Older versus younger adults with gastric cancer receiving perioperative treatment: results from the CRITICS trial

Slagter, A.E.; Tudela, B.; Amelsfoort, R.M. van; Sikorska, K.; Sandick, J.W. van; Velde, C.J.H. van de; ... ; Verheij, M.

European Journal of Cancer 130 (2020) 146–154

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Older versus younger adults with gastric cancer receiving perioperative treatment: Results from the CRITICS trial☆,☆☆

Astrid E. Slagter [a], Benjamin Tudela [a,b], Romy M. van Amelsfoort [a], Karolina Sikorska [c], Johanna W. van Sandick [d], Cornelis J.H. van de Velde [e], Nicole C.T. van Grieken [f], Pehr Lind [g,h], Marianne Nordsmark [i], Hein Putter [j], Maarten C.C.M. Hulshof [k], Hanneke W.M. van Laarhoven [l], Cecile Grootscholten [m], Jeffrey P.B.M. Braak [e], Elma Meershoek-Klein Kranenbarg [e], Edwin P.M. Jansen [a], Annemieke Cats [m], Marcel Verheij [a,n,*]

[a] *Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[b] *Department of Radiation Oncology, Universidad de Valparaíso, Valparaíso, Chile*
[c] *Department of Biometrics, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[d] *Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[e] *Department of Surgical Oncology, Leiden University Medical Center, Leiden, the Netherlands*
[f] *Department of Pathology, Amsterdam University Medical Centers, Location VUmc, Amsterdam, the Netherlands*
[g] *Department of Oncology, Stockholm Söder Hospital, Stockholm, Sweden*
[h] *Karolinska Institutet, Stockholm, Sweden*
[i] *Department of Medical Oncology, Aarhus University, Aarhus, Denmark*
[j] *Department of Biometrics, Leiden University Medical Center, Leiden, the Netherlands*
[k] *Department of Radiation Oncology, Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands*
[l] *Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands*
[m] *Department of Gastrointestinal Oncology/Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[n] *Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands*

Received 19 November 2019; received in revised form 6 February 2020; accepted 8 February 2020
Available online 21 March 2020

☆ This paper has been presented in part at the Gastrointestinal Symposium held in San Francisco, USA, January 17–19, 2019 and has received the 2019 Conquer Cancer Foundation Merit Award (AES).
☆☆ This paper has been presented in part at the American Society for Radiation Oncology (ASTRO) annual meeting, Chicago, USA, September 15–18, 2019.

* *Corresponding author*: Department of Radiation Oncology, Radboud University Medical Center, Geert Grooteplein 32, 6500 HB Nijmegen, the Netherlands. Fax: +31 (0)243164023.
E-mail address: Marcel.Verheij@radboudumc.nl (M. Verheij).

https://doi.org/10.1016/j.ejca.2020.02.008

KEYWORDS
Older adults;
Chemotherapy;
Chemoradiotherapy;
Resectable gastric cancer

Abstract ***Aim:*** To evaluate treatment-related toxicity, treatment compliance, surgical complications and event-free survival (EFS) in older (≥70 years) versus younger (<70 years) adults who underwent perioperative treatment for gastric cancer.
Methods: In the CRITICS trial, 788 patients with resectable gastric cancer were randomised before start of any treatment and received preoperative chemotherapy (3 cycles of epirubicin, cisplatin or oxaliplatin and capecitabine), followed by surgery, followed by either postoperative chemotherapy or chemoradiotherapy (45Gy + cisplatin + capecitabine).
Results: 172 (22%) patients were older adults. During preoperative chemotherapy, 131 (77%) older adults versus 380 (62%) younger adults experienced severe toxicity ($p < 0.001$); older adults received significantly lower relative dose intensities (RDIs) for all chemotherapeutic drugs. Equal proportions of older versus younger adults underwent curative surgery: 137 (80%) versus 499 (81%), with comparable postoperative complications and postoperative mortality. Postoperative therapy after curative surgery started in 87 (64%) older adults versus 391 (78%) younger adults ($p < 0.001$). Incidence of severe toxicity during postoperative chemotherapy was 22 (54%) in older adults versus 113 (59%) in younger adults ($p = 0.541$); older adults received significantly lower RDIs for all chemotherapeutic drugs. Severe toxicity rates for postoperative chemoradiotherapy were 22 (48%) older adults versus 89 (45%) for younger adults ($p = 0.703$), with comparable chemotherapy RDIs and radiotherapy dose. Two-year EFS was 53% for older adults versus 51% for younger adults.
Conclusion: Perioperative treatment compliance, especially in the postoperative phase, was poorer in older adults compared with younger adults. As comparable proportions of patients underwent curative surgery, future studies should focus on neo-adjuvant treatment.
Trial registration: ClinicalTrials.gov identifier: NCT00407186. EudraCT number: 2006–00413032.

