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European Journal of Cancer 139 (2020) 107–118

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Hospital volume and beyond first-line palliative systemic treatment in metastatic oesophagogastric adenocarcinoma: A population-based study

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Received 4 August 2020; accepted 11 August 2020
Available online 25 September 2020

KEYWORDS
oesophageal neoplasms;
Gastric neoplasms;

Abstract ***Background:*** Beyond first-line palliative systemic treatment can be beneficial to selected oesophagogastric cancer patients, but experience with its administration may be limited and vary among hospitals. In a population-based study, we analysed the association between hospital systemic treatment volume and administration of beyond first-line treatment

Part of this study was presented at the European Society for Medical Oncology (ESMO) Congress 2019, Barcelona, Spain and at ESMO Virtual Congress 2020.

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https://doi.org/10.1016/j.ejca.2020.08.010

Drug therapy;
Palliative treatment

in oesophagogastric adenocarcinoma, as well as the effect on overall survival (OS).
Methods: Synchronous metastatic oesophagogastric adenocarcinoma patients (2010–2017) were selected from the Netherlands Cancer Registry. Hospitals were categorised in volumes quartiles. The association between hospital systemic treatment volume and the use of beyond first-line treatment was assessed using trend and multivariable logistic regression analyses. OS was compared between hospitals with high and low beyond first-line treatment administration and treatment strategies using Kaplan–Meier curves with log-rank test and multivariable Cox proportional hazard regression.
Results: Beyond first-line treatment was administered in 606 of 2,466 patients who received first-line treatment, and increased from 20% to 31% between 2010 and 2017 ($P < 0.001$). The lowest hospital volumes were independently associated with lower beyond first-line treatment administration compared to the highest volume (OR 0.62, 95% CI 0.39–0.99; OR 0.67, 95% CI 0.48–0.95). Median OS was higher in all patients treated in hospitals with a high versus low beyond first-line treatment administration (7.9 versus 6.2 months, $P < 0.001$). Second-line paclitaxel/ramucirumab was administered most frequently and independently associated with longer OS compared to taxane monotherapy (HR 0.74, 95% CI 0.59–0.92).
Conclusion: Higher hospital volume was associated with increased beyond first-line treatment administration in oesophagogastric adenocarcinoma. Second-line paclitaxel/ramucirumab resulted in longer survival compared to taxane monotherapy.

1. Introduction

Life expectancy of patients with metastatic oesophagogastric cancer is poor [1]. Palliative systemic therapy aims to prolong survival while maintaining quality of life [2–5]. Median time from start of first-line systemic treatment to failure was only 4.6 months in a real-world patient cohort [6]. Therefore, beyond first-line, i.e. second and third-line, treatment options are needed.

Single-agent chemotherapy such as irinotecan [7] or a taxane [8,9] have demonstrated activity in second line. A second-line regimen containing the VEGF inhibitor ramucirumab with or without a taxane has shown to have an additional survival benefit when administered for oesophagogastric adenocarcinoma [10,11]. Although trials on third-line treatment are still scarce, increasing evidence confirms this could be beneficial in highly selected patients [12].

Since oesophagogastric cancer has a relatively low incidence, and only a part of patients who receive palliative systemic therapy are eligible for beyond first-line treatment, the experience in its administration of might be limited within individual centers. Therefore, the beyond first-line treatment administration could vary between hospitals. If so, it could be related to the number of patients treated in a hospital, i.e. hospital volume, as this has been observed in the administration of first-line systemic treatment [13] and the probability of undergoing curative treatment [14,15] of oesophagogastric cancer as well.

The effect of hospital volume on the use of beyond first-line treatment has not been described yet. Moreover, the proportion of patients that receives beyond first-line treatment, the type of treatment that is administered, and the outcomes of these patients in clinical practice are unknown. Nationwide real-world data on the use and benefit of beyond first-line treatment in oesophagogastric adenocarcinoma patients could provide valuable information on outcomes of patients who have received these treatments. In this population-based study, we analysed the association between hospital volume and the use of beyond first-line treatment, and the effects of beyond first-line palliative systemic treatment strategies on overall survival (OS) and time to failure of treatment (TTF).

2. Materials and methods

2.1. Data collection

Patients of ≥18 years with an adenocarcinoma of the oesophagus, gastro-oesophageal junction, or stomach ((International Classification of Diseases for Oncology (ICD-O), ICD-O-3: C15 and C16 [16]) with synchronous metastases who received palliative systemic treatment, were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that covers the total Dutch population of more than 17 million people and is directly linked to the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA) [17] that comprises all histologically confirmed cancer diagnoses. Patients were included if diagnosed during 2015–2017, or in a subset of Dutch hospitals during 2010–2014. This subset was selected because of logistic limitations, and regarded as a representative sample of all Dutch hospitals [6]. Two hospitals were excluded, because of missing details on treatment.

Patient, tumour and treatment characteristics were extracted from medical records by specially trained registrars. Human epidermal growth factor receptor 2 (HER2) data were retrieved from PALGA [18]. Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020.

2.2. Systemic treatment

Assumptions regarding systemic treatment are listed in Supplementary Table 1. A systemic treatment line was defined as systemic therapy agents that started within 3 days of each other and were given until suspension, as described earlier [6]. A sequential treatment line was specified as treatment in which an agent of a drug group was administered that was not used in the preceding line, with the exception of trastuzumab and ramucirumab.

