European Journal of Cancer 170 (2022) 140–148

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Neoadjuvant chemotherapy improves survival in patients with oesophageal mucinous adenocarcinoma: Post-hoc analysis of the UK MRC OE02 and OE05 trials

Drolaiz H.W. Liu [a,b,1], Nina Šefčovičová [a,1], Jake Emmerson [c], Louisa N. Spaans [a,d], Yuichi Saito [a,e], Gordon Hutchins [f], Matthew G. Nankivell [g], Ruth E. Langley [g], William Allum [h], David Cunningham [i], Rupert Langer [b], Heike I. Grabsch [a,f,*]

[a] *Department of Pathology, GROW School for Oncology and Reproduction, Maastricht University Medical Center+, Maastricht, the Netherlands*
[b] *Institute of Clinical Pathology and Molecular Pathology, Kepler University Hospital and Johannes Kepler University, Linz, Austria*
[c] *Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK*
[d] *Department of Surgery, Maxima Medical Centre, Eindhoven/Veldhoven, the Netherlands*
[e] *Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan*
[f] *Division of Pathology and Data Analytics, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK*
[g] *Medical Research Council Clinical Trials Unit at University College London, London, UK*
[h] *Department of Oncology and Department of Surgery, Royal Marsden NHS Foundation Trust, London, UK*
[i] *Department of Medicine, Royal Marsden Hospital, Sutton, Surrey, UK*

Received 19 January 2022; received in revised form 8 April 2022; accepted 16 April 2022
Available online 27 May 2022

KEYWORDS
Mucinous adenocarcinoma;
Oesophageal adenocarcinoma;
Neoadjuvant chemotherapy;
Survival

Abstract ***Background:*** Adenocarcinoma with more than 50% extracellular mucin is a relatively rare histological subtype of gastrointestinal adenocarcinomas. The clinical impact of extracellular mucin in oesophageal adenocarcinoma (OeAC) has not been investigated in detail. We hypothesised that patients with mucinous OeAC ($OeAC_{mucin}$) do not benefit from neoadjuvant chemotherapy.
Methods: OeAC patients either treated by surgery alone in the OE02 trial (S-patients) or by neoadjuvant chemotherapy followed by surgery (CS-patients) in OE02 or OE05 trials were included. Cancers from 1055 resection specimens (OE02 [test cohort]: 187 CS, 185 S; OE05

* *Corresponding author*: Department of Pathology, GROW – School for Oncology and Reproduction, Maastricht University Medical Center+, P. Debyelaan 25, 6229HX, Maastricht, the Netherlands.
E-mail address: h.grabsch@maastrichtuniversity.nl (H.I. Grabsch).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejca.2022.04.026

[validation cohort]: 683 CS) were classified as either mucinous (more than 50% of the tumour area consists of extracellular mucin, $OeAC_{mucin}$) or non-mucinous adenocarcinoma ($OeAC_{non\text{-}mucin}$). The relationship between histological phenotype, clinicopathological characteristics, survival and treatment was analysed.

Results: Overall, 7.3% and 9.6% OeAC were classified as $OeAC_{mucin}$ in OE02 and OE05, respectively. In OE02, the frequency of $OeAC_{mucin}$ was similar in S and CS-patients. Patients with $OeAC_{mucin}$ treated with surgery alone had a poorer overall survival compared with $OeAC_{non\text{-}mucin}$ patients (hazard ratio: 2.222, 95% confidence interval: 1.08–4.56, $P = 0.025$). Patients with $OeAC_{mucin}$ treated with neoadjuvant chemotherapy and surgery had similar survival as $OeAC_{non\text{-}mucin}$ patients in test and validation cohort.

Conclusions: This is the first study to suggest in a post-hoc analysis of material from two independent phase III clinical trials that the poor survival of patients with mucinous OeAC can be improved by neoadjuvant chemotherapy. Future studies are warranted to identify potential underlying biological, biochemical or pharmacokinetic interactions between extracellular mucin and chemotherapy.

1. Introduction

Adenocarcinoma where more than 50% of the tumour area consists of extracellular mucin is a relatively rare subtype of adenocarcinomas in the gastrointestinal (GI) tract and usually classified as mucinous adenocarcinoma. Most studies about the clinical impact of mucinous adenocarcinoma in the GI tract investigated patients with colorectal cancer (CRC). CRC patients with mucinous adenocarcinoma were more often diagnosed with advanced disease stage [1], and rectal cancer patients with mucinous adenocarcinoma seemed to have a poorer prognosis after neoadjuvant chemoradiotherapy [2–8]. A recent study using Surveillance, Epidemiology, and End Results (SEER) data reported that gastric cancer patients with early or localised 'mucinous' adenocarcinoma have a similar survival when treated with surgery or chemotherapy [9]. Unfortunately, in this study, signet ring cell cancer with intracellular mucin and adenocarcinomas with extracellular mucin were analysed together as 'mucinous' adenocarcinoma [9].