1. Introduction

Gastric cancer is one of the leading causes of cancer-related deaths worldwide [1]. In the Netherlands, the incidence of gastric cancer was 8.8 per 100,000 in 2018 [2]. A population-based study from Germany indicated that among 8601 gastric cancer diagnoses, 59% of the patients were 70 years or older [3].

Age has a significant influence on treatment choices in the management of resectable gastric cancer. The German population-based study included patients with all stages of gastric cancer; older adults were diagnosed in a slightly lower stage compared with younger adults, but they were less frequently operated, and surgery was less often combined with (neo-)adjuvant treatment [3]. Older adults are generally less fit than younger patients and may be more prone to experience treatment-related toxicity. Several studies have compared tolerability of treatment in older versus younger adults with gastric cancer. Results on toxicity during chemotherapy in patients with locally advanced/metastatic gastric cancer [4,5] and on postoperative complication rates [6–9] in patients with resectable gastro-oesophageal cancer are not uniform. Importantly, randomised clinical trials have not provided detailed sub-analyses on older adults with resectable gastric cancer, hence information on tolerability of these treatments in older adults who were fit to undergo (neo-) adjuvant treatment are presently lacking.

Surgical resection is the cornerstone of treatment in patients with potentially curable gastric cancer [10]. In the Western world, 5-year overall survival (OS) after surgery alone is 20–35% [11,12]. Improvement in survival over surgery alone can be achieved with perioperative chemotherapy [13], postoperative chemotherapy [14,15] or postoperative chemoradiotherapy [11]. These different approaches have been integrated in multidisciplinary guidelines used over the world.

In the CRITICS trial [16,17], patients were randomised to receive either preoperative chemotherapy and postoperative chemotherapy or preoperative chemotherapy and postoperative chemoradiotherapy. According to intention to treat, no differences in OS and event-free survival (EFS) were observed. This is an unplanned post-hoc analysis evaluating older (≥70 years) versus younger (<70 years) adults in all phases of their perioperative treatment.

2. Material and methods

2.1. Study design and participants

The CRITICS trial was an international, multicentre, phase III study which recruited 788 patients between

2007 and 2015. The main outcomes were described previously [16]. Eligible patients had stage Ib-IVa resectable gastric or gastro-oesophageal junction adenocarcinoma according to the American Joint Committee on Cancer, sixth edition, and had World Health Organisation (WHO) performance status of 0–1. No upper age limit was applied, and age was not a stratification factor in this trial. In the current analysis, we defined patients ≥70 years at time of randomisation as older adults.

2.2. Procedures

Patients were treated with three cycles of preoperative chemotherapy: epirubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1) or oxaliplatin (130 mg/m^2 on day 1) and capecitabine (1000 mg/m^2 twice daily for 14 days in combination with epirubicin and cisplatin (ECC) or 625 mg/m^2 twice daily for 21 days in combination with epirubicin and oxaliplatin [EOC]). Patients were randomised before the start of preoperative treatment between postoperative chemotherapy (another three cycles of ECC/EOC) or postoperative chemoradiotherapy, which consisted of 45 Gy in 25 fractions of 1.8 Gy, combined with capecitabine (575 mg/m^2 twice daily on radiotherapy days) and weekly cisplatin (20 mg/m^2).

2.3. Outcomes

Baseline characteristics included age, sex, WHO performance status, Lauren classification, tumour localisation, allocated treatment and comorbidity. Toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0). For both preoperative and postoperative treatment, we evaluated starting dose, severe toxicity and treatment compliance for older versus younger adults. In addition, we reported the proportion of older versus younger adults who were treated with cisplatin and oxaliplatin, respectively. For the surgical part of treatment, we compared intent of surgery, extent of resection, postoperative complications and postoperative mortality.

2.4. Statistical analysis

All data were analysed using R statistical software i386 version 3.5.2/IBM SPSS statistics, version 25. Continuous variables are presented as medians and interquartile ranges (IQRs) and categorical outcomes as frequencies and percentages. Between group comparisons were tested using Mann–Whitney U test for continuous variables or Fisher exact test for categorical variables. Threshold for statistical significance was set at 0.05. Relative dose intensities (RDIs) were defined as $\frac{\text{dose received (mg)}}{\text{dose planned (mg)}} \times \frac{\text{time planned (days)}}{\text{time planned+days of delay}} \times 100\%$. EFS was defined as time between randomisation until date of progression, irresectability during surgery, recurrence or death, whichever occurred first. OS was defined as time between randomisation until death from any cause. OS and EFS were estimated using the Kaplan–Meier procedure.

