consists of epirubicin 50 mg/m^2 on day 1, oxaliplatin 130 mg/m^2 on day 1 and capecitabine 625 mg/m^2 twice daily on days 1-21, cycle length 21 days. All patients were scheduled to receive three cycles of EOX in the neoadjuvant setting and another three cycles in the adjuvant setting, with the exception of nine patients participating in a trial who were scheduled for chemoradiotherapy for the adjuvant part. The individual factors, dose index (DI) and time index (TI), constituting RDI, were calculated for each patient as described by Nakayama et al. [9], see definitions in Figure 2a. EOX DI, TI and RDI are composite measures consisting of mean values of the three individual drugs.

Histopathologic response

The extent of residual cancer cells (0%, 1–10%, 11–50% or > 50%) in the primary tumor site of the resected specimens were histologically assessed (blinded to treatment data) using the tumor regression grading system described by Chirieac et al. [10].

Statistical analysis

Based on the distributions of EOX DI, TI and RDI, various cutoffs in steps of 0.05 or 0.10 were used in binary logistic regression to calculate odds ratios (OR) for dichotomized histopathologic response. Since no other factor than DI and TI, respectively, had a statistically significant OR and because of the limited sample size no adjusted analyses were performed. Receiver operating characteristic (ROC) curves were also applied for DI and TI but did not add any information of additional value. Differences in patient and clinical characteristics between dichotomized groups of neoadjuvant DI and TI were assessed using chi-square test for categorical variables and Mann–Whitney *U* test for continuous variables. Time to recurrence (TTR) was defined as time from diagnosis to time to biopsy or radiology proven recurrence (excluding death) and overall survival (OS) was defined as time from diagnosis to date of death (regardless of cause). Differences in Kaplan-Meier survival curves were estimated using log-rank test. Follow-up time was calculated using inverse Kaplan-Meier estimation. All statistical tests were 2-sided and a p-value < 0.05 was considered statistically significant. IBM® SPSS® Statistics version 25.0.0.2 for Mac was used for all statistical analyses.

Results

Distributions of neoadjuvant EOX DI, TI and RDI

In the cohort of 63 patients that proceeded to surgical resection the distributions of neoadjuvant EOX DI, TI and RDI were heavily left-skewed as depicted in Figure 2b. Median value for DI was 0.93, for TI 1.00 and for RDI 0.89. All patients but one had a DI less than 1.00 due to rounding down of the capecitabine dose to the nearest multiple of tablets (500 mg and 150 mg). For the majority (60.3%) of the patients TI was 1.00, i.e. the treatments were delivered without delays.

Neoadjuvant EOX DI and TI vs. histopathologic response

As shown in Table 2, the only factor with a significant OR for a major response (0-10% residual cancer cells) was TI ³ 0.95 with OR 8.40. For response with 0-50% residual cancer cells the only factor with a significant OR was DI ³ 0.95 with OR 3.14. The distributions of four-tiered histopathologic response across dichotomized DI and TI are shown in Figure 3. There were no significant differences in patient or clinical characteristics between dichotomized groups of DI and TI at cutoff 0.95 (Additional file 1: Table S1).

TTR and OS in relation to histopathologic response

TTR and OS were significantly improved in patients with better histopathologic response (Figure 4), with the largest difference noted with the cutoff at 10% residual cancer cells. Patients with a major response had a 5-year OS of 87% compared to 47% for patients with more than 10% residual cancer cells.

Discussion

The main finding of the present study is that tight adherence (TI ³ 0.95) to the chemotherapy time schedule was associated with a higher probability of a major histopathologic response (0-10% residual cancer cells) in patients receiving neoadjuvant EOX for resectable gastric or esophageal adenocarcinoma. We also found a significant association between a high cumulative dose (DI ³ 0.95) and a more modest response (0-50% residual cancer cells). Since the aim of neoadjuvant chemotherapy is to reduce the tumor burden before surgery, the goal should be to achieve as good a response as possible. Therefore, an interpretation of our results could be that it is more important to avoid treatment delays than to give full dose in this context. The TI cutoff at 0.95 implies that the total treatment duration should not be delayed by more than a factor 1/0.95 » 1.05, i.e. not more than one day per 21-day cycle.