The proportion of patients that received beyond first-line treatment was described in all patients, and in those considered eligible for this treatment, i.e. if they survived >90 days after stop of first-line treatment. This time frame was chosen because systemic treatment administration in the last months before death is generally considered undesirable [19,20].

2.3. Hospital volume

Per hospital, the volume of all oesophagogastric adenocarcinoma patients who received systemic treatment in curative setting, or palliative setting for synchronous metastatic disease was calculated. With the aim to reflect current practice, the volume of recent years (2015–2017) was used. Hospitals were categorised

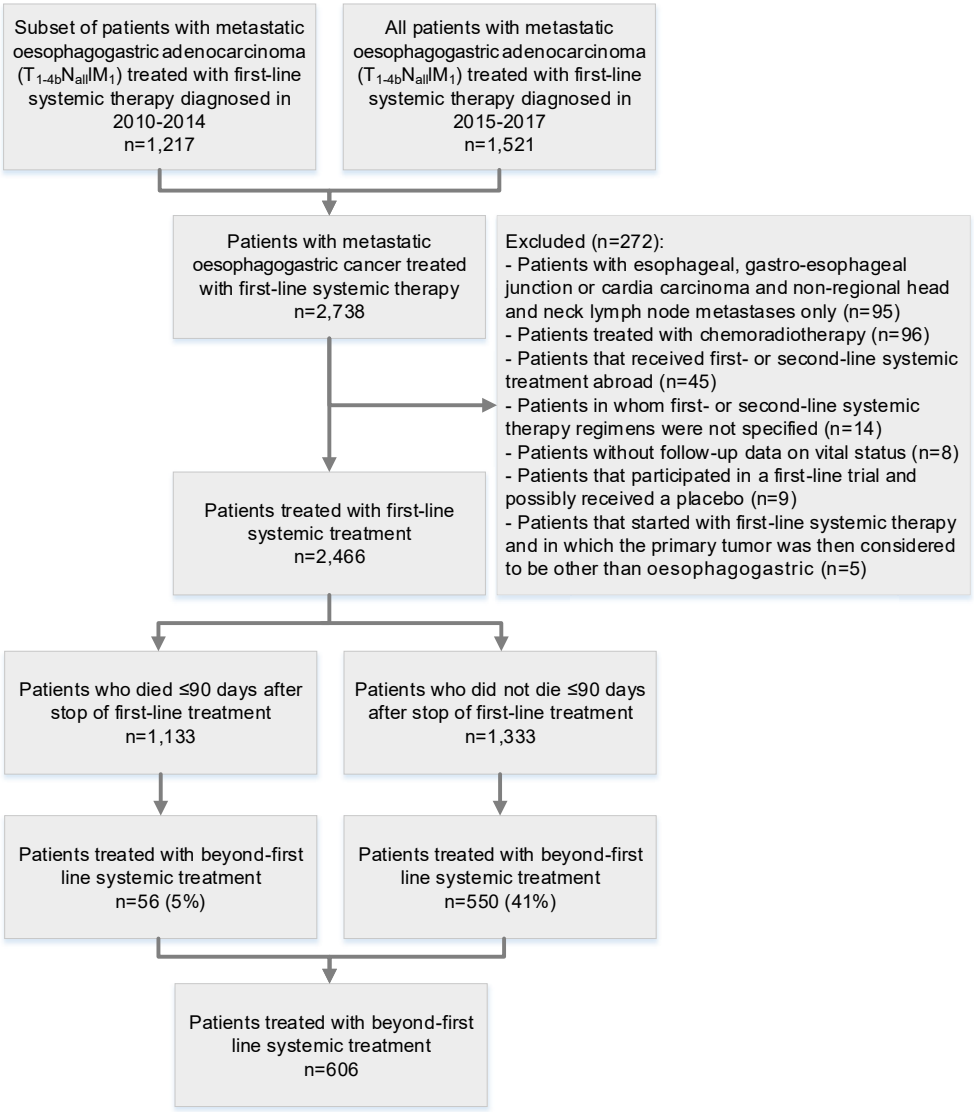

Fig. 1. Patient selection.

into quartiles according to these volumes to compare the proportion of patients that received beyond first-line treatment. Furthermore, hospitals were divided above and below the median proportion of patients that received beyond first-line treatment per hospital, and OS of all patients was compared between these categories.

2.4. Overall survival and time to failure

OS was assessed from start of a treatment line until death or end of follow-up. To take into account all reasons for treatment discontinuation besides progressive disease, we used TTF as a proxy for progression-free survival (Supplementary Table 1). OS and TTF of second-line treatment strategies that were applied in at least 10% of the patients were compared.

2.5. Statistical analysis

Patient and tumour characteristics are displayed with counts and percentages, or medians and interquartile ranges (IQRs). Differences between groups were analysed using chi-squared tests, Fisher's exact tests or Mann–Whitney *U* tests, whichever was appropriate. The association between beyond first-line treatment administration with hospital volume and over time were analysed using the Chi-square and Cochran-Armitage trend test. The association between first-line hospital volume and the probability of receiving beyond first-line treatment was tested using multivariable logistic regression, with adjustment for factors that could be associated with treatment administration. OS/TTF of second-line treatment were analysed with Kaplan–Meier curves and log-rank tests. The association between hospital volume, second-line treatment strategies and OS/TTF were tested using multivariable Cox proportional hazard regression analyses by adjusting for relevant patient and tumour characteristics. P values < 0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

3. Results

3.1. Beyond first-line treatment administration

Of all 2,466 patients who received first-line systemic treatment, second-, third-, fourth- and fifth-line treatment were administered in 25% (n = 606), 4% (n = 107), 1% (n = 19) and 0.1% (n = 3), respectively. Three patients had not finished first-line treatment at end of follow-up. We observed a gradual increase in the administration of beyond first-line treatment between 2010 and 2017 (from 20% to 31%; $P < 0.001$). First-line mono and triplet chemotherapy administration

Table 1
Patient characteristics before start of second-line systemic treatment and details of first-line treatment in patients who received second-line therapy (n = 606).