There are currently very few studies on the incidence, survival and potential response to cytotoxic chemotherapy of oesophageal adenocarcinoma (OeAC) patients with mucinous adenocarcinoma ($OeAC_{mucin}$). This could be related to lack of awareness of this particular adenocarcinoma subtype in OeAC patients amongst pathologists and clinicians, potentially because the most recent World Health Organisation (WHO) classification of digestive tumours (5th ed, 2019) does not recommend the classification of OeAC into different histological subtypes [10]. Furthermore, whilst oesophageal cancer treatment guidelines distinguish between squamous cell carcinoma and adenocarcinoma, there are currently no treatment recommendations for different adenocarcinoma subtypes most likely due to lack of evidence [11].

Two studies investigated the relationship between $OeAC_{mucin}$ and neoadjuvant therapy [12,13]. Chirieac *et al.* [12] suggested a favourable survival after preoperative chemoradiotherapy in 'mucinous' OeAC compared with conventional adenocarcinoma. Unfortunately, patients with adenocarcinoma containing extracellular mucin and patients with signet ring cell cancer with intracellular mucin were combined for analyses; thus, the relationship between 'true' $OeAC_{mucin}$ and neoadjuvant therapy remained unclear. No firm conclusions about the prognostic significance of $OeAC_{mucin}$ can be drawn from the second study by Hornick *et al.* [13] because of the very small sample size ($n = 40$).

We hypothesised (1) that patients with $OeAC_{mucin}$ have a poorer survival compared with $OeAC_{non\text{-}mucin}$ when treated by surgery alone and (2) that neoadjuvant chemotherapy cannot improve the survival of patients with $OeAC_{mucin}$.

The aim of the present study was to analyse the relationship between histological phenotype (mucinous adenocarcinoma versus non-mucinous adenocarcinomas) in the resection specimen, survival and treatment first in OeAC patients from the OE02 trial (test cohort) and validate findings in OeAC patients from the OE05 trial (validation cohort).

2. Methods

The study was approved by the South East Research Ethics Committee, London, UK, REC reference: 07/H1102/111.

2.1. OE02 trial patients (test cohort)

In the OE02 trial, 802 patients with localised oesophageal cancer were randomly allocated to receive two

cycles of cisplatin and 5-fluorouracil (5-FU) chemotherapy followed by surgery (experimental arm, CS-patients) or surgery alone (control arm, S-patients) [14,15]. This trial was the first to demonstrate the benefit of neoadjuvant chemotherapy in oesophageal cancer patients changing clinical practice. In total, 345 CS-patients and 398 S-patients had surgery. Haematoxylin/Eosin (HE) stained slides and paraffin blocks from resection specimens were collected retrospectively. Patients with complete pathological response of the primary tumour or with squamous cell cancer were excluded from the present study. Slides from 187 CS-patients and 185 S-patients were available for analyses (consort diagram, see Supplement Figure 1). Overall, 50% of the OE02 trial patients with adenocarcinoma who had a resection were included in the present study. Clinicopathological data such as histological tumour type, grade of tumour differentiation, tumour regression grade (TRG; Mandard classification), depth of invasion ((y)pT) and lymph node (LN) status ((y)pN) were established during central histopathology review or extracted from the original reports (tumour size, tumour location, number of LNs with metastases and resection margin status) and classified according to UICC TNM 6th edition [16]. Resection margin status was classified according to the definition provided by the Royal College of Pathologists (R1 is defined as tumour within 1 mm) [17]. Clinical outcome data were extracted from the UK MRC OE02 clinical trial database.

The clinicopathological data from the study cohort were compared with the whole cohort of OE02 trial patients who had a resection to confirm the representativeness of the patient subset included in the present study.

2.2. OE05 trial patients (validation cohort)

The OE05 trial was the successor of the OE02 trial recruiting 897 patients with resectable oesophageal or junctional adenocarcinoma who were randomly allocated to receive two cycles of cisplatin and 5-FU chemotherapy followed by surgery (OE02-style treatment [control arm]) or four cycles of epirubicin, cisplatin, capecitabine (ECX) chemotherapy followed by surgery (experimental arm) [18]. There was no significant difference in survival between the two treatment arms, see publication of the clinical results [18]. In total, 751 (84%) patients had surgery. HE slides and paraffin blocks from the resection specimen were collected partly retrospectively, partly prospectively. Patients with complete pathological response of the primary tumour were excluded from the present study. Slides from 683 patients were available for analyses (consort diagram, see Supplement Figure 1). Overall, 91% of the OE05 trial patients with adenocarcinoma who had a resection were included in the present study.

Clinicopathological data such as grade of tumour differentiation, depth of invasion (ypT) and LN status (ypN) were extracted from the UK MRC OE05 clinical trial database and classified according to UICC TNM 6th edition [16]. Resection margin status was classified according to the definition provided by the Royal College of Pathologists (R1 is defined as tumour within 1 mm) [17]. TRG (Mandard classification) was established during central histopathology review. Clinical outcome data were extracted from the UK MRC OE05 clinical trial database.

The clinicopathological data from the study cohort were compared with the OE05 trial patients who had a resection to confirm the representativeness of the subset included in the present study.

