Gastric Cancer (2017) 20:379–386
DOI 10.1007/s10120-016-0604-6

ORIGINAL ARTICLE

Surgical resection of hepatic metastases from gastric cancer: outcomes from national series in England

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Received: 11 December 2015 / Accepted: 17 February 2016 / Published online: 3 March 2016

Abstract

Background The objectives of this national study were to examine the short-term safety and long-term survival benefit associated with surgical resection of hepatic metastases from gastric cancer.

Methods Patients from the Hospital Episode Statistics database were classified by disease and treatment approach. Gastric cancer: 1. Without liver metastases treated by gastrectomy (GG). 2. With liver metastases treated by gastrectomy and hepatectomy (GGH). 3. With liver metastases treated by gastrectomy without hepatectomy (GGNH). 4. With liver metastases treated with no surgery (GNS). Propensity score matching and multivariable analyses were used to compensate for differences in some baseline characteristics.

Results During the study period, 87,482 were patients diagnosed with gastric cancer, of whom 13,841 underwent partial or total gastrectomy. Of those who underwent gastrectomy, 336 had a diagnosis of liver metastases and 78 of these had a hepatectomy. Propensity-matched analysis showed no significant differences in 30- or 90-day mortality between the GGH and GG groups. The GGH group had significantly improved 1-year mortality (35.9 % vs. 50.0 %, $p = 0.049$) and 5-year mortality (61.5 % vs. 75.7 %, $p = 0.031$) compared to the GGNH group, and compared to the GNS group, the GCH group had 1-year mortality (35.9 % vs. 84.6 %, $p < 0.001$) and 5-year mortality (61.5 % vs. 90.8 %, $p < 0.001$).

Conclusions This study showed that hepatectomy for synchronous gastric cancer hepatic metastases may carry survival benefits in selected patients. The data presented should not be a rationale to change current clinical practice but rather a stimulus to prospectively study the role of surgery in a selected group of patients who are currently treated with palliative chemotherapy.

Keywords Gastric cancer · Hepatic metastases · Hepatectomy · Survival

S. R. Markar and H. Mackenzie should be acknowledged with first authorship.

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Introduction

Gastric cancer remains one of the most common cancers, with more than 139,000 new cases in Europe and more than 951,000 new cases worldwide diagnosed in 2012 [1]. The majority of gastric cancer cases in Western centers present in advanced stage, with only 30 % of patients eligible for treatment with curative intent [2]. Gastrectomy in Eastern centers is associated with improved long-term survival compared to the West after controlling for disease stage and patient demographics [3]. Furthermore, in Eastern centers more attention has been given to the surgical treatment of liver metastases from gastric cancer [4–7] and toward gastrectomy as a reduction surgical strategy in the presence of a single noncurable factor that showed no survival improvement over chemotherapy alone [8].

Current treatment protocols in the UK do not recommend surgical resection of gastric cancer hepatic metastases [9], with most patients treated with palliative chemotherapy, which has been shown to improve survival by up to 12 months when compared to supportive care [10]. This finding is in contrast to the uptake of surgical resection of colorectal cancer liver metastases that has resulted in substantial survival benefits [11].

A recent meta-analysis of resection of hepatic metastases from gastric adenocarcinoma revealed a survival benefit most marked in those with solitary metastases [12]. However, this study was mostly composed of small case series of which only nine studies included 254 patients from Western centers. The aims of the present study from a large English national database are (1) to examine postoperative mortality following surgical resection of gastric cancer hepatic metastases and (2) to investigate whether there is a long-tem survival benefit associated with resection of gastric cancer hepatic metastases.

Methods

Data were derived from the Hospital Episode Statistics (HES) database [13]. All patients over the age of 17 who were admitted to hospital with gastric cancer between April 1, 1997 and March 31, 2012 were included in the study. Local institutional review board approval was obtained for this study. Gastric cancer diagnoses were identified using International Classification of Disease 10th revision (ICD-10) codes C160-9 and D001. All patients who underwent total or partial gastrectomy were ascertained using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS), codes G27.1-5 and G28.1-3, respectively. Linking HES data with data from the Office for National Statistics (ONS) identified mortality and survival. Patients were classified by disease and treatment approach into four groups: (1) gastric cancer without liver metastases treated by gastrectomy (GG); (2) gastric cancer with liver metastases (ICD-10 code C787) treated by gastrectomy and hepatectomy (OPCS codes J02.1-9) (GGH); (3) gastric cancer with liver metastases treated by gastrectomy without hepatectomy (GGNH); (4) gastric cancer with liver metastases treated with no surgery (GNS).