Characteristics	Patients who received second-line therapy (n = 606) No. (%)
Female	139 (23%)
Age, years, median (IQR)	64 (57, 70)
<60	214 (35%)
60-69	234 (39%)
70-79	146 (24%)
≥80	12 (2%)
Performance status	
0 or 1	300 (49%)
≥2	42 (7%)
Unknown	264 (44%)
Number of comorbidities	
0	381 (63%)
1	155 (26%)
≥2	51 (8%)
Unknown	19 (3%)
Tumour location	
Oesophagus	272 (45%)
Gastro-oesophageal junction or cardia	134 (22%)
Stomach	200 (33%)
Lauren classification	
Intestinal	288 (48%)
Diffuse	123 (20%)
Mixed	19 (3%)
Indeterminate	20 (3%)
Unknown	156 (26%)
HER2 overexpression	
Positive	119 (20%)
Negative	355 (59%)
Unknown	3 (0%)
Not tested	129 (21%)
Metastatic sites	
1	230 (38%)
≥2	376 (62%)
Distant lymph node metastases	280 (46%)
Liver metastases	369 (61%)
Peritoneal metastases	188 (31%)
Lung metastases	151 (25%)
Bone metastases	99 (16%)
Other metastatic sites	108 (18%)
First-line treatment characteristics	
First-line systemic treatment strategy	
Monotherapy	26 (4%)
Doublet chemotherapy	303 (50%)
Triplet chemotherapy	183 (30%)
Trastuzumab-containing regimen	90 (15%)
Non-trastuzumab targeted therapy-containing regimen	4 (1%)
Duration first-line treatment, months, median (IQR)	3.7 (2.3, 6.2)
Unknown	7 (1%)
Reasons discontinuation first-line treatment	
Progressive disease	568 (94%)
Toxicity	18 (3%)
Patient's request	0 (0%)
Other	4 (1%)
Unknown	16 (3%)

decreased in 2015–2018 compared to 2010–2014 (14% to 6% and 44% to 21%, respectively), while the use of first-line doublet and trastuzumab therapy increased (34% to 57%, and 6% to 16%, respectively). Nevertheless, still most patients were treated with doublets or triplets (79% in 2010–2014 and 77% in 2015–2018).

Of the patients who did not die within 90 days and therefore were considered eligible to receive beyond first-line treatment, 41% received beyond first-line treatment, compared to 5% of non-eligible patients (Fig. 1). Over time, this proportion increased in eligible patients from 31% to 48% between 2010 and 2017 ($P < 0.001$). Eligible patients had a better performance status, less comorbidities, less affected and different metastatic sites, more frequently a oesophageal/GEJ tumour and HER2 overexpression compared to non-eligible patients (Supplementary Table 2). Moreover, they received less often first-line monotherapy, and more often a doublet or trastuzumab-containing regimen.

3.2. Second-line treatment

Median age before start of second-line treatment was 64 years (n = 606, Table 1). Performance status was 0–1 in 49% of the patients, ≥2 in 7%, and unknown in 44%. Half of the patients (n = 303) received first-line doublets. Patients treated with first-line trastuzumab-containing regimens received most often second-line treatment (32%), followed by first-line doublet (26%) and triplet (24%) chemotherapy, non-trastuzumab targeted therapy-containing treatment (15%) and monotherapy (11%; $P < 0.001$; Fig. 2).

Forty-four different second-line regimens were administered (Fig. 2). Paclitaxel and ramucirumab was used most frequently (35%), followed by taxane monotherapy (20%) and doublet chemotherapy (20%; Supplementary Table 3). Of the 44 patients who received trastuzumab-containing treatment, 23 also received first-line trastuzumab with a different chemotherapy backbone.

In 2011, 38% of the patients received taxane monotherapy, which decreased to 8% in 2017. The administration of paclitaxel and ramucirumab increased from 22% in 2015, i.e. the first year that ramucirumab was available apart from clinical studies in the Netherlands, to 58% in 2017.

3.3. Beyond second-line treatment

Twenty-seven different third-line regimens were administered (n = 107), consisting of combination (doublet or triplet) chemotherapy (30%), non-trastuzumab targeted therapy-containing regimens (18%), irinotecan (16%) and non-irinotecan monotherapy (16%), paclitaxel and ramucirumab (10%) and trastuzumab-containing regimens (10%).

Fourth-line systemic treatment was applied in 19 patients, consisting of irinotecan (n = 8) and non-irinotecan monotherapy (n = 3), trastuzumab-containing regimens (n = 3), paclitaxel and ramucirumab (n = 2), combination chemotherapy (n = 2), and non-trastuzumab targeted therapy-containing regimens (n = 1). Fifth-line treatment was applied in three patients, of whom one received a trastuzumab-containing regimen, and two monotherapy.