3. Results

3.1. Patients

Out of 788 patients, 172 (22%) patients were older adults, and 616 (78%) were younger adults and had a median follow-up time of 35 months (IQR 13–56) versus 37 months (IQR 12–68), respectively (p = 0.778). Baseline characteristics are presented in Table 1, and more details on comorbidities are shown in Table A1. WHO performance status was slightly better in younger adults, and comorbidities were more frequently present in older adults. Tumour localisation tended to be more distal in older adults (non-significant). Detailed information on reasons for drop-out are shown in Figure A1.

3.2. Preoperative chemotherapy: treatment-related toxicity and compliance

A total of 781 patients started preoperative therapy. Median starting dose during the first cycle was not significantly different (Table A2). More older adults

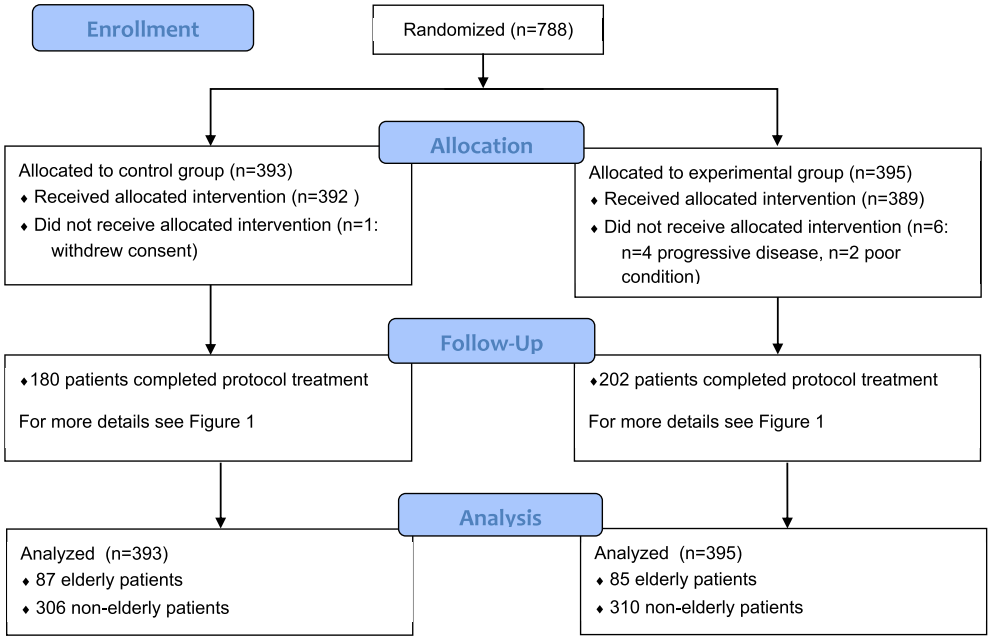
Table 1
Baseline characteristics for older versus younger adults.

Variable	≥70 years (n = 172)	<70 years (n = 616)	p value
Age (median; range)	73 (70–82)	59 (28–69)	**<0.001**
Sex			0.359
Male	121 (70%)	408 (66%)	
Female	51 (30%)	208 (34%)	
WHO performance status Missing (n = 3)			**0.030**
0	104 (60%)	430 (70%)	
1	54 (31%)	155 (25%)	
Not performed	14 (8%)	28 (5%)	
Lauren classification (biopsy)			0.142
Intestinal	58 (34%)	195 (32%)	
Diffuse	42 (24%)	191 (31%)	
Mixed	14 (8%)	28 (5%)	
Unknown	58 (34%)	202 (33%)	
Tumour localisation			0.433
GE-junction	26 (15%)	109 (18%)	
Proximal	30 (17%)	133 (22%)	
Middle	58 (34%)	179 (29%)	
Distal	58 (34%)	195 (32%)	
Allocated postoperative treatment			0.863
CRT	85 (49%)	310 (50%)	
CT	87 (51%)	306 (50%)	
Any comorbidity	108 (63%)	261 (42%)	**<0.001**

GE-junction, gastro-oesophageal junction; CRT, chemoradiotherapy; CT, chemotherapy.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT Flow Diagram CRITICS trial: elderly versus non-elderly patients



experienced severe (grade III–V) toxicity than younger adults: 131 (77%) patients versus 380 (62%) patients ($p < 0.001$), respectively (Table 2).