Previous studies [11–16] in this treatment setting have proposed small tumor size (but not T stage), differentiated tumor and Laurén intestinal subtype as predictors for histopathologic response to chemotherapy, but there are conflicting results regarding Laurén subtype [17]. We found no other factors than TI and DI to be associated with histopathologic response, though we did not have data on tumor size.

In the present study we chose to use histopathologic response, rather than survival, as primary endpoint. The reason for this is that response is usually a direct effect of the given treatment, whereas survival may be influenced by several other factors, such as age, comorbidities, tumor stage, surgical quality and complications. Therefore, the neoadjuvant setting, where chemotherapy is followed by surgical resection with histopathologic response evaluation, is a very good model for studies on chemotherapy dose intensity.

Regarding the clinical significance of histopathologic response, the literature is conflicting, as some studies have found it to be an independent predictor for survival [18] and others have not [19]. The present study showed significant associations between survival and histopathologic response, especially

in patients with 0-10% residual cancer cells who had an excellent survival. It should however be pointed out that these were univariable analyses, not taking other prognostic factors into account.

In the present investigation we applied a similar methodological approach as in a study by Nakayama et al. [9] on patients with metastatic colorectal cancer, evaluating irinotecan-based (FOLFIRI regimen) and oxaliplatin-based (FOLFOX regimen) chemotherapy, wherein it was demonstrated that dose reductions of irinotecan and treatment delays of oxaliplatin, respectively, were independent negative prognostic factors for progression-free survival. Another study, on platinum-based chemotherapy in patients with ovarian cancer [20], showed that treatment delays, but not dose reductions, were independently associated with worse survival. Furthermore, a randomized phase II trial [21] in metastatic gastric and gastroesophageal junction adenocarcinoma, with standard DCF (docetaxel, cisplatin and fluorouracil) given every three weeks compared to reduced dose DCF given every two weeks, demonstrated a six months longer OS in favor of the latter regimen, further emphasizing the importance of having short intervals between treatments. Even though these studies were made on different chemotherapy regimens and in different malignancies, a possible interpretation could be that delayed dosing of platinum-based chemotherapy has a negative impact on outcome, which is also in accordance with our results. However, additional studies are needed to confirm this hypothesis.

The previous literature on RDI in gastric cancer is very sparse. In the metastatic setting Kitagawa et al. [5] found no differences in survival whether RDI of cisplatin and the fluoropyrimidine analogue S-1 was above or below 80%. Another study [6] showed that low RDI (89.5% or less) of adjuvant S-1 was an independent predictor of poor disease-free survival. To the best of our knowledge, the present study is the first to examine RDI, as well as DI and TI, of neoadjuvant chemotherapy in gastric and esophageal adenocarcinoma.

A major limitation of this exploratory, retrospective study is the relatively small sample size with few events, precluding multivariable analyses. Thus, our results should be interpreted with caution and considered mainly as hypothesis generating with a need for validation in additional studies. Moreover, we did not assess the impact of DI and TI for the individual drugs (although TI is usually the same) and it is possible that larger studies could identify cutoffs for the separate chemotherapy components. Based on a preliminary report in 2017 on the now published FLOT4-AIO trial [22], EOX has been gradually replaced by FLOT (fluorouracil, oxaliplatin and docetaxel) as the new standard perioperative regimen, and it would be of interest to assess DI and TI in patients receiving FLOT, which shares the common backbone of oxaliplatin and a fluoropyrimidine with the EOX regimen.

Given that side-effects of chemotherapy commonly result in dose reductions and/or treatment delays, the paucity of reports in the literature about how this affects outcome is somewhat surprising. Whether the dose should be reduced or the treatment delayed, in case of non-manageable toxicity, is a clinically very common and important question that needs to be further addressed, not only in this specific disease setting, but also in other malignancies and treatment situations.