2.3. Study design

HE stained slides were scanned at 40× magnification (Aperio XT Scanner; Aperio Technologies, Vista, CA, USA). All slides from the test cohort (OE02 trial) and the validation cohort (OE05 trial) were reviewed by at least two independent observers blinded to any treatment information. The histological phenotype of the primary tumour was classified as either $OeAC_{mucin}$ (more than 50% of the tumour area consisted of extracellular mucin, see WHO classification [10]) or $OeAC_{non\text{-}mucin}$. In case of disagreement between observers, the final decision was made by a third independent observer. Three adenocarcinomas with neuroendocrine differentiation from the OE05 trial were included in the $OeAC_{non\text{-}mucin}$ group.

2.4. Statistical analyses

As the tumour in the resection specimen was used to determine the histological phenotype, patients with complete pathological response of the primary tumour were excluded from the study. The relationship between histological phenotype ($OeAC_{mucin}$ versus $OeAC_{non\text{-}mucin}$), clinicopathological data, overall survival (OS) and treatment (surgery alone versus neoadjuvant chemotherapy followed by surgery) was analysed. From each trial, the clinicopathological characteristics (sex, depth of invasion ((y)pT), LN status ((y)pN), TRG (Mandard classification) and resection margin status (R)) were summarised and compared between patients with $OeAC_{mucin}$ or $OeAC_{non\text{-}mucin}$ (Table 1) using the chi-squared test for binary variables and Mann–Whitney U-test for ordinal variables. Data were analysed per trial arm in the test cohort (OE02 trial) and validation cohort (OE05 trial).

For survival analyses, follow-up time was calculated from the date of randomisation. Kaplan–Meier plots were used to compare OS of patients with $OeAC_{mucin}$ versus $OeAC_{non\text{-}mucin}$. Formal comparisons were carried out using log-rank tests and hazard ratios (HRs) calculated from unadjusted Cox proportional hazards models. The assumption of proportional hazards was tested for each Cox model using the numerical methods

Table 1
Clinicopathological characteristics of the study cohorts stratified by mucinous phenotype.

	OE02 trial													OE05 trial						
	Surgery alone							Neoadjuvant 5-FU/cisplatin plus surgery							Neoadjuvant chemotherapy [#] plus surgery						
	Total		$OeAC_{non\text{-}mucin}$		$OeAC_{mucin}$		*P* value	Total		$OeAC_{non\text{-}mucin}$		$OeAC_{mucin}$		*P* value	Total		$OeAC_{non\text{-}mucin}$		$OeAC_{mucin}$		*P* value
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Sex							***0.030***							0.270							0.333
Male	135	82.3	130	96.3	5	3.7		148	88.6	136	91.9	12	8.1		569	89.9	512	90.0	57	10.0	
Female	29	17.7	25	86.2	4	13.8		19	11.4	16	84.2	3	15.8		64	10.1	60	93.8	4	6.2	
Tumour regression grade (Mandard)														0.215							***<0.001***
2	N/A							5	2.9	5	100	0	0		23	3.7	16	69.6	7	30.4	
3								22	12.9	19	86.4	3	13.6		79	12.6	61	77.2	18	22.8	
4								66	38.6	58	87.9	8	12.1		356	56.6	326	91.6	30	8.4	
5								74	43.3	70	94.6	4	5.4		171	27.2	165	96.5	6	3.5	
Depth of invasion ((y)pT)*							0.731							0.097							0.855
T1	12	7.3	11	91.7	1	8.3		15	9.0	15	100	0	0		65	10.3	59	90.8	6	9.2	
T2	20	12.2	19	95.0	1	5.0		19	11.4	18	94.7	1	5.3		113	17.9	102	90.3	11	9.7	
T3	129	78.7	122	94.6	7	5.4		129	77.3	116	89.9	13	10.1		431	68.3	391	90.7	40	9.3	
T4	3	1.8	3	100	0	0		4	2.4	3	75.0	1	25.0		22	3.5	19	86.4	3	13.6	
Lymph node status ((y)pN)*							0.322							0.138							0.177
N0	41	25.0	40	97.6	1	2.4		63	37.7	60	95.2	3	4.8		204	32.3	189	92.6	15	7.4	
N1	123	75.0	115	93.5	8	6.5		104	62.3	92	88.5	12	11.5		428	67.7	382	89.3	46	10.7	
Resection margin status							0.092							***0.004***							0.953
R0	97	65.1	94	96.9	3	3.1		102	66.8	97	95.1	5	4.9		405	65.1	367	90.6	38	9.4	
R1	52	34.9	47	90.4	5	9.6		51	33.3	41	80.4	10	19.6		217	34.9	195	89.9	22	10.1	

$OeAC_{mucin}$, mucinous adenocarcinoma (more than 50% of the tumour consists of extracellular mucin); $OeAC_{non\text{-}mucin}$, all other adenocarcinomas.
[#] Two cycles of cisplatin and 5-fluorouracil or four cycles of epirubicin, cisplatin, capecitabine chemotherapy.
* TNM classification 6th edition.

as described by Lin et al. [19] with piecewise analyses carried out for any curves that failed to satisfy the assumption (see OE05 trial results). Statistical analyses were conducted using SAS version 9.4. *P* values <0.05 were considered significant.

3. Results

3.1. Test cohort (OE02 trial)

Primary tumour slides were analysed from 372 resections (185 S-patients and 187 CS-patients). The median (range) age of the patients was 64 years (30–79 years) in S-patients and 62 years (30–83 years) in CS-patients. The median (range) follow-up time was 5.7 years (0.3–11.6 years).

