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Original Study

Survival in Advanced Esophagogastric Adenocarcinoma Improves With Use of Multiple Lines of Therapy: Results From an Analysis of More Than 500 Patients

Michael Davidson, Catherine Cafferkey, Emily Frances Goode, Kyriakos Kouvelakis, Daniel Hughes, Pablo Reguera, Eleftheria Kalaitzaki, Clare Peckitt, Sheela Rao, David Watkins, Ian Chau, David Cunningham, Naureen Starling

Abstract

We report on the treatment and survival of 511 patients with advanced esophagogastric adenocarcinoma treated during a 6-year period at a single center. During the period of analysis, the uptake of sequential lines of treatment in the second line and beyond increased, and such an approach was associated with improved survival outcomes.

Background: Although progress has been made in the molecular stratification of esophagogastric adenocarcinoma, the outlook for advanced disease remains poor. The present evaluation of over 500 patients treated at a single European high-volume tertiary center during a 6-year period gives important information on current and developing "real-world" treatment patterns and outcomes. **Results:** The overall survival for the whole cohort was 11.5 months, with a range of treatments used in first-, second-, and third-line settings. Treatment with sequential lines of therapy was associated with better outcomes, although only 39% and 14% of patients subsequently received treatment in the second- and third-line setting, respectively. Treatment within a therapeutic clinical trial was associated with significantly improved survival. **Conclusion:** At present, a substantial proportion of patients with advanced esophagogastric adenocarcinoma will not proceed beyond first-line therapy, and for this group refinement of initial systemic therapies are required to improve outcomes. Although a number of established first- and second-line treatment options are now available, the therapeutic landscape of the disease continues to change, most notably in the application of immunotherapy and increasing interest in establishing evidence-based interventions in the third-line setting and beyond. A small but growing proportion of patients will benefit from sequential treatment approaches incorporating multiple lines of therapy, and improved selection of such patients will be a key challenge for clinicians moving forwards. Data such as these provide an overview of current treatment patterns and outcomes which can be used to inform planning of future research effectively within existing treatment frameworks.

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Keywords: Cancer, Gastric, Chemotherapy, Esophageal, Treatment

Introduction

Esophagogastric (EG) adenocarcinomas represent a challenging health problem globally. Gastric cancer is the fifth most common malignancy worldwide and the third leading cause of cancer mortality.[1] Although the incidence of non—cardia gastric cancers has been decreasing in Western populations, the incidence of distal esophageal and junctional adenocarcinomas has been increasing.[2] Specific to the United Kingdom, this has been reflected by an

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increasing incidence rate of esophageal cancer, which represents the sixth most common cause of cancer death, accounting for 7800 deaths annually.[3] Despite recent advances in both genetic characterization and the development of novel targeted agents, the outlook for patients with advanced disease remains poor, with a median overall survival (OS) not extending beyond 12 months in most trials. The treatment paradigms for esophageal and junctional adenocarcinomas compared with gastric cancer in the early disease setting are diverging. However, in the advanced setting, these cancers are still generally considered together in clinical trial populations, and the treatment approaches have been similar.[4-7] The evidence base is well-established for both first- and second-line chemotherapy. The standard reference regimens in the first-line setting consist of a fluoropyrimidine combined with a platinum agent, with the possible addition of either an anthracycline or a taxane.[8-10] Randomized studies of irinotecan, docetaxel, and paclitaxel have all demonstrated a survival advantage compared with best supportive care alone in the second-line setting.[11-13] A benefit has been shown in the first-line setting for the ~20% of *HER2*-amplified cancers through the use of trastuzumab plus chemotherapy. Also, the anti-*VEGFR2* monoclonal antibody ramucirumab has been established both as monotherapy and in combination with paclitaxel in the second-line setting, although it did not show a survival benefit when combined with chemotherapy in the first-line setting.[14-17] Further trials of molecularly targeted agents have proved disappointing, with trials targeting dual-*HER2*, *EGFR*, *MET*, *P13K/mTOR*, and *PARP* inhibition all yielding negative results. Data are now starting to emerge for treatment beyond the second line, with meta-analyses suggesting a modest survival benefit.[18,19] The ATTRACTION-2 study has confirmed the effectiveness of *PD-1* targeting in this context, and it is expected that further agents under investigation will also become available.[20,21] Administration of later lines of therapy is clinically challenging as cancer and chemotherapy-related symptoms often precipitate a deterioration in clinical status, limiting patient tolerance to further treatment. The margins of benefit appear greater for fitter patients and thus consideration of patient suitability and the toxicities of the planned treatment regimen are paramount.[22] A number of groups have reported their institutional experience of advanced EG cancer management, although the included patient numbers have generally been small.[23-25] The colorectal cancer treatment paradigm has been instructive as an exemplar of rational sequencing of multiple lines of therapy to incrementally improve survival outcomes in the advanced disease setting. As the treatment landscape for EG cancer continues to evolve, it can be expected that a greater proportion of patients will subsequently receive sequential lines of therapy and that targeted and immunotherapeutic agents will be increasingly used. At present it is a challenge for clinicians to select patients and rationally sequence available treatment regimens in such a way as to provide optimal benefit. In order to both guide treatment decisions and plan relevant clinical trials in the field it is important to understand current treatment patterns and outcomes in "real world"patient populations.