Median RDIs were lower for all chemotherapeutic drugs in older adults compared with younger adults: epirubicin 88% (IQR 67–99%) versus 97% (IQR 84–100%) ($p < 0.001$), cisplatin/oxaliplatin 87% (IQR 66–99%) versus 97% (IQR 87–100%) ($p < 0.001$), and capecitabine 82% (IQR 55–95%) versus 93% (81–100%) ($p < 0.001$). Older adults were less likely to complete (3 cycles) preoperative treatment: 120 (70%) versus 535 (88%) ($p < 0.001$). After correcting for age, there was a significant correlation between presence of comorbidities at baseline and RDI. A total of 237 (59%) patients without comorbidities received an RDI of ≥85% for all chemotherapeutic drugs, compared with 175 (48%) of patients who had comorbidities at baseline (odds ratio 1.443, 95% confidence interval (CI) 1.077–1.933, $p = 0.014$). A total of 30 (18%) older adults received the oxaliplatin chemotherapy combination compared with 119 (20%) younger adults ($p = 0.563$). In older adults, RDIs for cisplatin and oxaliplatin, respectively, were comparable: 87% (IQR 64–99%) for cisplatin versus 87% (IQR 70–100%) for oxaliplatin ($p = 0.383$).

3.3. Surgery

The majority of patients underwent curative surgery: 137 (80%) older adults versus 499 (81%) younger adults ($p = 0.743$). Surgical characteristics are summarised in Table 3. Older adults more frequently underwent a subtotal gastrectomy, whereas younger patients more frequently underwent an oesophagus-cardia resection. Resection margin, extent of lymph node dissection, postoperative complication rate and postoperative mortality were comparable.

3.4. Postoperative therapy

After curative surgery, 87 (64%) older adults and 391 (78%) younger adults started postoperative therapy ($p < 0.001$). Reasons for not starting postoperative

Table 2
Severe (grade III–V) toxicity during preoperative and postoperative treatment.

Variable	Preoperative chemotherapy			Postoperative chemotherapy			Postoperative chemoradiotherapy		
	≥70 years (n = 171)	<70 years (n = 610)	p value	≥70 years (n = 41)	<70 years (n = 192)	p value	≥70 years (n = 46)	<70 years (n = 199)	p value
Any severe toxicity	**131 (77%)**	**380 (62%)**	**<0.001**	**22 (54%)**	**113 (59%)**	0.541	**22 (48%)**	**89 (45%)**	0.703
Any severe haematological	**76 (44%)**	**206 (34%)**	**0.012**	**13 (32%)**	**68 (35%)**	0.720	**7 (15%)**	**15 (8%)**	0.147
Anaemia	9 (5%)	15 (2%)		0 (0%)	1 (1%)		0 (0%)	2 (1%)	
Neutropenia	61 (36%)	189 (31%)		13 (32%)	66 (34%)		6 (13%)	5 (3%)	
Febrile neutropenia	20 (12%)	44 (7%)		0 (0%)	5 (3%)		1 (2%)	4 (2%)	
Other	8 (5%)	16 (3%)		0 (0%)	2 (1%)		1 (2%)	6 (3%)	
Any severe gastrointestinal	**53 (31%)**	**142 (23%)**	**0.045**	**7 (17%)**	**38 (20%)**	0.829	**9 (20%)**	**39 (20%)**	1.000
Nausea	24 (14%)	60 (10%)		2 (5%)	25 (13%)		2 (4%)	21 (11%)	
Vomiting	18 (11%)	43 (7%)		0 (0%)	10 (5%)		3 (7%)	9 (5%)	
Mucositis/stomatitis	11 (6%)	21 (3%)		1 (2%)	5 (3%)		1 (2%)	1 (1%)	
Diarrhoea	29 (17%)	73 (12%)		4 (10%)	9 (5%)		2 (4%)	6 (3%)	
Other	10 (6%)	36 (6%)		3 (7%)	13 (7%)		4 (9%)	14 (7%)	
Any severe vascular	**30 (18%)**	**79 (13%)**	0.134	**0 (0%)**	**9 (5%)**	0.367	**0 (0%)**	**7 (4%)**	0.353
Ischemic event/sudden death	12 (7%)	15 (2%)		0 (0%)	3 (2%)		0 (0%)	1 (1%)	
Thromboembolic event	14 (8%)	51 (8%)		0 (0%)	5 (3%)		0 (0%)	3 (2%)	
Other	11 (6%)	16 (3%)		0 (0%)	1 (1%)		0 (0%)	3 (2%)	
Any severe constitutional	**64 (37%)**	**146 (24%)**	**<0.001**	**5 (12%)**	**46 (24%)**	0.144	**14 (30%)**	**51 26%)**	0.579
Fatigue	20 (12%)	45 (7%)		3 (7%)	17 (9%)		6 (13%)	21 11%)	
Dehydration	16 (9%)	28 (5%)		1 (2%)	2 (1%)		3 (7%)	5 (3%)	
Infection with normal neutrophils	20 (12%)	47 (8%)		0 (0%)	10 (5%)		4 (9%)	10 (5%)	
Other	32 (19%)	82 (13%)		2 (5%)	27 (14%)		8 (17%)	31 16%)	
Any severe other	**43 (25%)**	**106 (17%)**	**0.027**	**3 (7%)**	**22 (11%)**	0.583	**4 (9%)**	**33 17%)**	0.235
Pain	8 (5%)	22 (4%)		0 (0%)	11 (6%)		1 (2%)	11 (6%)	
Metabolic disorder	22 (13%)	50 (8%)		2 (5%)	4 (2%)		2 (4%)	11 (6%)	
Other	14 (8%)	37 (6%)		1 (2%)	10 (5%)		1 (2%)	14 (7%)	