Clinicopathological characteristics and survival of patients in the present study were similar to those of all OE02 trial patients with adenocarcinoma who had a resection (Supplement Table 1 and Supplement Fig. 2).

Twenty-four (7%) adenocarcinomas were classified as $OeAC_{mucin}$. Typical examples of mucinous adenocarcinoma are shown in Fig. 1. The frequency of $OeAC_{mucin}$ was similar between treatment arms (9 [6%] and 15 [9%] in S- and CS-patients, respectively).

3.2.1. Relationship between mucinous phenotype and clinicopathological characteristics

In S-patients, $OeAC_{mucin}$ was seen more frequently in females (4% male versus 14% female, $P = 0.030$). Overall, 66% CS-patients with $OeAC_{mucin}$ had a positive resection margin compared with 30% CS-patients with $OeAC_{non\text{-}mucin}$ ($P = 0.004$). No other significant relationships were found between mucinous phenotype and clinicopathological variables (see Table 1).

3.2.2. Relationship between mucinous phenotype and overall survival

S-patients with $OeAC_{mucin}$ had poorer 5-year OS compared with S-patients with $OeAC_{non\text{-}mucin}$ (HR: 2.222, 95% confidence interval [CI]: 1.082–4.562, $P = 0.0252$; Fig. 2A). There was no difference in 5-year OS comparing CS-patients with $OeAC_{mucin}$ versus CS-patients with $OeAC_{non\text{-}mucin}$ (HR: 0.870, 95% CI: 0.468–1.619, $P = 0.6602$; Fig. 2B).

3.3. Validation cohort (OE05 trial)

Primary tumour slides were analysed from 683 resections (353 cisplatin/5-FU [CF] and 330 ECX-treated patients). The median (range) age of patients was 62 years (30–83 years). The median follow-up time was 6.3 years (0.4–11.4 years).

The clinicopathological characteristics and survival of patients included in the present study were similar to those of all OE05 trial patients with adenocarcinoma who had a resection (Supplement Table 1 and Supplement Fig. 2).

Sixty-one (10%) adenocarcinomas were classified as $OeAC_{mucin}$. The frequency of $OeAC_{mucin}$ was similar between treatment arms (37 [11%] in CF and 24 [8%] in ECX group).

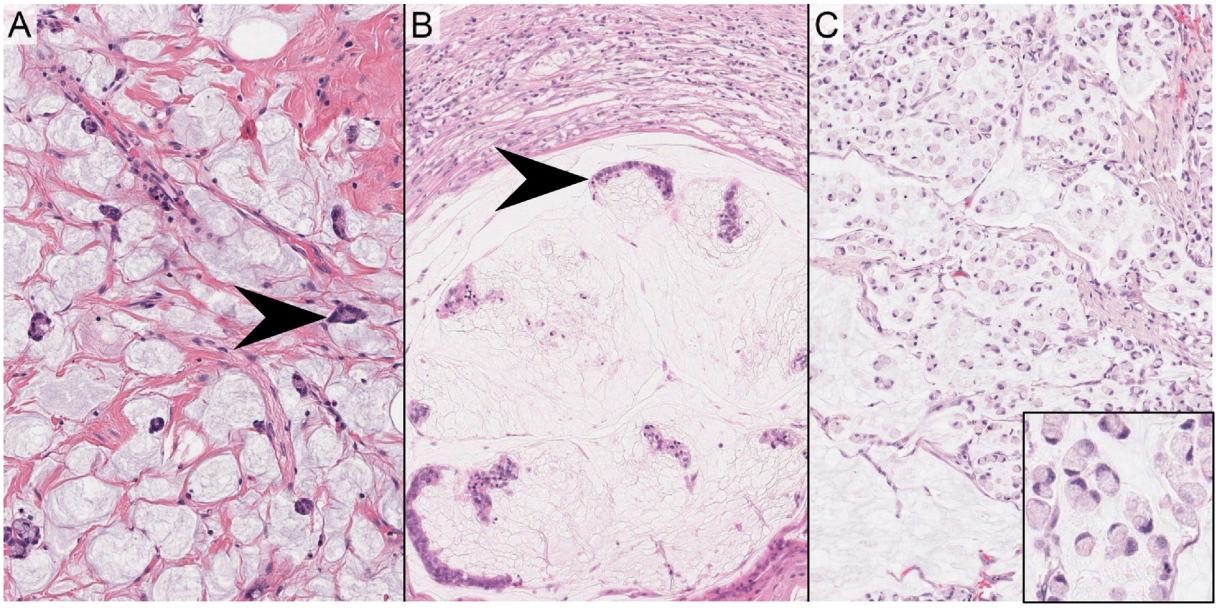

Fig. 1. Typical examples of oesophageal mucinous adenocarcinoma (haematoxylin/eosin staining). (A) Groups or nests of tumour cells free floating in extracellular mucin (arrow). (B) Longer strands of tumour cells floating in extracellular mucin (arrow). (C) Individual tumour cells with a signet ring cell appearance floating in extracellular mucin (inset). Note although there are signet ring cells present in the extracellular mucin, this type of adenocarcinoma should not be classified as a signet ring cell carcinoma.