Materials and Methods

A retrospective analysis was undertaken of consecutively treated patients who had received ≥ 1 cycle of chemotherapy for EG adenocarcinoma in the advanced disease setting at the Royal Marsden Hospital from April 2009 to November 2015. Potential patients were identified through the use of hospital diagnostic coding. Data were collected by review of the electronic patient medical records. The demographic data, treatment, response, and survival outcomes were recorded. Radiologic responses were recorded for each treatment line at the first response assessment point, on completion of treatment, and at any subsequent progression assessment point. Statistical analysis was performed using Stata 13 statistical software.

This retrospective study did not require patient consent to participate. A study protocol outlining the rationale, methods and statistical analysis plan was approved by an internal Committee for Clinical Research prior to commencement and is available on request.

Results

Demographic Data

A total of 511 patients were identified, of whom 384 (75%) were men and 127 (25%) were women. The median age at diagnosis was 66 years (range, 24-90 years). The performance status of patients at cycle 1 of first-line treatment was Eastern Cooperative Oncology

Table 1 Patient Characteristics

Characteristic	n (%)
Total patients	511 (100)
Sex	
Male	384 (75)
Female	127 (25)
Age at diagnosis, y	
Median	66
Range	24-90
ECOG PS	
0	64 (13)
1	276 (54)
2	87 (17)
3	1
Not recorded	83 (16)
Site of primary tumor	
Esophagus	148 (29)
EGJ	173 (34)
Stomach	190 (37)
Disease extent at beginning of first-line treatment	
Locally advanced (unresectable)	68 (13)
De novo metastatic	335 (66)
Relapsed metastatic after radical treatment	108 (21)
HER2 status	
Positive	73 (14)
Negative	296 (58)
Not recorded	142 (28)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGJ = esophagogastric junction; PS = performance status.

Group performance status 0 in 64 (13%), 1 in 276 (54%), 2 in 87 (17%), 3 in 1, and not recorded in 83 patients (16%). The site of the primary tumor was the esophagus in 148 patients (29%), esophagogastric junction in 173 (34%), and stomach in 90 patients (37%). The disease extent at the beginning of first-line treatment was locally advanced (unresectable) in 68 (13%), de novo metastatic disease at presentation in 335 (66%), and relapsed metastatic disease after previous radical treatment in 108 (21%) patients. *HER2* status was positive in 73 (14%), negative in 296 (58%), and not recorded in 142 (28%) patients. The patient characteristics are summarized in Table 1.

Treatment

In the first-line treatment setting, 320 patients (63%) received a triplet chemotherapy regimen. These were predominantly platinum/fluoropyrimidine doublets with the addition of either trastuzumab or an anthracycline. Of the 511 patients, 171 (33%) received doublet therapy, predominantly a platinum/fluoropyrimidine doublet, and 20 (4%) received single-agent treatment. Of the 511 patients, 200 (39%) subsequently received second-line treatment. Of these 200 patients, 24 (12%), 68 (34%), and 108 (54%) received triplet-, doublet-, or single-agent treatment, respectively. Of the 511 patients, 71 (14%) subsequently received third-line treatment. Of these 71 patients, 2 (3%), 26 (37%), and 42 (60%) received triplet-, doublet-, or single-agent therapy, respectively. Of the patients treated in the first-line setting, 20% participated in a clinical trial compared with 29% and 36% of those receiving second- and third-line treatment, respectively. Clinical trials in the first-line setting predominantly involved standard chemotherapy with the addition of a targeted agent, such as REAL-3 (EOX [epirubicin, oxaliplatin, capecitabine] with or without panitumumab; 60 participants), RILOMET (ECX [epirubicin, cisplatin, capecitabine] with or without rilotumumab; 12 participants), and JAGUAR (FOLFOX [folinic acid, 5-fluorouracil, oxaliplatin] with or without ipatasertib; 9 participants). The most common trials in the third-line setting were phase I trials (9 participants). The combinations of chemotherapy received and a breakdown of the clinical trials of first-, second-, and third-line therapy are shown in Figure 1.