Conclusions

Our results suggest that treatment delays should be avoided in patients receiving neoadjuvant chemotherapy for gastric and esophageal adenocarcinoma.

Abbreviations

DI: dose index; EOX: epirubicin, oxaliplatin, capecitabine; OR: odds ratio; OS: overall survival; RDI: relative dose intensity; ROC: receiver operating characteristic; TI: time index; TTR: time to recurrence

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Ethical Review Board at Lund University (ref. nr 445/07), whereby the committee waived the need for consent other than by the option to opt out.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DB: conception and design, acquisition of clinical and treatment data, statistical analyses and manuscript drafting. CH: histopathological re-evaluation, assessment of histopathologic response, manuscript drafting. KJ: conception and design, manuscript drafting. AJ: conception and design, manuscript drafting. All authors read and approved the final manuscript.

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Not applicable.

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Additional Material

Additional file 1: Table S1. Differences in patient and clinical characteristics for neoadjuvant EOX DI and TI at cutoff 0.95 (DOCX 20 kb)

Figures

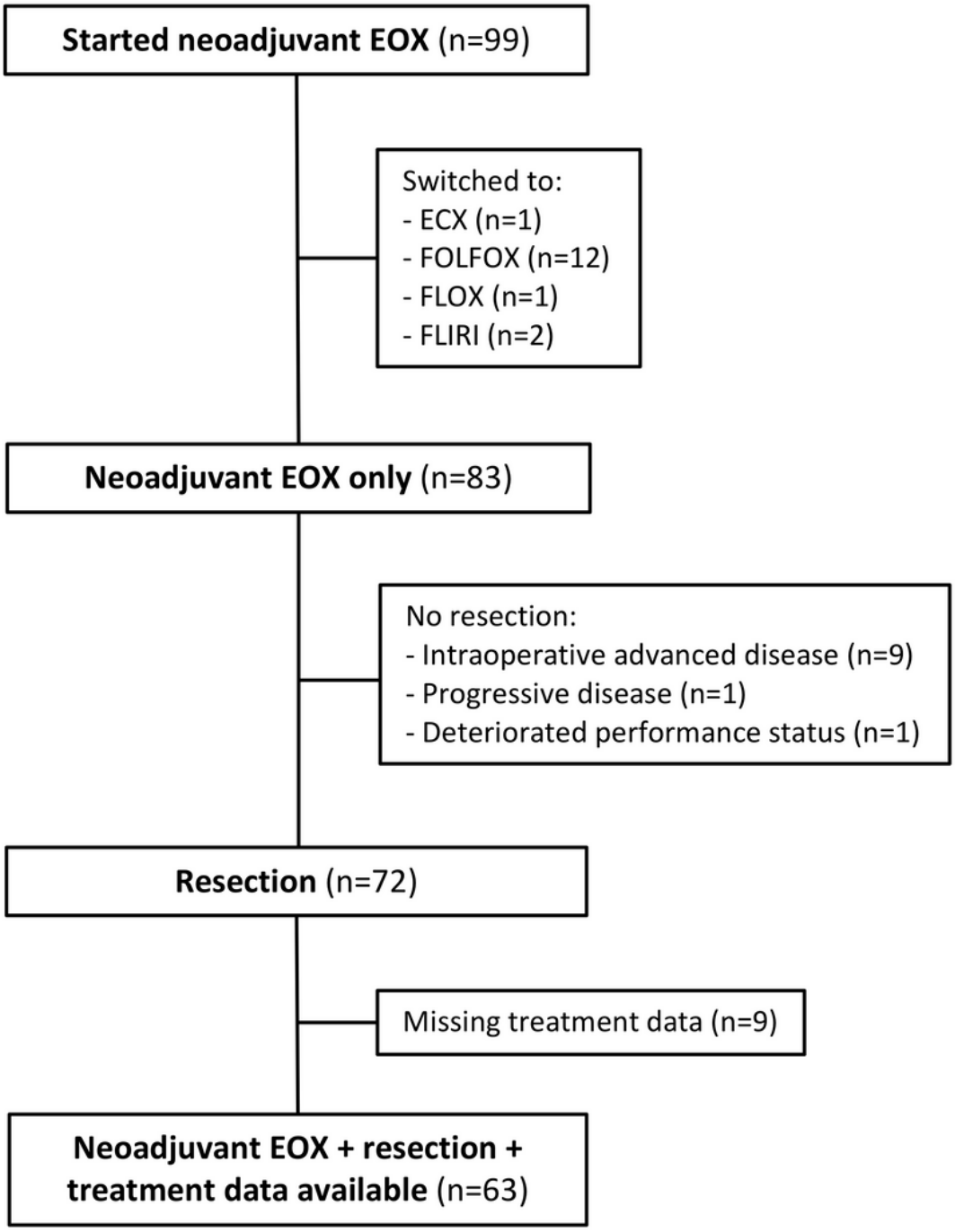

Figure 1

Overview of the cohort

a

$$\textbf{Dose intensity} = \frac{\textbf{Cumulative dose } (mg/m^2)}{\textbf{Total duration } (week)}$$

$$\textbf{Relative dose intensity } (\textbf{RDI}) = \frac{\textbf{Actual dose intensity}}{\textbf{Planned dose intensity}}$$

$$= \frac{\frac{Actual\ cumulative\ dose}{Actual\ total\ duration}}{\frac{Planned\ cumulative\ dose}{Planned\ total\ duration^*}} = \frac{Actual\ cumulative\ dose \times Planned\ total\ duration^*}{Planned\ cumulative\ dose \times Actual\ total\ duration}$$

$$\textbf{Dose index } (\textbf{DI}) = \frac{\textbf{Actual cumulative dose}}{\textbf{Planned cumulative dose}}$$

$$\textbf{Time index } (\textbf{TI}) = \frac{\textbf{Planned total duration}^*}{\textbf{Actual total duration}}$$

$$\textbf{RDI} = \textbf{DI} \times \textbf{TI}$$

*of actual treatment cycles

b

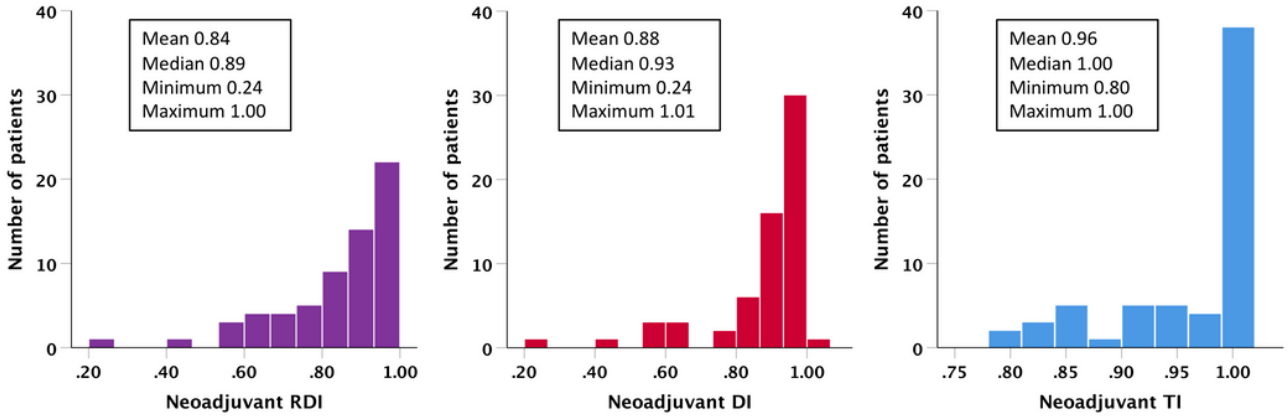

Figure 2

Definitions (a) of dose intensity, relative dose intensity (RDI), dose index (DI) and time index (TI). Distributions (b) of neoadjuvant EOX RDI, DI and TI