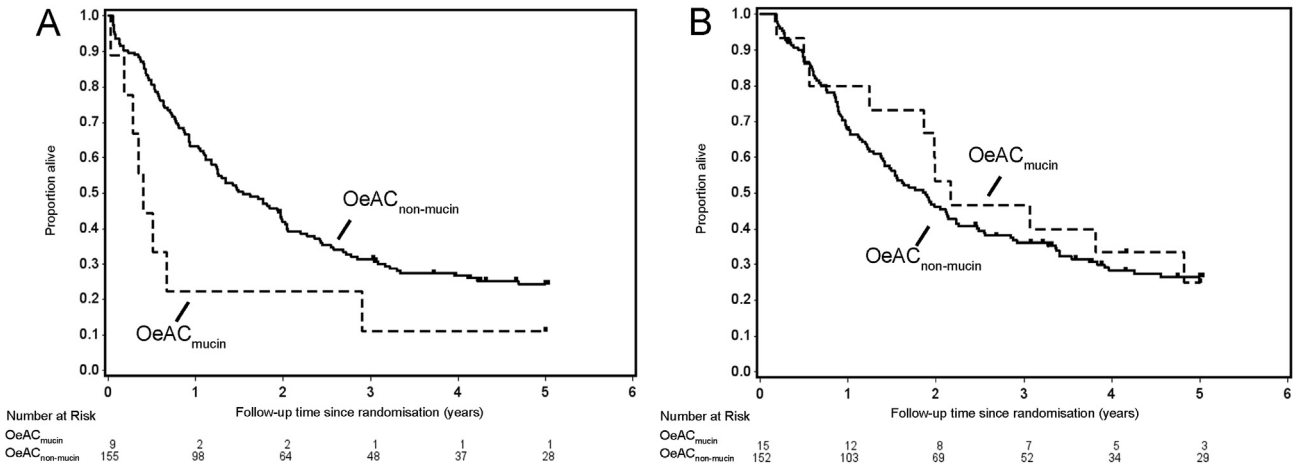

Fig. 2. Kaplan–Meier plots showing 5-year overall survival stratifying patients by histological phenotype in the OE02 trial cohort. (A) OE02 trial patients treated by surgery only. Patients with mucinous adenocarcinoma have significantly poorer survival compared with those with other phenotypes ($P = 0.0252$). (B) OE02 trial patients treated by neoadjuvant chemotherapy plus surgery. There is no survival difference between patients with mucinous adenocarcinoma and those with other phenotypes ($P = 0.6602$).

3.3.1. Relationship between mucinous phenotype and clinicopathological characteristics

Patients with $OeAC_{mucin}$ showed more frequently a better primary tumour regression than $OeAC_{non\text{-}mucin}$ ($P < 0.001$; see Table 1). No other significant relationships were found between mucinous phenotype and clinicopathological variables (see Table 1).

3.3.2. Relationship between mucinous phenotype and overall survival

Patients with $OeAC_{mucin}$ had a similar 5-year OS compared with patients with $OeAC_{non\text{-}mucin}$ (HR: 0.785, 95% CI: 0.550–1.121, $P = 0.1807$; Fig. 3A). However, visual inspection of the survival curves suggested that the relationship between mucinous phenotype and survival differs before and after a follow-up time of approximately 1.5 years. As the Kaplan–Meier analysis failed the assumption of proportional hazards, a piecewise analysis was carried out. This analysis confirmed that after 1.5 years of follow-up, the survival of patients with $OeAC_{mucin}$ is better compared with patients with $OeAC_{non\text{-}mucin}$ (before 1.5 years HR: 0.624, 95% CI: 0.385–1.012; after 1.5 years HR 0.526, 95% CI 0.300–0.922). There was no significant difference in 5-year OS comparing patients with $OeAC_{mucin}$ versus patients with $OeAC_{non\text{-}mucin}$ within treatment arms (Fig. 3B and C).

4. Discussion

Adenocarcinoma where more than 50% of the tumour consists of extracellular mucin is a relatively rare subtype of adenocarcinomas in the gastrointestinal tract and is usually classified as 'mucinous' adenocarcinoma. Mucinous adenocarcinoma needs to be distinguished from signet ring cell adenocarcinoma with intracellularly localised mucin. The literature on the incidence, survival and potential response to cytotoxic chemotherapy of oesophageal cancer (OeAC) patients with mucinous adenocarcinoma ($OeAC_{mucin}$) is currently very limited.