An increase in the proportion of patients continuing to second-line therapy was observed during the study period. In the first quarter of the study period, 45 of 136 patients (33%) proceeded to second-line therapy. In contrast, in the fourth quarter of the study period, 63 of 135 patients (47%) had proceeded to second-line therapy (Figure 2). The uptake of *HER2* testing over time also increased, with 74% of cases before April 2010 not reported compared with no cases from April 2015 onward (Table 2).

Response

In the first-line setting, the overall best response was complete response in 2%, partial response (PR) in 47%, stable disease (SD) in 29%, and progressive disease (PD) in 22% (Table 3). The overall response rates in the first line were similar between patients with and without confirmed *HER2*$^{+}$ and *HER2*$^{-}$ disease (48% vs. 49%). In the second-line setting, the overall best response was a PR in 21%, SD in 34%, and PD in 45%. In the third-line setting, the best overall response was a PR in 19%, SD in 24%, and PD in 57%.

Figure 1 (A) Breakdown of Treatments Received in First-Line Setting (n = 511). *Including Raltitrexed-Based Regimens and Capecitabine Monotherapy; †Clinical Trials in First Line Included REAL 3 (EOX [Epirubicin, Oxaliplatin, Capecitabine] With or Without Panitumumab; n = 60), RILOMET 1 (ECX [Epirubicin, Cisplatin, Capecitabine] With or Without Rilotumumab; n = 12), JAGUAR (FOLFOX [Folinic Acid, 5-Fluorouracil, Oxaliplatin] With or Without Ipatasertib; n = 9), MET MAB (FOLFOX With or Without Onartuzumab; n = 8), PLATFORM (Randomized Maintenance; n = 6), BRIGHTER (Paclitaxel With or Without Napabucasin; n = 2), and RAINFALL (CX [Cisplatin, Capecitabine] With or Without Ramucirumab; n = 2). (B) Breakdown of Treatments Received in the Second-Line Setting (n = 200). *Included Trastuzumab, Raltitrexed, Irinotecan, and Docetaxel-Based Regimens; †Clinical Trials in the Second Line Included BRIGHTER (Paclitaxel With or Without Napabucasin; n = 11), MK3475 (Paclitaxel vs. Pembrolizumab; n = 5), IMCLONE (Ramucirumab vs. Placebo; n = 5), PEP0206 (Liposomal Irinotecan vs. Irinotecan vs. Docetaxel; n = 5), RAINBOW (Paclitaxel With or Without Ramucirumab; n = 4), and COUGAR (Docetaxel vs. Best Supportive Care BSC; n = 4). (C) Breakdown of Treatments Received in Third-Line Setting (n = 70). *Included Docetaxel and Irinotecan Monotherapy. †Clinical Trials in Third Line Included Phase I Trials (Drug Development Unit; n = 9), JVDF (Ramucirumab Plus Pembrolizumab; n = 4), CHECKMATE 032 (Nivolumab vs. Nivolumab Plus Ipilimumab; n = 3), COG (Gefitinib vs. Placebo; n = 2), and Fibroblast Growth Factor Receptor (AZD4547; n = 2)