3.4. Hospital volume

Hospital volumes were categorised in <18 (Q1), 18–40 (Q2), 41–82 (Q3) and ≥83 (Q4) adenocarcinoma patients treated with systemic therapy in 2015–2017 (Table 2). A positive trend was observed in the proportion of patients who received second-line treatment over the hospital volume quartiles, which increased from 17% to 28% ($P < 0.001$). Q1 and Q2 were associated with a lower probability of beyond first-line treatment administration compared to Q4 (adjusted odds ratio [OR] 0.62, 95% confidence interval [CI] 0.39–0.99 and OR 0.67, 95% CI 0.48–0.95; Table 2).

Table 2
Probability of receiving beyond first-line systemic treatment per hospital volume quartile in patients who received palliative systemic treatment (n=2,466).

Hospital volume	Hospitals No.	Patients No.	Beyond first-line treatment No. (%)	P value	Multivariable logistic regression		
					OR[b]	95% CI	P value
Q1 - <18 patients	17	233	40 (17%)	<0.001[a]	0.62	0.39–0.99	0.045
Q2 - 18–41 patients	19	451	88 (20%)		0.67	0.48–0.95	0.024
Q3 - 42–82 patients	19	749	184 (25%)		0.99	0.76–1.30	0.945
Q4 - ≥83 patients	19	1033	294 (28%)		Ref		

OR, odds ratio, CI, confidence interval, Q1-Q4, quartiles 1–4.
Hospitals in which patients received first-line systemic treatment were categorised in quartiles based on the hospital volume of oesophagogastric adenocarcinoma patients treated with systemic therapy with either curative or palliative intent, and who were diagnosed between 2015 and 2017.
[a] Cochran-Armitage trend test.
[b] Odds ratios were adjusted for sex, age, number of comorbidities, primary tumour location, Lauren classification, year of diagnosis and death within 90 days after stop of systemic treatment.