Based on clinical experience, we hypothesised that patients with $OeAC_{mucin}$ do not benefit from neoadjuvant chemotherapy. We classified the histological phenotype in resection specimens from a test cohort (OE02 trial patients with OeAC treated either with surgery alone or neoadjuvant chemotherapy followed by surgery [14]) and confirmed that $OeAC_{mucin}$ is also rare in OeAC with a similar frequency as reported in gastric and colorectal adenocarcinoma (CRC) [20,21]. In the test cohort, patients with $OeAC_{mucin}$ had poorer survival compared with patients with $OeAC_{non\text{-}mucin}$ when treated by surgery alone. In contrast to our hypothesis, neoadjuvant treatment with cisplatin/5-FU improved OS of patients with $OeAC_{mucin}$ up to the level of OeAC patients with $OeAC_{non\text{-}mucin}$. We validated this finding in a second independent validation cohort (OE05 trial [18]) and could confirm that OS was similar between patients with $OeAC_{mucin}$ and those with $OeAC_{non\text{-}mucin}$. There was a suggestion in the validation cohort that survival of patients with $OeAC_{mucin}$ might even be better after 1.5 years of follow-up. However, this finding needs to be viewed with some caution, as there is currently no obvious explanation for the change in survival at the 1.5 years timepoint.

To the best of our knowledge, there are no previous studies investigating the effect of neoadjuvant chemotherapy in OeAC patients stratifying patients by this specific adenocarcinoma subtype where more than 50% of the tumour consists of extracellular mucin.

In contrast to our findings in neoadjuvant chemotherapy–treated $OeAC_{mucin}$, the survival of patients with mucinous colorectal adenocarcinoma seemed to be poorer after neoadjuvant treatment [2–8]. However,