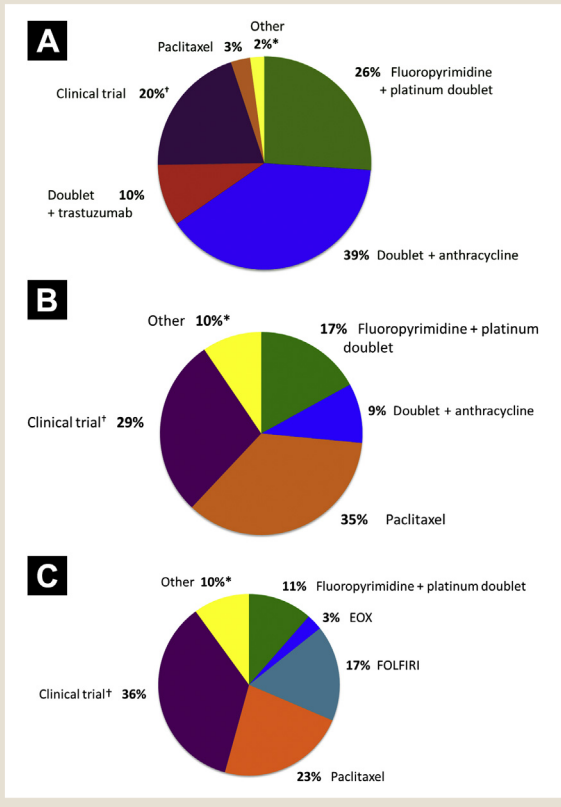
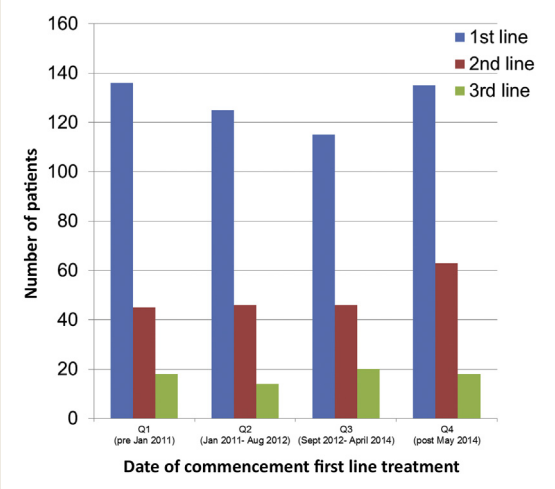


Figure 2 Changes in Uptake of Sequential Treatment Over Time



Survival

The median OS for the whole cohort from the date of diagnosis of advanced disease was 11.5 months (Figure 3A). OS from the beginning of second- and third-line treatment were 6.0 and 4.6 months, respectively (Figure 3B, C). Survival correlated significantly with the number of treatment lines received ($P < .001$; Figure 3D), with a median OS from diagnosis of 8.3, 14.0, 20.1, and 33.0 months for patients receiving 1, 2, 3, or > 3 lines of treatment, respectively. Progression-free survival (PFS) from the initiation of first-, second-, and third-line treatment was 5.5, 3.0, and 1.9 months, respectively (Table 3). No significant difference was found in OS in the advanced setting between patients with relapsed disease after previous radical treatment and those with metastatic disease at diagnosis (12.6 vs. 11.3 months; $P = .10$). PFS with first-line treatment was similar between patients with confirmed *HER2*$^+$ and *HER2*$^-$ disease (5.6 vs. 5.5 months; $P = .11$), although OS was significantly improved for the *HER2*$^+$ patients (15.0 vs. 11.9 months; $P = .02$; Figure 3E). OS was also significantly improved for those patients treated within a therapeutic clinical trial at any line of treatment compared with those who were not (13.5 vs. 10.1 months; $P = .02$).

Table 2 Changes in Uptake of HER2 Testing Over Time

Year of Treatment	HER2 Status		
	Positive	Negative	Not Documented
Before April 2010	8	23	89
April 2010 to March 2011	6	29	34
April 2011 to March 12	11	52	13
April 2012 to March 13	14	56	2
April 2013 to March 14	13	44	3
April 2014 to March 15	15	61	1
April 2015 onward	6	31	0
Total	73	296	142

