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Original Research

Histopathological regression predicts treatment outcome in locally advanced esophagogastric adenocarcinoma

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Abstract ***Background:*** Neoadjuvant chemotherapy (neoCTx) improves survival outcomes of patients with localised esophagogastric adenocarcinoma (EGA). This analysis evaluates the predictive value of histopathological response after neoCTx.
Methods: A total of 461 patients with locally advanced EGA (≥T2 and/or N+) who received neoCTx followed by surgery were analysed: 314 (68.1%) with intestinal, 94 (20.4%) with diffuse and 53 (11.5%) with mixed histological type according to Lauren classification. Histopathological response evaluation was available for 363 patients and performed locally. This analysis evaluates the predictive value of histopathological subtype on histopathological response after neoCTx. Response was correlated with survival.
Results: Median patients' age was 63 years, 79.8% were male. Tumours were localised in the stomach in 32.5% and EG junction in 67.5% of the patients. With a median follow-up of 49.4 months, median disease-free (DFS) and overall survival (OS) were 38.0 and 66.4 months, respectively.

Pathological complete response (TRG1a) was 8.8% and combined complete and subtotal regression (TRG1a/b) was 27.3% for all patients. Around 9.2% of patients with intestinal type

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had a TRG1a compared with 6.2% with diffuse and 10.8% with mixed type. TRG1a/b rate was higher in intestinal (31.0%) than in diffuse (15.4%) and in mixed type (21.6%).

For patients with intestinal type, 3-year DFS was 78.4% with TRG1a and 54.3% with other regression grades ($p = 0.031$). All patients with diffuse and mixed type and TRG1a were disease free after 3 years compared with 31.1% ($p = 0.056$) and 47.7% ($p = 0.044$) with other regression grades.

Conclusion: Histopathological subtype is predictive for histopathological response and outcome after neoCTx, with the highest response rates in intestinal differentiated EGA.

1. Introduction

Despite the introduction of perioperative chemotherapy, the survival chance for patients with resected locally advanced esophagogastric adenocarcinoma (EGA) remains unsatisfactory. More than half of all those diagnosed with locally advanced EGA experience disease recurrence, leading to a 5-year survival rate with standard perioperative chemotherapy below 40% [1,2].

Published data from EGA trials demonstrate that pathological features such as tumour histology may have a predictive value for neoadjuvant therapies. It has been long recognised that diffuse EGA (those with majority of signet ring cells) have a worse prognosis than intestinal-type tumours; however, the role of histology in determining response to neoadjuvant therapy remains undefined [3]. The overriding importance of histology and tumour location is supported by several analyses including large phase III trials [1,2], showing a stronger effect of pre-operative chemotherapy with higher pathological complete response (pCR) rates and an improved outcome in predominately intestinal differentiated gastroesophageal junction tumours compared with diffuse-type cancers [4–6]. Furthermore, retrospective analyses have suggested that certain EGA tumour histologies, specifically diffuse tumours, are inherently resistant to standard chemotherapy and therefore, would not benefit from pre-operative therapy and may even be harmed by the delay in surgical resection [7].

The aim of this study was to perform a pooled analysis of patients treated with neoadjuvant chemotherapy (neoCTx) to evaluate the predictive value of histopathological subtype on graded histopathological response after neoCTx.

For survival analysis, 3-year disease-free survival (DFS) has shown to be a good surrogate for 5-year overall survival (OS) [8] and was chosen as the primary end-point.

2. Patients and methods

Patients who underwent neoCTx followed by surgery with curative intent for EGA between 2000 and 2013 from four institutions of the Arbeitsgemeinschaft Internistische Onkologie steering group were analysed. Comparable staging procedures were used among the participating centres. All patients had histologically proven localised (≥cT2 and/or N+) EGA as assessed by computed tomography or magnetic resonance tomography imaging of the chest, abdomen and pelvis and by endoscopic ultrasound. Medical records included surgical and pathological records, imaging records, chemotherapy protocols showing dose reductions and delays and follow-up reports informing about date of progression, last follow-up and death.

2.1. Treatment plan

In all four institutions, neoCTx was considered the standard of care in potentially resectable tumours with clinical stages ≥cT2 and/or N+. Neoadjuvant chemotherapy was either a taxane-platinum-fluoropyrimidine (5FU)-based triplet (T-PLF, FLOT and DCX) or platinum-5FU-based doublet (PLF or OLF) regimen.

2.2. Histopathology

All patients included in this study underwent definitive resection and therefore had final tumour histology available for comparison (ypTNM). The pathologic stage was done by the local pathologist using the seventh edition of the TNM International Union against cancer (UICC) classification.

Histopathological evaluation was done at the respective centre by standardised protocols including the pTNM categories, tumour localisation, subtype according to Lauren classification [9] and resection margins, as demanded in the guidelines of the UICC.

The resected specimens were embedded into paraffin after formalin fixation according to standard guidelines [10,11].

The samples were locally reviewed by an experienced pathologist, and histopathological tumour regression in the primary tumour was assessed. Examination of the resection specimens included the measurement of the macroscopic identifiable residual tumour or scarring,