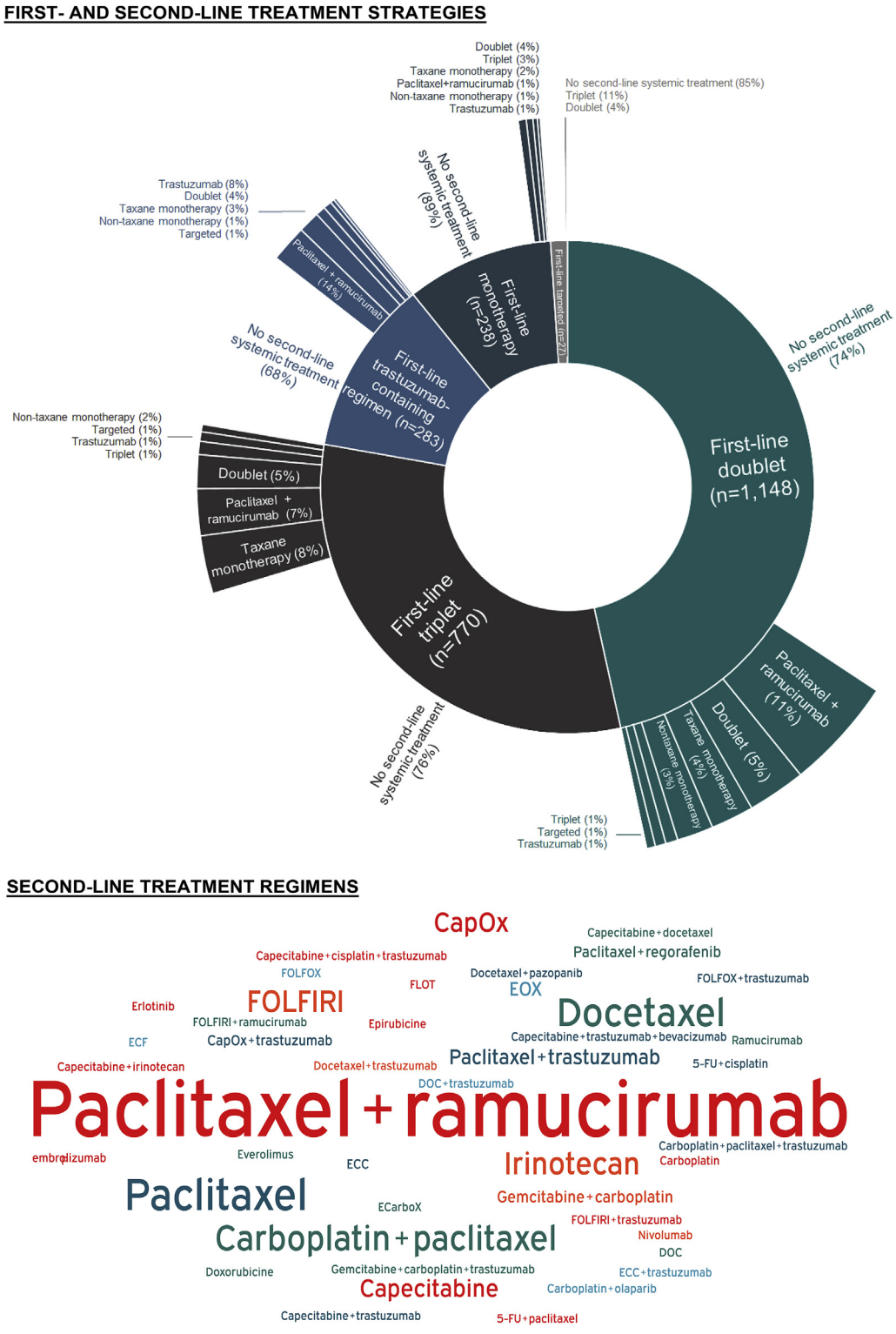

Fig. 2. First- and second-line systemic treatment strategies in all patients (n = 2,466) and second-line treatment regimens (n = 606). First-line systemic treatment strategies were subdivided in chemotherapy regimens (monotherapy, doublet and triplet), trastuzumab-containing regimens and non-trastuzumab targeted therapy-containing regimens. Second-line treatment strategies were administered in 606 patients, and subdivided in chemotherapy regimens (taxane monotherapy, non-taxane monotherapy, doublet and triplet), paclitaxel and ramucirumab, trastuzumab-containing regimens, and non-trastuzumab targeted therapy-containing regimens. The word cloud shows all 44 second-line systemic therapy regimens that were administered. Font size of the word corresponds to the number of patients that received the regimen.

The interhospital variation in the proportion of patients that received beyond first-line treatment was 0–71%, with a median of 21% (IQR 13%, 32%). When categorised in either high (≥21%) or low (<21%) proportions of beyond first-line treatment administration, median OS of all patients who received first-line treatment in hospitals that treated a high proportion of their patients with beyond first-line treatment was longer (7.9 months) compared to hospitals with a low proportion (6.2 months; P < 0.001; Fig. 3).

3.5. Overall survival and time to failure

Overall, median OS since start of second-line treatment was 5.4 (IQR 2.8, 9.0) and TTF 3.4 (IQR 1.8, 5.6) months (n = 606). Median OS since start of third-line treatment was 5.4 (IQR 3.0, 9.1) months, and TTF 3.1 (IQR 1.8, 6.2) months (n = 107). Survival of fourth- and fifth-line treatment was not calculated because of the limited number of patients.

Median OS of second-line paclitaxel and ramucirumab, doublet chemotherapy and taxane monotherapy was 6.1, 5.5 and 4.1 months, respectively (Fig. 4). Paclitaxel and ramucirumab resulted in longer OS and TTF in univariable (P = 0.008 and P = 0.002, respectively) and multivariable analyses (adjusted hazard ratio [HR] 0.71, 95%CI 0.52–0.95) and TTF (HR 0.61, 95% CI 0.44–0.83) compared to taxane monotherapy (Table 3). Doublets resulted neither in better OS (HR 0.76, 95% CI 0.57–1.01) nor TTF (HR 0.75, 95% CI 0.56–1.01) than taxane monotherapy. Compared to doublets, paclitaxel and ramucirumab resulted in similar OS (HR 0.93, 95% CI 0.70–1.24) and TTF (HR 0.81, 95% CI 0.60–1.10).

Lastly, the impact of hospital volume of second-line treatment on OS was assessed. Adjusted HRs of patients treated with second-line treatment in lower treatment volume hospitals (Q1, Q2 and Q3) compared to the highest volume (Q4) were 1.41, 1.56 and 1.15, respectively, although this was only statistically significant in Q2 hospitals (Table 4).

4. Discussion

In this nationwide cohort of 2,466 patients with synchronous metastatic oesophagogastric adenocarcinoma who received first-line palliative systemic treatment, we observed an association between hospital volume and the probability of receiving beyond first-line treatment, and overall survival. In recent years, studies in the curative setting showed that oesophagogastric cancer patients treated in high-volume hospitals have a higher chance of receiving treatment, and better outcomes [14,15,21–25]. Our study adds to the increasing body of evidence that this finding also applies in the metastatic setting [13,18]. Clearly, the simple fact that a patient received treatment could explain the improved survival in high-volume centers, as beyond first-line treatment has been shown to improve survival compared to best supportive care [9,10]. However, importantly, we

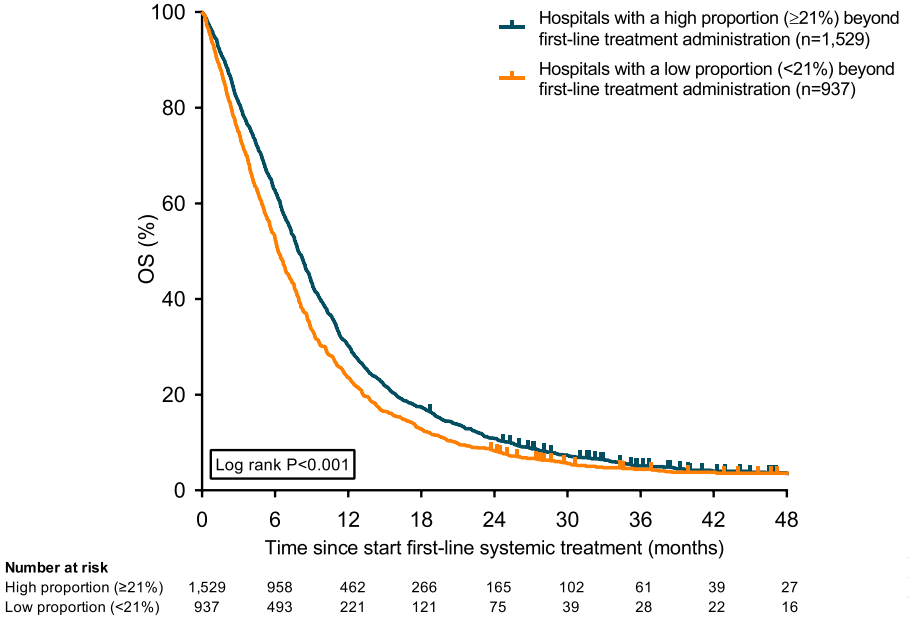

Fig. 3. Kaplan Meier curves for overall survival in patients who received palliative systemic treatment stratified for hospitals with a high and low proportion of beyond first-line treatment administration. Overall survival in all patients who received at least first-line systemic treatment (n = 2,466), stratified for hospitals with a high and low proportion (above and below the median 21%) of patients treated with beyond first-line systemic treatment.