Discussion

The present comprehensive analysis of treatment and survival for advanced EG adenocarcinoma patients treated within a large volume tertiary referral center in the United Kingdom reflects both the current landscape and developing trends in treatment. The patient population of predominantly men (75%), with a median age of 66 years is typical of the demographics for this disease. Unlike most of the large trial populations, however, the performance status distribution showed that 17% of patients had a recorded performance status of > 2 at baseline and would have typically been excluded from most clinical trials. A platinum doublet with or without an additional third drug was most commonly used in the first line, and single-agent paclitaxel in the second line; however, a substantial proportion of second-line patients were treated with doublet or triplet combination therapies. Most of these cases represented rechallenges of a regimen that had previously been efficacious. This reflects what is often seen in day-to-day practice, in which a few patients maintain sensitivity to platinum/fluoropyrimidine combinations and thus benefit from multiple rechallenges. Emerging data from the field of colorectal cancer have shown the utility of using sequential circulating tumor DNA analysis to investigate dynamic mechanisms of sensitivity and resistance during therapy.[26] Whether such approaches have a role in EG cancer in identifying patients with more intrinsically chemotherapy-sensitive disease suitable for multiple lines of therapy remains an ongoing research question.

Participation in clinical trials was high, with 20%, 29%, and 36% of patients participating in first-, second-, and third-line trials, respectively. This exceeded the reported 14% rate of trial participation in the United Kingdom as a whole, which, in itself, has been purported to exceed that of other countries, with as few as 3% of US cancer patients participating in clinical trials.[27,28] The increase in the use of subsequent lines of treatment reflects the accumulating level-1 evidence base during the study period. Many of the major second-line gastric cancer studies were reported from 2011 to 2014, giving clinicians a greater selection of evidence-based options for later line treatment. Similarly, *HER2* testing trends changed considerably during the analysis period. This coincided with both the landmark ToGA trial results and the funding of trastuzumab in the United Kingdom for *HER2*$^+$ gastric cancer patients, which was approved in November 2010. Before November 2010, 24% of patients beginning first-line treatment underwent *HER2* testing of their tumor. In contrast, after 2010, 89% underwent testing.

The overall response rates were comparable with the reported trial data; however, a significant proportion of patients did not maintain a response for the duration of their treatment. Of the 349 patients with SD or better at the scan assessment of their initial response during first-line therapy, 119 (34%) had documented radiologic PD by the end of treatment and 38 (11%) did not undergo further scanning because of unacceptable toxicity, clinical progression, or death curtailing treatment completion. Thus, although the initial disease control rates have been reasonable, they have often been followed by rapid radiologic progression or clinical deterioration during the same treatment line. Interest is increasing in using maintenance therapies for EG cancer, with a number of ongoing

Table 3 Variables Stratified by Treatment Line

Variable	First Line	Second Line	Third Line	> 3 Lines
Patients, n (%)	511 (100)	200 (39)	70 (14)	15 (3)
Treatment, %				
Triplet	63	12	3	0
Doublet	33	34	37	0
Single	4	54	60	0
Clinical trial participation, n (%)	103 (20)	57 (29)	25 (36)	5 (33)
Median cycles, n	6	3	3	NA
Overall best response, %				
CR	2	0	0	0
PR	47	20	19	0
SD	29	34	24	0
PD	22	41	57	0
PFS, mo	5.5	3.0	1.8	
OS, mo				
Whole cohort	11.5			
According to treatment line received	8.3 (first line only)	14.0 (first and second line)	20.1 (first to third line)	33.0 (>3 lines)

Abbreviations: CR = complete response; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

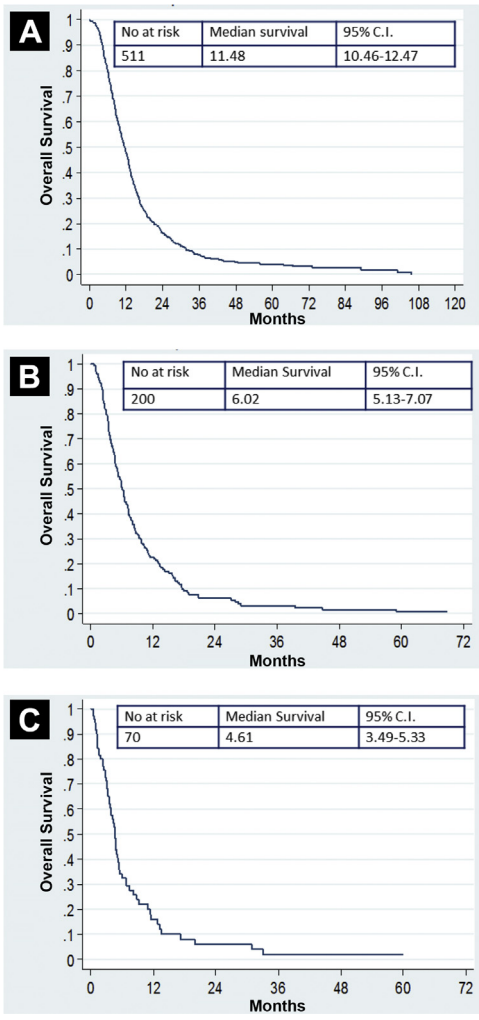
trials using de-escalated chemotherapy or targeted or immunotherapeutic agents to augment and maintain the response to first-line chemotherapy.[29,30] Given that the disease control rates decrease substantially during the course of chemotherapy, this presents a challenge to researchers investigating such maintenance strategies.

