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## Impact of age on the feasibility and efficacy of neoadjuvant chemotherapy in patients with locally advanced oesophagogastric cancer

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### KEYWORDS

Elderly patients  
Toxicity  
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**Abstract Introduction:** Neoadjuvant chemotherapy (neoCTx) improves the prognosis of patients with localised oesophagogastric adenocarcinoma (EGC), but its value is unknown in elderly patients.

**Patients and methods:** Patients who received neoCTx followed by surgery for EGC between 2000 and 2012 were analysed. The aim of this study was to compare the feasibility and outcome between patients aged  $\geq 70$  (cohort I) and their younger counterparts (cohort II).

**Results:** Data were available for 460 patients among which 174 (38%) were  $\geq 70$  years. Older age was associated with an increased rate of comorbidities (66% versus 42%,  $p < 0.001$ ). As compared to the younger, elderly patients were more likely to receive doublet instead of triplet neoCTx (65% versus 37%,  $p < 0.001$ ) and oxaliplatin-instead of cisplatin-based regimens (60% versus 32%,  $p < 0.001$ ). No significant difference was observed in the rate of  $\geq$  grade 3

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toxicities for cohort I and II (48% versus 41%) and postoperative morbidity was also not different (24% versus 28%). 90 day mortality for cohort I and II was 6.5% and 3.9%. After a median follow-up of 38 months, median disease-free survival (DFS) was 29.4 months in cohort I and 33.8 months in cohort II, with a 5-years DFS of 37% and 40%, respectively. Median overall survival (OS) was not reached in cohort I and was 58.4 months in cohort II, with a 5-year OS of 51% and 50% for cohort I and II, respectively.

**Discussion:** Despite slightly more adverse events and dose reductions, neoCTx is feasible in elderly patients with EGC. Elderly patients achieve comparable survival outcomes compared with their younger counterparts.

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## 1. Introduction

Oesophagogastric cancer (EGC) represents a challenging global health problem, with approximately 1 million cases per year occurring around the world. The incidence of EGC increases continuously with rising age. Currently, the median age at diagnosis is 70 years [1].

As elderly patients tend to be under-represented in clinical trials, knowledge about treatment methods is mainly based on experience with patients younger than 70 years, and adequate data to allow robust conclusions regarding the tolerability and efficacy of specific regimens are lacking. In addition, particular concerns have emerged regarding the use of multimodal treatment strategies including major surgical procedures, such as oesophagectomy in elderly patients, leading to the exclusion of patients with an age  $\geq 65$  or  $\geq 70$  [2].

There is a worldwide debate about the most appropriate definition of ‘elderly’ patients and the definition varies from 65 years or older to 70 years or older, however many experts favour a more functional definition of elderly patients, which is based on the patient’s functional health status or co-morbidities that may interfere with treatment decision making. In our analysis the age cut-off of  $\geq 70$  years was chosen as it defines ‘elderly’ throughout a large portion of the epidemiological literature.

Based on the results of two randomised phase III trials, preoperative chemotherapy is the standard of care for locally advanced EGC in large parts of the western world, leading to an estimated improvement in the 5-year survival rate of 13% compared to surgery alone [3,4]. Of note, in the MAGIC trial [3] the median age was 62 years (range 23–85) and only 20% were  $\geq 70$  years. Clinical trials in general only include the fittest older adults, yielding data that cannot be generalised to a heterogeneous older cohort. Therefore, there are valid concerns regarding the use of neoadjuvant chemotherapy in elderly patients. On the other hand such age-based treatment biases may be detrimental to many fit elderly patients if they lead to appropriate cancer therapies being denied [5]. As data on feasibility, toxicities and efficacy of neoadjuvant chemotherapy in

older patients are lacking, this retrospective analysis addressed the following questions:

1. Is neoadjuvant chemotherapy feasible in older patients and do they experience a different pattern or severity of adverse events?
2. Do elderly patients have comparable rates of postoperative morbidity and mortality after neoadjuvant chemotherapy and surgical resection of their primary tumour?
3. Do patients older than 70 years derive the same benefit from neoadjuvant chemotherapy as assessed by means of pathological response and DFS?

## 2. Patients and methods

Patients who underwent neoadjuvant chemotherapy followed by surgery with curative intent for EGC between 2000 and 2012 from three institutions of the Arbeitsgemeinschaft Internistische Onkologie (AIO) steering group were analysed. On total, 192 of the 460 analysed patients had participated in three clinical trials [6–8]. All patients had histologically proven localised (cT3 or N+) EGC with no evidence of distant metastases. Medical records included surgical and pathological records, imaging records, chemotherapy protocols showing dose reductions and delays, patient’s charts where toxicity was documented and follow-up reports informing about date of progression, last follow-up and death. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEs) in its version valid at the time when the respective patients were treated. The relative safety and efficacy of neoadjuvant chemotherapy was compared in two cohorts: those aged  $\geq 70$  (cohort I,  $n = 174$ ) were compared with their younger counterparts (cohort II,  $n = 286$ ) in terms of co-morbidities, treatment delivery (type, dose reductions, early discontinuation of therapy), chemotherapy-associated toxicity (incidence of major toxic events  $\geq$  grade 3), postoperative morbidity, 90 day postoperative mortality and survival outcomes (overall survival [OS], disease-free survival [DFS]). In all four

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