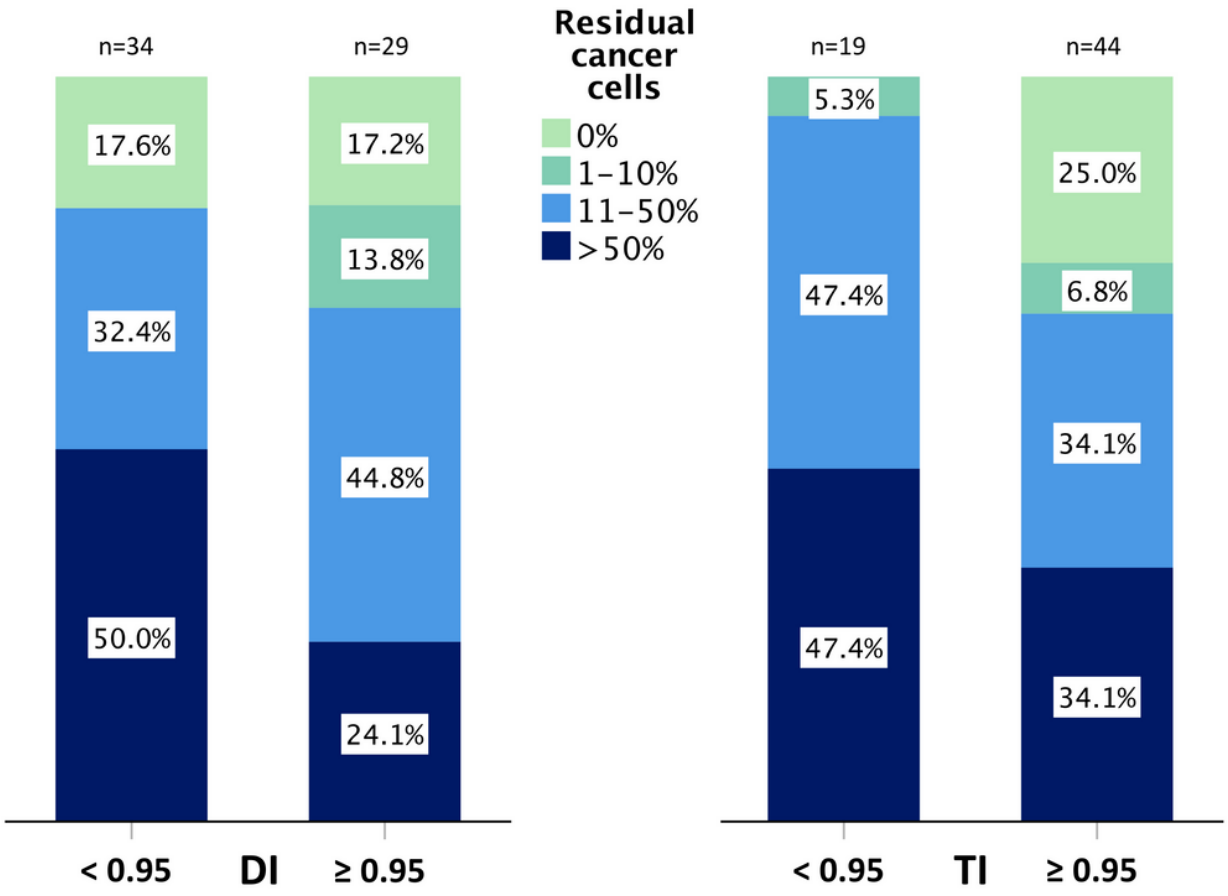

Figure 3

Histopathologic response for dichotomized neoadjuvant EOX DI and TI

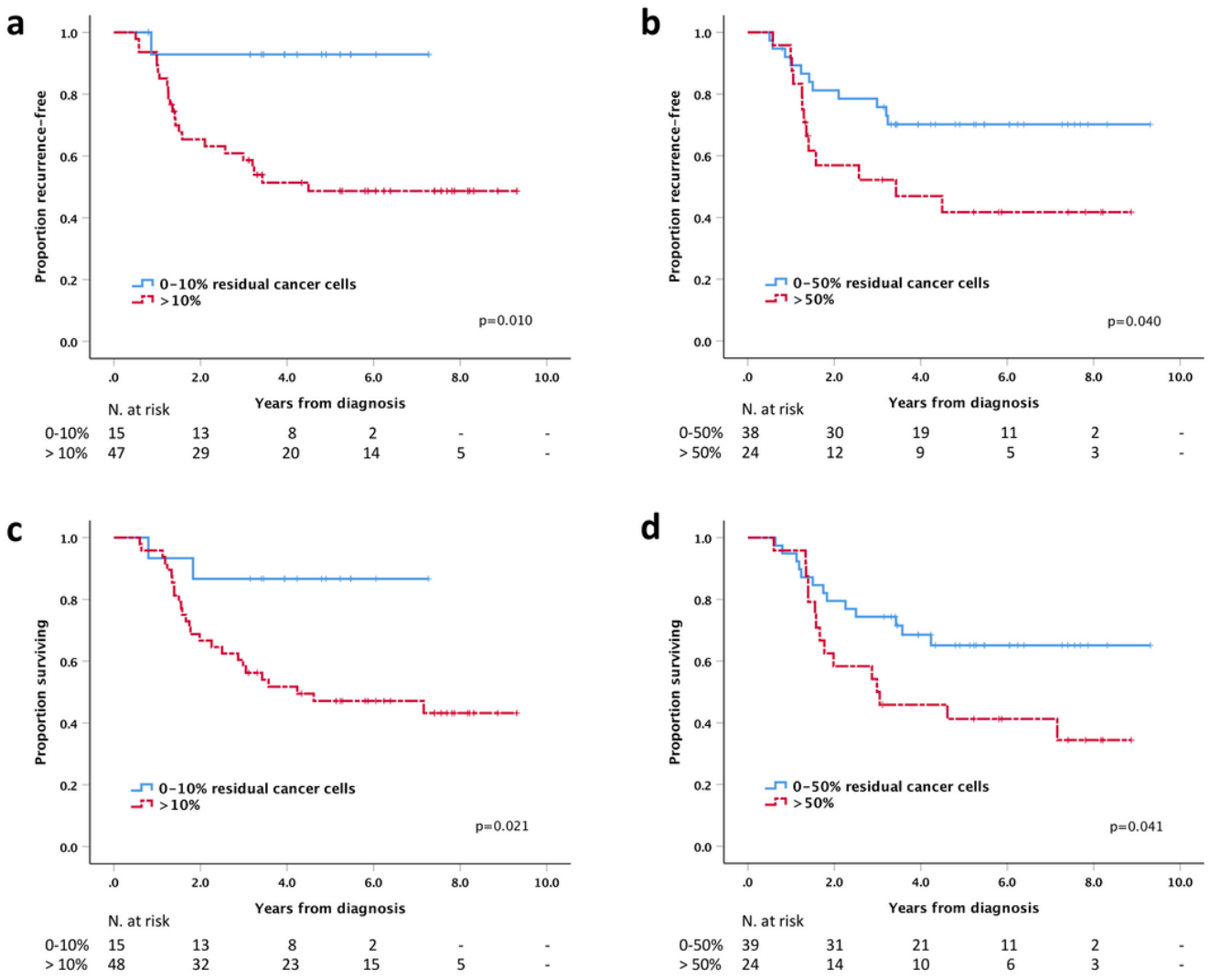

Figure 4

Kaplan-Meier plots of TTR (a, b) and OS (c, d) by histopathologic response

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf
- TableS1.pdf