The median OS and PFS were also similar to those reported in landmark trials of predominantly European patient populations. However, the OS of 15.0 months for *HER2*$^+$ patients was longer than the 13.8 months reported in the ToGA trial and also exceeded that of the chemotherapy plus trastuzumab arm of the recently presented JACOB study (14.2 months).[31] The present real world population differed from the populations in these trials in that 73% of confirmed *HER2*$^+$ patients received trastuzumab in the first line, with another 15% receiving it later in their treatment course. This seemingly more efficacious *HER2* targeting may have occurred because the UK National Institute for Health and Care Excellence guidelines allow funding for trastuzumab only for patients who display HER2 immunohistochemistry 3+ staining, a subgroup shown in a ToGA subgroup analysis to have superior survival times. More recent studies have investigated the relationship between *HER2* gene amplification and clinical benefit from trastuzumab.[32,33] These studies showed that the level of *HER2* amplification significantly predicts for sensitivity to therapy, and that the optimal *HER2* amplification ratio predicting for trastuzumab benefit is likely to be considerably greater than the currently mandated definitions of positivity.[32,33] Further refinement of biomarker selection could be necessary to optimize the benefit for this group of patients in the future.

As expected, survival correlated significantly with the number of treatment lines received. An obvious selection bias was present, as patients suitable for sequential treatment are likely to represent a self-selecting fitter group. Also, underlying tumor-biologic factors could render them more sensitive to existing chemotherapy regimens, with the selection of patients suitable for such sequential treatment becoming a more relevant clinical challenge. Previous attempts have been made to define relevant prognostic factors in advanced EG cancer, with ongoing work seeking to identify genetic signatures predictive of the response to both standard chemotherapy agents and immunotherapeutic agents.[34-36] The 70 patients who received third-line or beyond treatment in our cohort were slightly younger (median age, 55 years) and had had a longer PFS with first- and second-line treatment (9.3 and 4.2 months, respectively) compared with the cohort as a whole, factors that have previously been associated with a favorable response to third-line treatment.[37,38] Only 39% of the overall cohort subsequently received second-line therapy. Even within a modern clinical trial, such as the 2018 RAINFALL study, the rate of second-line treatment uptake reached only 51%,[17] underlining the importance of improving first-line interventions for patients who will often only have 1 opportunity to receive systemic therapy. The improved survival for the patients who subsequently received further lines of treatment highlights the positive effect sequential lines of therapy can have for carefully selected patients and should encourage physicians to pursue this approach where appropriate.

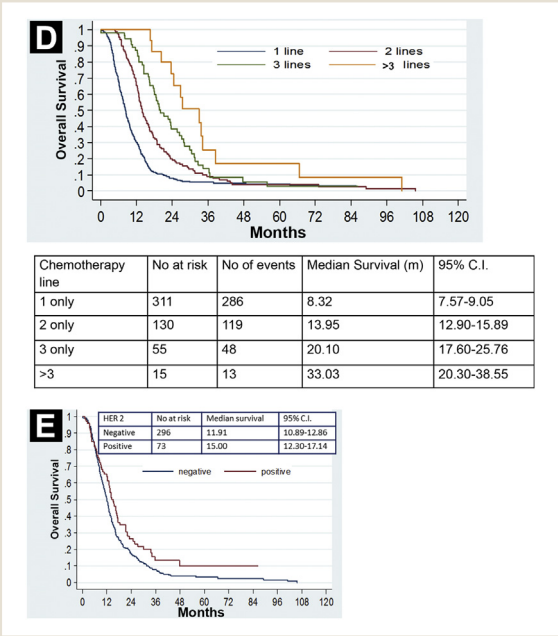
Known variations in treatment and outcome exist in advanced EG cancer globally, with greater uptake of sequential lines of therapy and improved survival in East Asian compared with European populations. Analyses of the treatment patterns in non–trial East Asian populations have reported rates of uptake of second-line chemotherapy ranging from 54% to as great as 80%, and such disparities have important implications for research in the field.[23,24,39] Subgroup analysis of the RAINBOW trial evaluating second-line paclitaxel with or without ramucirumab revealed only a nonsignificant OS benefit for ramucirumab in East Asian patients, despite significant improvements in both relapse rate and PFS.[40] This was likely to be as a result of substantially greater uptake of postprogression treatment lines in this patient group. Thus, the effect of differential uptake of further treatment must be considered when interpreting the survival outcomes in first- and