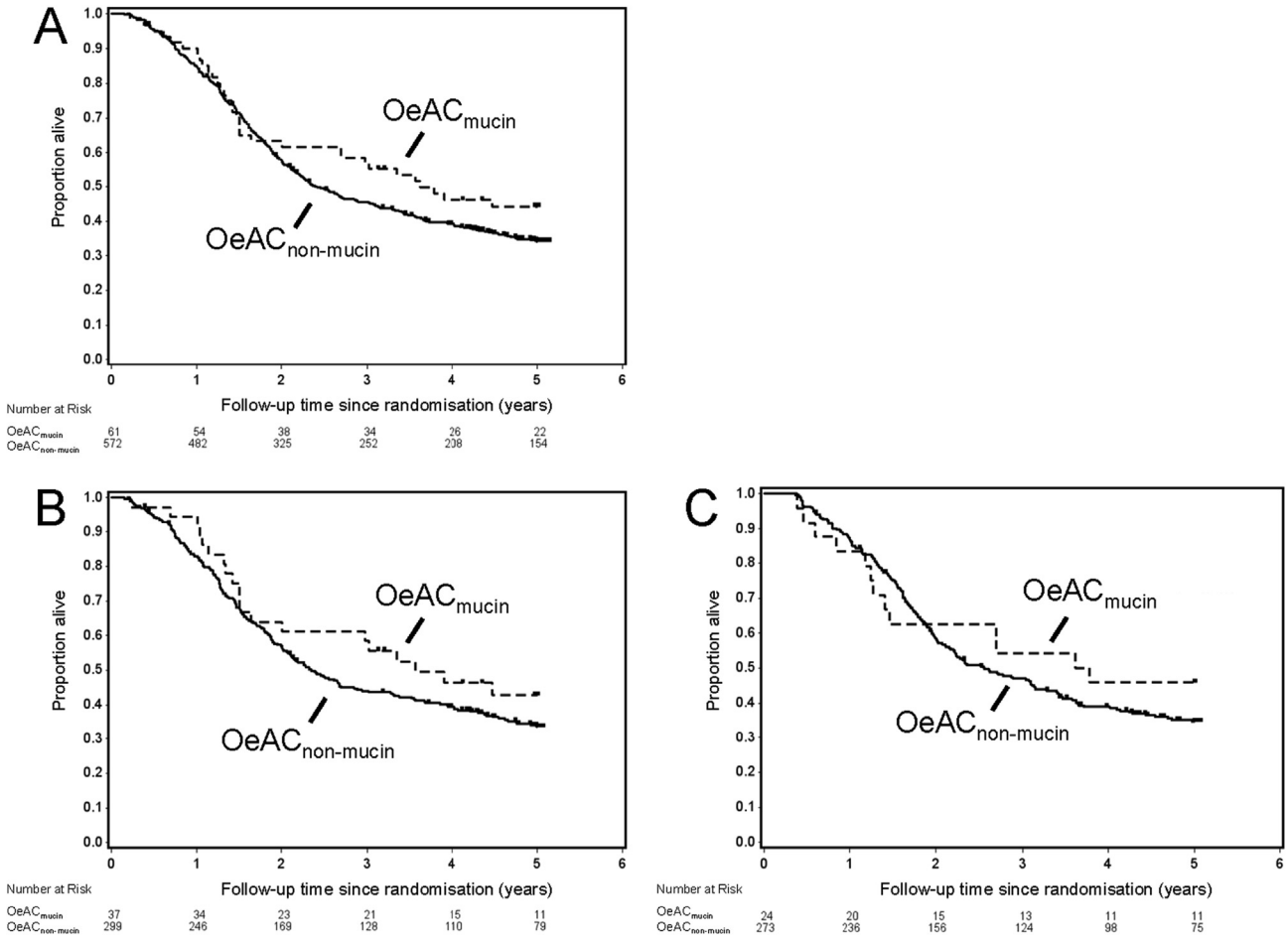

Fig. 3. Kaplan–Meier plots showing 5-year overall survival stratifying patients by histological phenotype in the OE05 trial cohort. (A) All OE05 trial patients treated with neoadjuvant chemotherapy plus surgery. Comparing survival between patients with mucinous adenocarcinoma and those with other phenotypes over the whole time period shows no significant survival difference (HR: 0.785, 95% CI: 0.550–1.121, $P = 0.1807$). (B) OE05 trial patients treated with neoadjuvant cisplatin/5-FU chemotherapy plus surgery. Comparing survival between patients with mucinous adenocarcinoma and those with other phenotypes over the whole time period shows no significant survival difference (HR: 0.768, 95% CI: 0.485–1.217, $P = 0.2587$). (C) OE05 trial patients treated with neoadjuvant epirubicin/cisplatin/capecitabine chemotherapy plus surgery. Comparing survival between patients with mucinous adenocarcinoma and those with other phenotypes over the whole time period shows no significant survival difference (HR: 0.804, 95% CI: 0.457–1.413, $P = 0.4469$).

these findings are not directly comparable, as CRC patients were treated with adjuvant chemotherapy and neoadjuvant treatment for rectal cancers consisted of a combination of radiotherapy and chemotherapy.

For CRC, it has been proposed that differences in gene expression and metabolism between colorectal adenocarcinoma with and without extracellular mucin may explain the chemotherapy resistance in adenocarcinoma with extracellular mucin [22,23]. Another study suggested that specific mucins may play a role in the ability of tumour cells to escape the effect of systemic therapy [2]. Whether similar or different mechanisms may be involved in the beneficial neoadjuvant chemotherapy effect in oesophageal mucinous adenocarcinoma is currently unknown.

Our study has some limitations. Although we studied two large cohorts of OeAC using material from two phase III randomised trials in a test-validation cohort approach, the still relatively low number of patients with OeAC$_{mucin}$ did not allow subgroup analyses to better understand the findings. Whilst, at least in part, the material was collected prospectively, the present study was a post-hoc retrospective study. Because of small numbers, we also decided to exclude all complete responders, which might have influenced our results. The histological phenotypes were classified on post-chemotherapy resection specimens as the assessment of whether a tumour consists of more than 50% extracellular mucin may be difficult if not impossible on diagnostic (pre-treatment) endoscopic biopsies. Although we did not classify matched diagnostic biopsies in the present study, a relatively high concordance between mucinous phenotype in the preoperative biopsies and the resection specimens has been suggested by other investigators [12]. It is difficult to compare our results with any of the very few published OeAC studies as

investigators seem to classify all adenocarcinomas with mucin irrespective of whether the mucin is located intracellularly or extracellularly as 'mucinous adenocarcinoma'. Based on our results, strict adherence to the WHO classification of mucinous adenocarcinoma is recommended to increase the evidence base.

In summary, mucinous adenocarcinoma is a relatively rare subtype of oesophageal adenocarcinoma, which has not attracted much clinical attention to date. The poor survival of patients with locally advanced, resectable oesophageal adenocarcinoma with extracellular mucin (mucinous adenocarcinoma) can be improved by cytotoxic neoadjuvant chemotherapy before surgery. However, whether the beneficial effect of neoadjuvant chemotherapy is related to potential biological, biochemical, and pharmacokinetic interactions of the extracellular mucin with the chemotherapy is currently unclear and warrants further studies.

Authors' contributions

D.L. and N.S. contributed to classification of cohorts, analysis and interpretation of data, creating tables and figures, literature review, and writing the article. J.E. contributed to statistical analysis and data interpretation. Y.S. and L.N.S. contributed to classification of cohorts and data acquisition; G.H., M.N., R.E.L., D.C., and W.A. contributed to data acquisition and interpretation. R.L. contributed to data acquisition and interpretation, supervision, and writing the article. H.G. contributed to study design, data acquisition and interpretation, supervision, and writing the article.

Funding

The material collection was funded by Cancer Research UK (PI: HIG, grant ward C26441/A8944; C26441/A16251).

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D.C. has received grant funding from MedImmune, Clovis, Eli Lilly, 4SC, Bayer, Celgene, Leap and Roche not related to the present study. H.I.G. received honoraria from AstraZeneca and Bristol-Myers Squibb not related to the study. Others declare no conflict of interests.

Acknowledgements

The authors would like to thank following centres for providing the material for this study: Aberdeen Royal Infirmary, Academisch Ziekenhuis Leiden (NL), Addenbrooke's Hospital Cambridge, Aintree Hospital Liverpool, Airedale General Hospital Steeton, Belfast City Hospital, Birmingham Heartlands Hospital, Bradford Royal Infirmary, Bristol Royal Infirmary, Castle Hill Hospital Cottingham, Cheltenham General Hospital, Clatterbridge Cancer Centre Birkenhead, Cookridge Hospital Leeds, Derriford Hospital Plymouth, Doncaster Royal Infirmary, Essex County Hospital, Aintree University Hospital Fazakerley, Frenchay Hospital, Glasgow Royal Infirmary, Gloucestershire Royal Hospital Gloucester, University Hospital Hairmyres East Kilbride, Leeds General Infirmary, Liverpool Heart and Chest Hospital, Middlesbrough General Hospital, Morriston Hospital Cwmrhydyceirw, Norfolk and Norwich University Hospital, Northern General Hospital Sheffield, Poole Hospital, Queen Elizabeth Hospital Birmingham, Raigmore Hospital Inverness, Royal Hallamshire Hospital Sheffield, Royal South Hants Hospital Southampton, Royal Victoria Hospital Belfast, South Cleveland Hospital Middlesbrough, St George's Hospital London, Western Infirmary Glasgow, Wythenshawe Hospital. D. Cunningham is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Trust and The Institute of Cancer Research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.04.026.