Table 3
Cox regression analyses for OS and TTF of second-line systemic treatment strategies.

	Overall survival (n = 457)										Time to failure of second-line treatment (n = 457)									
	Patients No.	Median OS (months)	Univariable analyses				Multivariable analyses				Median TTF (months)	Univariable analyses				Multivariable analyses				
			HR	95% CI		P value	HR	95% CI		P value		HR	95% CI		P value	HR	95% CI		P value	
Second-line systemic treatment strategy																				
Taxane monotherapy	122	4.1	Ref				Ref				2.5	Ref				Ref				
Doublet chemotherapy	120	5.5	0.86	0.67	1.11	0.246	0.76	0.57	1.01	0.057	3.9	0.83	0.64	1.09	0.185	0.75	0.56	1.01	0.056	
Paclitaxel + ramucirumab	215	6.1	0.73	0.59	0.92	0.007	0.71	0.52	0.95	0.021	4.1	0.69	0.55	0.88	0.002	0.61	0.44	0.83	0.002	
Sex																				
Male	350	5.5	Ref				Ref				3.6	Ref				Ref				
Female	107	5.0	0.90	0.72	1.12	0.346	0.89	0.70	1.14	0.358	3.4	0.99	0.79	1.25	0.925	1.01	0.78	1.30	0.953	
Age	–	–	0.99	0.98	1.00	0.149	1.00	0.99	1.01	0.443	–	0.99	0.98	1.00	0.073	0.99	0.98	1.00	0.145	
Performance status																				
0 or 1	224	5.9	Ref				Ref				3.6	Ref				Ref				
≥2	35	4.7	0.98	0.68	1.42	0.908	0.99	0.68	1.44	0.936	2.7	0.84	0.58	1.23	0.377	0.82	0.55	1.21	0.315	
Unknown	198	4.9	1.21	1.00	1.47	0.057	1.11	0.91	1.37	0.304	3.5	1.06	0.86	1.30	0.587	0.96	0.78	1.18	0.689	
Number of comorbidities																				
0	296	5,3	Ref				Ref				3.4	Ref				Ref				
1	113	5,1	1.07	0.85	1.33	0.576	1.07	0.85	1.36	0.568	3.4	1.01	0.80	1.26	0.954	1.07	0.84	1.36	0.602	
≥2	36	6.9	0.78	0.55	1.11	0.171	0.72	0.50	1.05	0.086	5.1	0.64	0.43	0.95	0.028	0.62	0.41	0.93	0.022	
Unknown	12	5.6	0.98	0.55	1.75	0.984	1.04	0.57	1.88	0.909	4.7	0.90	0.48	1.70	0.753	1.09	0.57	2.09	0.796	
Tumour location																				
sophagus	185	5.5	Ref				Ref				3.5	Ref				Ref				
Gastro-oesophageal junction or cardia	110	5.7	0.91	0.71	1.16	0.436	1.01	0.78	1.31	0.935	4.2	0.86	0.67	1.11	0.251	0.95	0.73	1.24	0.728	
Stomach	162	5.0	1.10	0.89	1.36	0.399	1.13	0.85	1.50	0.405	3.4	1.06	0.85	1.33	0.603	1.11	0.83	1.47	0.486	
Lauren classification																				
Intestinal	211	5.6	Ref				Ref				3.4	Ref				Ref				
Diffuse	104	4.6	1.35	1.06	1.72	0.014	1.21	0.92	1.58	0.177	3.1	1.16	0.90	1.48	0.248	1.01	0.76	1.34	0.950	
Mixed	11	4.7	1.03	0.56	1.89	0.923	0.78	0.41	1.48	0.443	4.7	0.80	0.39	1.62	0.533	0.65	0.31	1.36	0.253	
Indeterminate	15	4.8	1.81	1.07	3.08	0.028	1.75	1.02	3.01	0.042	2.7	1.52	0.86	2.67	0.150	1.40	0.79	2.49	0.250	
Unknown	116	6.1	1.12	0.89	1.41	0.335	1.25	0.98	1.60	0.077	4.7	0.87	0.69	1.11	0.267	0.93	0.72	1.20	0.565	
Distant lymph node metastasis	213	5.1	1.16	0.96	1.40	0.121	1.28	1.04	1.58	0.023	3.3	1.25	1.03	1.52	0.025	1.41	1.14	1.75	0.002	
Liver metastasis	270	5.5	0.96	0.79	1.16	0.673	1.28	1.01	1.61	0.041	3.4	1.05	0.86	1.28	0.646	1.41	1.10	1.81	0.008	
Peritoneal metastasis	160	4.8	1.25	1.03	1.53	0.024	1.33	1.03	1.71	0.027	3.1	1.24	1.02	1.52	0.035	1.41	1.09	1.83	0.009	
Lung metastasis	115	5.1	1.25	1.01	1.56	0.040	1.28	1.02	1.61	0.037	3.5	1.19	0.95	1.48	0.134	1.12	0.88	1.42	0.368	
Bone metastasis	68	3.6	1.70	1.30	2.21	<0.001	1.86	1.39	2.50	<0.001	2.5	1.63	1.25	2.13	<0.001	1.81	1.35	2.43	<0.001	
Other metastases locations	90	4.8	1.20	0.91	1.51	0.126	1.07	0.82	1.38	0.622	3.4	1.20	0.94	1.53	0.140	1.15	0.88	1.50	0.316	
Year of diagnosis	-	-	0.96	0.92	1.00	0.071	0.98	0.93	1.04	0.592	-	0.95	0.91	0.99	0.027	1.00	0.94	1.06	0.983	