All severe toxicities with a percentage ≥5% (in one or both subgroups) are shown. Patients could have experienced one or more toxicities per subgroup. Preoperative grade V toxicities occurred in three (2%) older adults and 10 (2%) younger adults. No postoperative grade V toxicity occurred.

therapy were not significantly different between both groups: death in 4 (8%) versus 13 (13%) patients, recurrence in 7 (14%) versus 21 (21%) patients, patient refusal in 10 (20%) versus 21 (21%) patients, postoperative complications in 7 (14%) versus 19 (19%) patients, preoperative toxicity in 13 (27%) versus 17 (17%) patients, poor condition in 7 (14%) versus 3 (3%) patients, protocol deviation in 1 (2%) versus 4 (4%) patients and other reasons in none versus 2 (2%) patients, in older versus younger adults (p = 0.140).

3.5. Postoperative chemotherapy group: treatment-related toxicity and compliance

After curative surgery, 41 (64%) older adults and 192 (78%) younger adults started postoperative chemotherapy (p = 0.034). Median starting dose during the first postoperative cycle is displayed in Table A3; most chemotherapeutics were started at a significantly lower dose in older adults. Median RDIs during the entire postoperative chemotherapy were also lower for elderly patients: epirubicin 73% (59–92%) versus 88% (66–99%) (p = 0.011), cisplatin/oxaliplatin 66% (51–88%) versus 88% (66–99%) (p < 0.001) and capecitabine 60% (49–79%) versus 81% (57–97%) (p = 0.002). Postoperatively, 11 (27%) older adults received the oxaliplatin chemotherapy combination compared with 40 (21%) younger adults (p = 0.399). During postoperative chemotherapy in older adults, there was no difference in RDI for cisplatin versus oxaliplatin (median for cisplatin was 66% with an IQR of 50–85%, and the median for oxaliplatin was 67% with an IQR of 45–90% [p = 0.914]).The occurrence of severe (grade III–IV) toxicity was not significantly different between groups (Table 2). A total of 28 (68%) older and 152 (79%) younger adults completed postoperative chemotherapy (p = 0.152).

3.6. Postoperative chemoradiotherapy group: treatment-related toxicity and compliance

After curative surgery, 46 (63%) older and 199 (79%) younger adults started postoperative chemoradiotherapy (p = 0.009). Median RDIs were comparable between groups: cisplatin 97% (78–99%) versus 98% (80–100%) (p = 0.437) and capecitabine 87% (69–100%) versus 91% (80–100%) (p = 0.249) for older versus younger adults, respectively. Median radiotherapy dose was equal in both groups: 45 Gy (IQR 45-45Gy) (p = 0.126). A total of 22 (48%) older versus 89

Table 3
Surgical details, postoperative complications and hospital stay (for patients who underwent curative surgery).

Variable		≥70 years (n = 137)	<70 years (n = 499)	p value
Surgical resection details	**Type of resection**			**0.035**
	Total gastrectomy	70 (51%)	248 (50%)	
	Subtotal gastrectomy	61 (45%)	194 (39%)	
	Oesophagus-cardia resection	6 (4%)	57 (11%)	
	Margin			0.999
	R0	119 (89%)	441 (89%)	
	R1	14 (11%)	53 (11%)	
	missing	4	5	
	Lymph node dissection			0.186
	D1 or less	21 (16%)	57 (12%)	
	D2 or more	111 (84%)	433 (88%)	
Postoperative complications	**General complications**			0.669
	Yes	41 (30%)	139 (28%)	
	Missing	2	0	
	Infectious complications			0.495
	Yes	35 (26%)	113 (23%)	
	Missing	2	0	
	Surgery-related complications			0.487
	Yes	34 (25%)	108 (22%)	
	Missing	2	0	
	Postoperative mortality	5 (4%)	9 (2%)	0.195
	30-day mortality	5 (4%)	10 (2%)	0.335
Hospital stay in days median (IQR)		12 (9–15)	11 (9–16)	0.347

General: Cardiovascular, pulmonary, renal and neurological complications. Infectious: abdominal wound, abscess and sepsis. Surgery-related complications: bleeding, anastomotic leakage, abdominal wound dehiscence, ileus and intestinal necrosis.

(45%) younger adults experienced severe (grade III–IV) toxicity (p = 0.703) (Table 2); 35 (76%) older and 167 (84%) older adults completed the 5 weeks of chemo-radiotherapy (p = 0.204).