Figure 3 (A) Overall Survival for Whole Cohort. (B) Overall Survival From Beginning Second-Line Therapy. (C) Overall Survival From Beginning Third-Line Therapy. (D) Overall Survival Stratified by Number of Treatment Lines Received. (E) Overall Survival Stratified by HER2 Status



Abbreviation: CI = confidence interval.

Figure 3 Continued.



Chemotherapy line	No at risk	No of events	Median Survival (m)	95% C.I.
1 only	311	286	8.32	7.57-9.05
2 only	130	119	13.95	12.90-15.89
3 only	55	48	20.10	17.60-25.76
>3	15	13	33.03	20.30-38.55

second-line trials involving both Eastern and Western patient cohorts.[41] The recent ATTRACTION-2 study was performed in East Asian centers only and demonstrated a survival benefit for nivolumab versus best supportive care in the third-line setting, although whether such results are transferable to primarily European populations is as yet unknown.[20] Cancer Genome Atlas data suggested no differences in the distribution of their proposed molecular subtypes between East Asian and Western patients; however, a further study has shown differential expression of genes related to inflammation and immunity between the 2 geographic groups.[42,43] In that analysis, tumors from non-Asian patients were enriched for immune T-cell markers, and tumors from Asian patients were enriched for immunosuppressive T-cell regulatory markers.[43] Such distinct tumor immunity signatures related to T-cell function could affect the immunotherapy response between the 2 geographic groups and emerging data from ongoing global immunotherapy studies should be considered with this in mind. In addition to intrinsic biologic differences in tumor characteristics potentially influencing response, the patient population of such a "third-line" study performed in a Western population is also likely to be significantly different in terms of comorbidity, fitness, and overall treatment tolerance.

Conclusion

As we move into an era in which immunotherapy and targeted agents become more closely integrated into advanced EG cancer treatment pathways it is hoped further survival improvements will be seen, with multiple lines of therapy exposure using these novel agents becoming more commonplace, especially in European practice in which such sequential treatment approaches remain relatively uncommon. It is important to understand current and evolving trends to tailor ongoing research effectively within existing treatment frameworks. Combining clinical and biologic characteristics to refine prognostic and predictive models could identify patients suitable for more prolonged and rationally sequenced treatments in the advanced disease setting.

Clinical Practice Points

- In recent years, the treatment options for advanced esophagogastric adenocarcinoma have expanded, resulting in incremental improvements in survival.
- The present report has provided a comprehensive overview of current patterns and evolving trends in treatment during recent years.
- Of our patients, 39% and 14% subsequently received second- and third-line treatment, respectively, and the uptake of sequential lines of therapy increased during the study period.

- The patients who received such sequential treatment approaches tended to be younger and to have experienced favorable responses to previous lines of therapy, factors previously been associated with improved outcomes in the third-line setting.
- Enrollment in clinical trials was high, and participation in a clinical trial was associated with improved survival.
- As more treatments become available for the management of advanced esophagogastric cancer, patient selection and rational sequencing of chemotherapy, targeted therapy, and immunotherapy drugs will become increasingly important.
- It is clear that a significant proportion of patients will benefit from a sequenced treatment approach incorporating multiple lines of therapy; thus, identifying and selecting such patients will be paramount.
- This will need to incorporate both disease-related biomarkers of treatment response and patient-related clinical characteristics.
- Data such as these highlight the potential benefits that can be gained by using such sequential treatment approaches and should encourage physicians to pursue these approaches, as appropriate.

Disclosure

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