References

[1] Simha V, Kapoor R, Gupta R, Bahl A, Nada R. Mucinous adenocarcinoma of the rectum: a poor candidate for neo-adjuvant chemoradiation? J Gastrointest Oncol 2014;5:276–9.
[2] Mekenkamp LJ, Heesterbeek KJ, Koopman M, Tol J, Teerenstra S, Venderbosch S, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. Eur J Cancer 2012;48:501–9.
[3] McCawley N, Clancy C, O'Neill BD, Deasy J, McNamara DA, Burke JP. Mucinous rectal adenocarcinoma is associated with a poor response to neoadjuvant chemoradiotherapy: a Systematic review and Meta-analysis. Dis Colon Rectum 2016;59:1200–8.
[4] Hosseini S, Nguyen N, Mohammadianpanah M, Mirzaei S, Bananzadeh AM. Predictive significance of mucinous histology on pathologic complete response rate following capecitabine-Based neoadjuvant chemoradiation in rectal cancer: a Comparative study. J Gastrointest Cancer 2019;50:716–22.
[5] Vernmark K, Sun XF, Holmqvist A. Mucinous and non-mucinous rectal adenocarcinoma-differences in treatment response to preoperative radiotherapy. J Pers Med 2020;10.
[6] Shin US, Yu CS, Kim JH, Kim TW, Lim SB, Yoon SN, et al. Mucinous rectal cancer: effectiveness of preoperative chemoradiotherapy and prognosis. Ann Surg Oncol 2011;18:2232–9.
[7] Catalano V, Bergamo F, Cremolini C, Vincenzi B, Negri F, Giordani P, et al. Clinical impact of first-line bevacizumab plus chemotherapy in metastatic colorectal cancer of mucinous histology: a multicenter, retrospective analysis on 685 patients. J Cancer Res Clin Oncol 2020;146:493–501.
[8] Catalano V, Loupakis F, Graziano F, Bisonni R, Torresi U, Vincenzi B, et al. Prognosis of mucinous histology for patients

with radically resected stage II and III colon cancer. Ann Oncol 2012;23:135–41.
[9] Wang Q, Zhong J, Huang Q, Chen Z, Wei J, Wei F, et al. A survival comparison of gastric mucin-producing adenocarcinoma to conventional adenocarcinoma: a SEER database analysis. BMC Cancer 2021;21:1138.
[10] Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182–8.
[11] Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50–7.
[12] Chirieac LR, Swisher SG, Correa AM, Ajani JA, Komaki RR, Rashid A, et al. Signet-ring cell or mucinous histology after preoperative chemoradiation and survival in patients with esophageal or esophagogastric junction adenocarcinoma. Clin Cancer Res 2005;11:2229–36.
[13] Hornick JL, Farraye FA, Odze RD. Prevalence and significance of prominent mucin pools in the esophagus post neoadjuvant chemoradiotherapy for Barrett's-associated adenocarcinoma. Am J Surg Pathol 2006;30:28–35.
[14] Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–7.
[15] Medical Research Council Oesophageal Cancer Working G. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002; 359:1727–33.
[16] TNM classification of Malignant tumours (UICC). 6th ed. 2002.
[17] The Royal College of Pathologists L, Uk: RCPath. Dataset for the histopathological reporting of oesophageal and gastric carcinoma. London, UK: RCPath; 2019.
[18] Alderson D, Cunningham D, Nankivell M, Blazeby JM, Griffin SM, Crellin A, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol 2017;18:1249–60.
[19] Lin D, Wei LJ, Ying Z. Checking the Cox model with Cumulative Sums of Martingale-Based Residuals. Biometrika 1993;80:557–72.
[20] Isobe T, Hashimoto K, Kizaki J, Matono S, Murakami N, Kinugasa T, et al. Characteristics and prognosis of mucinous gastric carcinoma. Mol Clin Oncol 2015;3:44–50.
[21] Hugen N, Brown G, Glynne-Jones R, de Wilt JH, Nagtegaal ID. Advances in the care of patients with mucinous colorectal cancer. Nat Rev Clin Oncol 2016;13:361–9.
[22] O'Connell E, Reynolds IS, McNamara DA, Burke JP, Prehn JHM. Resistance to cell Death in mucinous colorectal cancer-A review. Cancers 2021;13.
[23] O'Connell E, Reynolds IS, Salvucci M, McNamara DA, Burke JP, Prehn JHM. Mucinous and non-mucinous colorectal cancers show differential expression of chemotherapy metabolism and resistance genes. Pharmacogenomics J 2021 Aug;21(4):510–9. https://doi.org/10.1038/s41397-021-00229-5 [Epub 2021 Mar 17].