3.7. Survival

Two-year OS was 59% (95% CI 52–67%) for older adults and 61% (95% CI 57–65%) for younger adults. Two-year EFS was also comparable: 53% (95% CI 47–61%) for older adults compared with 51% (95% CI 47–55%) for younger adults. Fig. 1 shows the Kaplan–Meier curves for EFS.

4. Discussion

In this post-hoc analysis of the CRITICS trial, patient compliance of perioperative treatment for resectable gastric cancer was poorer in older adults compared with younger adults, especially in the postoperative phase. To our knowledge, this is the first subgroup analysis of a randomised trial comparing older adults to younger adults with gastric cancer in the curative setting.

The preoperative starting dose of chemotherapy was comparable for older and younger adults, whereas RDIs and completion rate were lower for older adults. This suggests that physicians do not adapt the chemotherapy dose for older adults on beforehand.

Toxicity during preoperative chemotherapy for gastric cancer has, to our knowledge, never been compared for older and younger adults. The only comparative studies available have been performed in the palliative setting. An example is a pooled analysis of eight trials including 367 patients with metastasised oesophagogastric cancer; 154 (42%) patients were ≥65 years. Various chemotherapy regimens were used, the majority of patients were treated with doublet chemotherapy. Severe toxicity rates were 73% in older adults versus 66% in younger adults (p = 0.02) [5]. In contrast, another pooled analysis included 1080 patients with metastatic oesophagogastric cancer, who were treated with fluorouracil-based chemotherapy; the majority of patients received triplet chemotherapy. No differences in toxicity rates were observed for older versus younger adults [4].

The explanation for higher treatment-related toxicities in older adults may (partially) lie in pharmacokinetics. For epirubicin, an interaction between age and clearance has been observed, leading to higher epirubicin serum concentration with increasing age. Platinum chemotherapeutics irreversibly bind to plasma proteins, free platinum is excreted by the kidneys and therefore plasma levels are dependent on the patient's renal function. No relationship has been confirmed between age and pharmacokinetics of platinum-based chemotherapy. However, renal function decreases with increasing age, and lower creatinine clearance was significantly associated with platinum maximum concentrations. For 5-FU and capecitabine, no relationship has been established between pharmacokinetics and age [18].

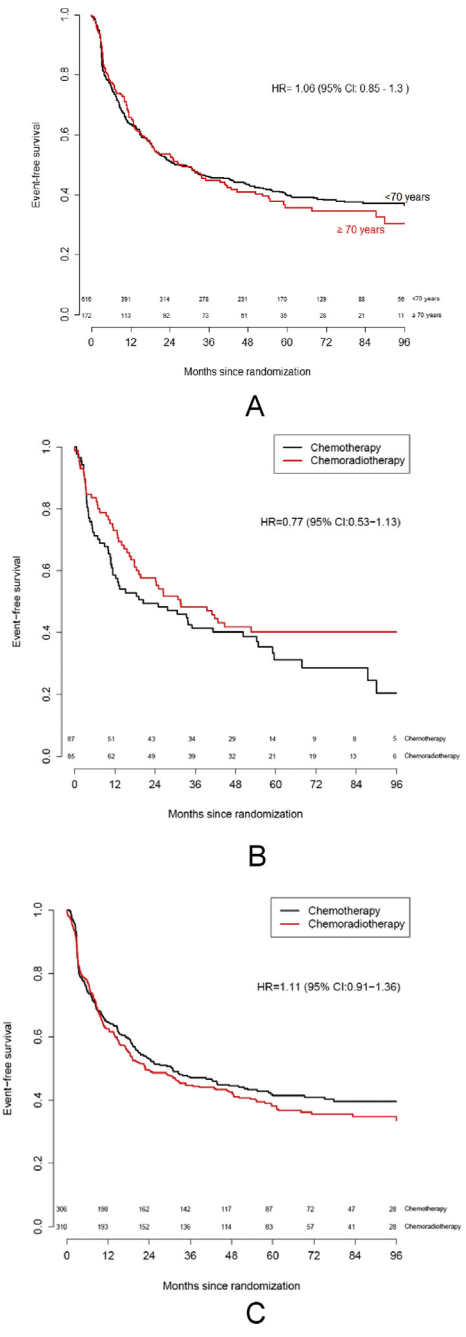


Fig. 1. Kaplan–Meier event-free survival (ITT). Interaction between age and arm was non-significant (p = 0.1). (A) Event-free survival older adults versus younger adults (ITT). (B) Event-free survival older adults per arm (ITT). (C) Event-free survival younger adults per arm (ITT). ITT,intention to treat.