Table 4
Cox regression analyses for the association between hospital volume and overall survival in patients who received beyond first-line treatment (n=606).

Hospital volume	Patients (n = 606) No. (%)	HR[a]	95% CI	P value
Q1 - <18 patients	34 (6%)	1.41	0.92–2.17	0.111
Q2 - 18–41 patients	82 (14%)	1.56	1.15–2.13	0.005
Q3 - 42–82 patients	188 (31%)	1.16	0.93–1.44	0.193
Q4 - ≥83 patients	302 (50%)	Ref		

HR, hazard ratio, CI, confidence interval, Q1-Q4, quartiles 1–4.
Hospitals in which patients received second-line systemic treatment were categorised in quartiles based on the hospital volume of oesophagogastric adenocarcinoma patients treated with (neo)adjuvant systemic therapy and synchronous metastatic oesophagogastric cancer patients treated with palliative systemic therapy between 2015 and 2017.
[a] Hazard ratios were adjusted for sex, age, performance status, number of comorbidities, primary tumour location, Lauren classification, metastatic sites, and year of diagnosis.

observed that OS of *all* patients who were treated with palliative systemic treatment (with or without beyond first-line treatment) in a hospital with a high use of beyond first-line treatment was longer compared to hospitals with a low use of beyond first-line treatment. In addition, we showed in multivariable analysis that HRs for death decreased when the hospital treatment volume increased, which suggests that not only patient, tumour and treatment characteristics are related to better patient outcomes, but also factors which may be specific to high-volume centers, such as well-developed structures and adequate resources for a multidisciplinary treatment approach [13,26].

The heterogeneity of 44 different second-line regimens is in line with the variety of 46 first-line regimens that we observed earlier [6]. The former Dutch gastric cancer guideline that was used until 2016 [27] and the current oesophageal cancer guideline [28] do not specify recommendations on systemic treatment regimens. This probably contributed to this heterogeneity, and to the limited number of patients who received beyond first-line treatment at all. The publication of the results of the landmark RAINBOW trial in 2014 [11] and the subsequent recommendation of its administration in the national gastric cancer guideline in 2016 [29] probably boosted the observed increase in the administration of paclitaxel and ramucirumab in 2017, and the overall rise in the use of beyond first-line treatment from 31% in 2010 to 48% of the eligible patients in 2017, i.e. the patients who survived >90 days after stop of first-line treatment, and will hopefully result in further uptake of beyond first-line treatment recommendations of (inter)national guidelines. The rise of beyond first-line treatment use could also be a result of a better performance status in patients after first-line treatment as a result of increased efficacy, e.g. due to the rise in the administration of trastuzumab-containing regimens and decrease in monotherapy use [18], or less toxicity in first line, e.g. due to the increase in doublet and decrease in triplet chemotherapy administration [6]. Overall, beyond first-line treatment was administered in 41% of eligible patients, which is similar to a recent real-world

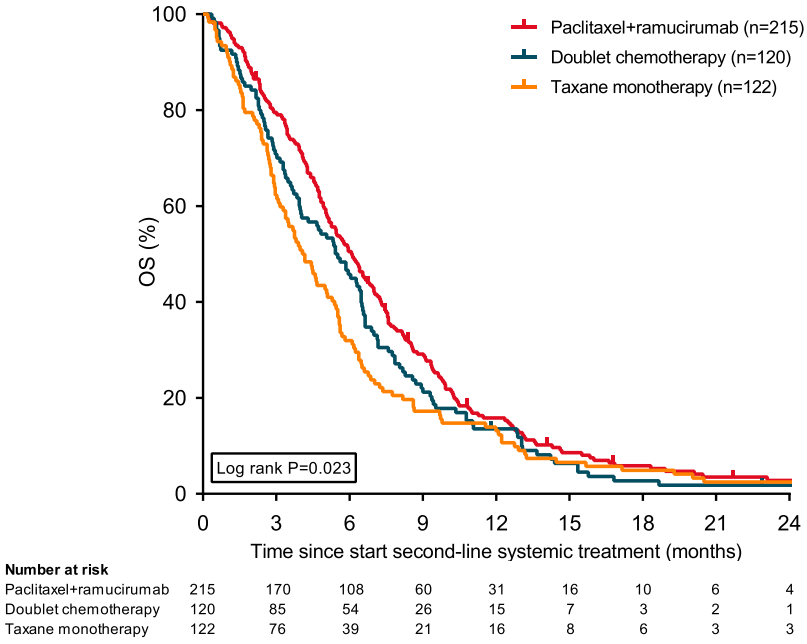

Fig. 4. Kaplan-Meier curves displaying overall survival in patients who received second-line systemic treatment. Overall survival in 457 patients receiving second-line systemic treatment. Second-line systemic treatment strategies that were administered in at least 10% of the patients are displayed.

study [30], and in 5% of non-eligible patients. These results suggest that patient selection for this treatment and assessment of life expectancy is performed adequately in most cases [19,20].