In our study, older adults started at a lower postoperative chemotherapy dose. Guidelines for dose-reductions were described in the study protocol. However, age may play a role in the physician's choice. Toxicity and completion rate were not significantly different during postoperative chemotherapy, which could be because of lower dose in older adults or because of patient selection. For postoperative chemoradiotherapy, older adults were treated with a comparable chemotherapy and radiotherapy dose without increased toxicity.

In our study, older adults have less oesophagus-cardia resections and more subtotal gastrectomies compared with younger patients, probably because of (non-significant) differences in tumour localisation. Some retrospective studies observed more subtotal gastrectomies in older adults, while younger adults underwent relatively more total gastrectomies [9]. In addition, some studies described a less extended lymph node dissection in older [8,9]. Furthermore, there are studies which showed that the postoperative complication rate, and the postoperative mortality rate was higher in older adults [8]. We did not confirm any of these observations in our analysis. Based on our results, fit older adults were similarly able to undergo surgical resection for gastric cancer compared with younger adults, without increased complication rate and postoperative mortality.

Older adults more frequently experienced toxicities and had poorer treatment compliance, which may raise the question whether all older adults should receive lowered chemotherapy dose to prevent toxicities. Recently, the outcomes of a phase III study were presented at the 2019 ASCO annual meeting. A total of 541 patients with advanced oesophagogastric cancer who were considered unable to tolerate full doses of the combination therapy epirubicin, oxaliplatin and capecitabine because of age or frailty were enrolled. Patients were considered fit for a combination of oxaliplatin and capecitabine and were 1:1:1 randomised between level A (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 625 mg/m^2 on days 1–21, every 21 days), level B (80% of level A doses) and level C (60% of level A doses). The preliminary results showed that patients randomised to the lowest dose experienced less toxicity and had non-inferior progression-free survival compared with the patients randomised to level A or level B [19]. Al-Batran *et al.* performed a randomised clinical trial specifically addressing older adults (≥65 years) with oesophagogastric cancer in the palliative setting. This study included 143 patients with locally advanced or metastatic oesophagogastric cancer. Patients were randomised between 5-FU, folinic acid and oxaliplatin with (FLOT) or without docetaxel (FLO). In the FLOT group, severe (grade III–V) toxicity was more common, and quality of life was negatively influenced compared with FLO alone. Although treatment duration and treatment discontinuation were similar between the two arms, the addition of docetaxel did not improve response rates in patients of 70 years or older and patients with metastatic disease [20].

This analysis expands our insights in fit older adults with gastric cancer undergoing perioperative therapy and will help us to make evidence-based treatment

choices for fit older adults. Although treatment compliance is poorer in older adults undergoing perioperative treatment for gastric cancer, they were not disadvantaged by this treatment based on OS and EFS. Therefore, older adults should not be excluded for multimodality treatment solely based on age. This conclusion is in line with results as shown in the forest plot from the MAGIC trial, which indicated similar efficacy of perioperative chemotherapy in older adults [13]. It should be noted that the standard perioperative chemotherapy regimen in Europe has recently been changed from ECC/EOC to FLOT [21].

Based on the postoperative compliance, a switch to a complete neo-adjuvant approach [22] was suggested in the key-publication of the CRITICS trial [16]. As the postoperative compliance was poorer in older adults, the switch to an exclusive neo-adjuvant approach would be even more desirable, whether or not with adapted dose. Future studies are needed to elaborate the optimal treatment strategy in (subgroups of) older adults with gastric cancer. Other factors, such as comorbidities, should be taken into account in defining an optimal treatment strategy for older adults.

5. Limitations

The major limitation of this analysis is the selection of fit older adults. The proportion of older adults (≥70 years) among patients diagnosed with gastric cancer of all stages is around 60% [3]. It is known that older adults are usually underrepresented in randomised trials, with reported proportions between 21 and 26% [13,14,16,23]. For evaluation of the postoperative treatment phase, they not only had to be eligible for the CRITICS trial but they also completed preoperative treatment, underwent resection and started postoperative therapy, so these patients represent a highly selected subgroup of older adults with gastric cancer. Another limitation is that we used comorbidities as a surrogate marker to present the health status of patients. However, in a report on older adults, geriatric assessment would have been helpful, which was unfortunately unavailable in this analysis. Finally, we have chosen for a break-point of 70 years to define older adults, which can be seen as an arbitrary selection. In the literature, no clear break-point has been described to define older adults. The break-point of 70 years is in line with the majority of the literature.

Funding

This study was supported by the Dutch Cancer Society, the Dutch Colorectal Cancer Group and Hoffmann La Roche. The funding sources had no role in the design, collection, analysis and interpretation of the data.

Conflicts of interest statement

N.C.T. van Grieken reported receiving grants from the Dutch Cancer Society and The Netherlands Organisation for Health Research and Development, and serving on an advisory board for Bristol-Myers Squibb and Merck Sharp & Dohme. H.W.M. van Laarhoven reported receiving grants/medication support from Bayer, BMS, Celgene, Janssen, Lilly, Nordic Pharma, Philips, Roche, Servier, and serving on an advisory board for BMS, Lilly, MSD, Nordic Pharma, Novartis, Servier E.P.M. Jansen, A. Cats and M. Verheij reported receiving grants from the Dutch Cancer Society, the Dutch Colorectal Cancer Group and Hoffmann La Roche. All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors thank all patients, treating physicians and research support staff in all participating centres.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.008.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Canc J Clin 2018:1–31. 0.
[2] https://www.cijfersoverkanker.nl.
[3] Schlesinger-Raab A, Mihaljevic AL, Egert S, Emeny R, Jauch KW, Kleeff J, et al. Outcome of gastric cancer in the elderly: a population-based evaluation of the Munich Cancer Registry. Gastric Canc 2016;19:713–22. https://doi.org/10.1007/s10120-015-0527-7.
[4] Trumper M, Ross PJ, Cunningham D, Norman AR, Hawkins R, Seymour M, et al. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. Eur J Canc 2006;42:827–34. https://doi.org/10.1016/j.ejca.2005.08.044.
[5] Jatoi A, Foster NR, Egner JR, Burch PA, Stella PJ, Rubin J, et al. Older versus younger patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and stomach: a pooled analysis of eight consecutive North Central Cancer Treatment Group (NCCTG) trials. Int J Oncol 2010;36:601–6. https://doi.org/10.3892/ijo.
[6] Hamilton TD, Mahar AL, Haas B, Beyfuss K, Law CHL, Karanicolas PJ, et al. The impact of advanced age on short-term outcomes following gastric cancer resection: an ACS-NSQIP analysis. Gastric Canc 2017;21:710–9. https://doi.org/10.1007/s10120-017-0786-6.
[7] Gretschel S, Estevez-Schwarz L, Hünerbein M, Schneider U, Schlag PM. Gastric cancer surgery in elderly patients. World J Surg 2006;30:1468–74. https://doi.org/10.1007/s00268-005-0633-5.
[8] Fujiwara Y, Fukuda S, Tsujie M, Ishikawa H, Kitani K, Inoue K, et al. Effects of age on survival and morbidity in gastric cancer patients undergoing gastrectomy. World J Gastrointest Oncol 2017;9:257–62. https://doi.org/10.4251/wjgo.v9.i6.257.

[9] Orsenigo E, Tomajer V, Palo S Di, Carlucci M, Vignali A, Tamburini A, et al. Impact of age on postoperative outcomes in 1118 gastric cancer patients undergoing surgical treatment. Gastric Canc 2007;10:39–44. https://doi.org/10.1007/s10120-006-0409-0.

[10] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27: v38–49. https://doi.org/10.1093/annonc/mdw350.

[11] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30. https://doi.org/10.1056/NEJMoa010187.

[12] Msika S, Benhamiche AM, Jouve J-L, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. Eur J Canc 2000;36:390–6. https://doi.org/10.1016/S0959-8049(99)00308-1.

[13] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20. https://doi.org/10.1056/NEJMoa1513750.

[14] Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315–21. https://doi.org/10.1016/S0140-6736(11)61873-4.

[15] Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer. J Am Med Assoc 2010;303:1729–37.

[16] Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:616–28. https://doi.org/10.1016/S1470-2045(18)30132-3.

[17] Dikken JL, van Sandick JW, Maurits Swellengrebel H, Lind PA, Putter H, Jansen EP, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemo-radiotherapy for patients with resectable gastric cancer (CRITICS). BMC Canc 2011;11:1–8. https://doi.org/10.1186/1471-2407-11-329.

[18] Crombag MRBS, Joerger M, Thürlimann B, Schellens JHM, Beijnen JH, Huitema ADR. Pharmacokinetics of selected anti-cancer drugs in elderly cancer patients: focus on breast cancer. Canc (Basel) 2016;8:1–22. https://doi.org/10.3390/cancers8010006.

[19] Hall PS, Swinson D, Waters JS, Wadsley J, Falk S, Roy R, et al. Reduced chemotherapy dosages in elderly patients with advanced gastroesophageal cancer. In: 2019 ASCO annual meeting: abstract 4006; 2019.

[20] Al-Batran S, Pauligk C, Homann N, Moehler M, Probst S, Rethwisch V, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Canc 2013;49:835–42. https://doi.org/10.1016/j.ejca.2012.09.025.

[21] Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393: 1948–57. https://doi.org/10.1016/S0140-6736(18)32557-1.

[22] Slagter AE, Jansen EPM, van Laarhoven HWM, van Sandick JW, van Grieken NCT, Sikorska K, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resecta. BMC Canc 2018;18.

[23] Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357: 1810–20. https://doi.org/10.1056/NEJMoa072252.