The paclitaxel and ramucirumab regimen was administered in 58% of the patients who received second-line treatment in 2017, and independently associated with a longer OS and TTF compared to taxane monotherapy, which confirms the result of the RAINBOW trial [11]. Although the median OS in both groups was lower than in this trial, the median OS difference of 2.2 months was comparable to our study (RAINBOW: 9.6 versus 7.4 months; our study: 6.1 versus 4.1 months), as well as the hazard ratios (RAINBOW: HR 0.80, 95%CI 0.68–0.96; our study: HR 0.71, 95% CI 0.52–0.95). Inferior survival rates in population-based studies compared to trials have been identified frequently [31]. Although we could not analyze treatment-related toxicity because of missing data, paclitaxel and ramucirumab have been considered well-tolerated in both the RAINBOW trial and real world [11,32]. Because the introduction of ramucirumab changed the landscape of second-line treatment from 2015 onwards, we adjusted for year of diagnosis in the Cox regression analyses. When we restrict our analyses to patients diagnosed in 2015–2017, the survival benefit of paclitaxel and ramucirumab compared to taxane monotherapy is even larger (OS: HR 0.61, 95% CI 0.42–0.88; TTF: HR 0.53, 95% CI 0.36–0.79).

There was no survival benefit of doublet chemotherapy over taxane monotherapy, which supports the findings of an earlier meta-analysis [8], while doublet chemotherapy probably induces more toxicity [6,8]. Other population-based studies on beyond first-line treatment in oesophagogastric cancer did not compare outcomes or toxicity between these two strategies [30,33]. More real-world data on the actual benefit and harms of second-line doublet chemotherapy are needed to justify its administration.

Beyond second-line treatment was used in only a few patients, probably because evidence of its efficacy was scarce until 2017, and still is. Recent results showing that trifluridine/tipiracil and nivolumab are third-line treatment options [34,35] will probably result in increased third-line treatment administration in the coming years.

A limitation of this study is that we missed data on performance status in a considerable number of patients. We therefore not only adjusted for performance status, but also for the number of comorbidities, age, and death within 90 days after stop of systemic treatment, as a proxy for performance status, in order to achieve the most optimal adjustment for confounders that could be associated with a patient's condition and subsequently, beyond first-line treatment administration. Unfortunately, toxicity data were unknown no in 76% of the patients. Furthermore, the heterogeneity in second-line regimens and the subsequent small group size per regimen resulted in lack of statistical power to compare regimens. Moreover, although we included a nationwide oesophagogastric cancer population, our data are restricted to The Netherlands, and therefore comparable studies in other countries are needed to confirm our results in different populations. Lastly, consensus about the definition of systemic treatment lines in real-world data is currently lacking, although some suggestions have been made [36]. This hindered us from optimally comparing this with other population-based studies [30,33]. An international agreement on the definition of treatment lines and the best approach to analyze these data should be considered in order to enable fair comparisons between outcomes of population-based studies.

Improving patient selection for beyond first-line immunotherapy using molecular tumour analysis could further improve patient outcomes. Results of studies comparing treatment with the checkpoint inhibitor pembrolizumab with chemotherapy in patients who have a tumour with high levels of microsatellite instability and PD-L1 expression are promising [37,38]. In first-line treatment, we observed that still not all patients are tested for the only target that is currently available, i.e. HER2 [18]. In the light of upcoming targeted therapies, uptake for biomarker testing must be improved in order to enhance personalised treatment. The rise of beyond first-line targeted treatment options should ideally result in increased administration of it in clinical practice and improved outcomes in oesophagogastric cancer patients.

Role of the funding source

This study has been financially supported by an unrestricted research grants from Eli Lilly and Bristol-Myers Squibb. The funders of the study had no role in the study design, the collection, analysis, and interpretation of the data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper GI Cancer Group. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [39].

Author contributions

Conceptualization: WD, RHAV, MGHvO, HWMvL; Methodology: WD, RHAV, MGHvO,

HWMvL; Software: WD, RHAV, MGHvO; Validation: WD, RHAV, MGHvO, HWMvL; Formal analysis: WD; Investigation: WD, RHAV, MGHvO, HWMvL; Resources: WD, MP; Data Curation Management: WD; Writing - Original Draft: WD, RHAV, MGHvO, HWMvL; Writing - Review & Editing: All authors; Visualization: WD, RHAV, MGHvO, HWMvL; Supervision: RHAV, MGHvO, HWMvL; Project administration: WD; Funding acquisition: RHAV, MGHvO, HWMvL.

Conflict of interest statement

RHAV reports grants from BMS and Roche. JdV reports non-financial support from BTG, a consult/advisory role for Shire, and grants and non-financial support (consultancy) from Servier. NHM reports a consult/advisory role for BMS, MSD Servier, Eli Lilly, research grant from Servier. TvV reports non-financial support from Astellas, Ipsen, Roche, and Bayer. MGHvO reports grants from Amgen, BMS, Eli Lilly, Nordic, Merck, Roche and Servier. VEPPL received educational grants and unrestricted research grants from Roche. HWMvL reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Eli Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.08.010.

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