Statistical analysis

The primary outcome was 30-day mortality; secondary outcomes included 90-day mortality, 1-year mortality, 5-year mortality, overall survival, and postoperative medical complication (pneumonia, cardiac events, pleural effusion, thromboembolic events). Comorbidities, age, and gender were obtained from the HES database. These risk factors were included in a logistic regression model to identify risk factors for 30-day mortality in all patients undergoing gastrectomy. The presence of lymph node disease and peritoneal involvement at the time of surgery, based upon pathological analysis, was also recorded.

To negate selection bias in the hepatectomy group (group 2), propensity score matching was performed with the other three groups. Propensity score was estimated using a multivariable logistic regression model, with the treatment groups as the dependent variables and all potential confounders as covariates. Confounders included in the propensity matching included age, male gender, medical comorbidities such as renal and liver failure, diabetes, ischemic heart disease, chronic obstructive pulmonary disease and other pulmonary disease, hypertension and congestive cardiac failure, and tumor-related factors such as lymph node and peritoneal disease.

All patients in groups 1, 3, and 4 were matched to patients in group 2 according to the propensity score using the global optimum method.

Comparison of survival in both the matched and unmatched groups was performed using Kaplan–Meier curves and the log-rank test. Categorical data were represented as percentages and compared using the chi-squared test; age was represented as mean (S.D.) and compared using the independent sample t test. For statistical analysis, SPSS software was used (Statistical Package for the Social Sciences software, Version 22; SPSS, Chicago, IL, USA).

Results

During the study period, 87,482 patients were diagnosed with gastric cancer, of whom 13,841 underwent partial or total gastrectomy. Of those who had gastrectomy, 336 had a diagnosis of liver metastases and 78 of these had a hepatectomy for a synchronous tumor. Seventy-one (91 %) of these had hepatectomy during the same operation and the remaining 7 underwent it within 3 months. The majority had minor liver resections; however, 11 (14.1 %) underwent left hepatectomy and 1 (1.3 %) had a right hepatectomy; no patients underwent extended hepatectomy. The overall 30-day mortality following gastrectomy was 7.2 %; however, this decreased from 8.9 % in 1997 to 3.8 % in 2012 ($p < 0.001$). In logistic regression analysis, congestive cardiac failure (CCF), hypertension, chronic obstructive pulmonary disease, ischemic heart disease, other pulmonary disease, renal failure, liver failure, age, and male gender were significant independent predictors of 30- and 90-day mortality following gastrectomy (Table 1).

Compared to patients who had gastrectomy in the absence of liver metastases (GG group), patients who underwent additional hepatectomy for liver metastasis (GGH group) were significantly younger (65 vs. 69 years, $p = 0.001$) but there were no significant differences in comorbidities (Table 2). There were no significant differences in the rate of peritoneal involvement and lymph node involvement (Table 2). Again, compared to the GGNH group, the GGH group was significantly younger (65 vs. 70 years, $p = 0.001$) and had significantly less peritoneal involvement (1.3 % vs. 13.6 %, $p = 0.002$). Those patients who did not undergo any operation (GNS group) were the eldest (65 vs. 71 years, $p < 0.001$), had more peritoneal involvement (7.1 % vs. 1.3 %, $p = 0.045$), but were coded as having less lymph node involvement (9.6 % vs. 29.5 %, $p < 0.001$). This finding is likely because lymph node disease is commonly diagnosed on histology as part of surgical treatment.

The median follow-up was 248 days (IQR, 70–785 days). Unmatched analysis revealed that patients who had gastrectomy and hepatectomy for liver metastases (GGH group) had no statistically significant differences in 30-day, 90-day, 1-year, and 5-year mortality compared to those who underwent gastrectomy only in absence of liver metastases (GG group) (Table 2). In addition, no significant differences were seen between the two groups in postoperative medical complications. However the GGH group had similar 30-day mortality to the GGNH group (10.3 % vs. 15.5 %, $p = 0.246$), but significantly improved 90-day mortality (12.8 % vs. 27.1 %, $p = 0.009$), 1-year mortality (35.9 % vs. 61.6 %, $p < 0.001$), and 5-year mortality (61.5 % vs. 81.8 %, $p < 0.001$). These results are consistent with the Kaplan–Meier curve analyses, which showed that patients who were selected to have gastrectomy with additional hepatectomy for liver metastases (GGH group) had survival similar to those who had gastrectomy in the absence of liver metastases (GG group) ($p = 0.196$) and improved survival compared to patients who had gastrectomy with no liver resection for liver metastases (GGNH group) ($p < 0.001$) (Fig. 1). The GNS group who did not have any surgical intervention had significantly worse mortality at all four time points and the worst overall survival of all the groups ($p < 0.0.001$).

Even after the groups were matched for propensity score, there were still no significant differences in 30- or 90-day mortality, or postoperative medical complications, between patients who had gastrectomy in the absence of liver metastasis (GG group) and those who underwent additional hepatectomy for liver metastases (GGH group). The group who underwent additional hepatectomy (GGH group) had significantly improved 1-year mortality (35.9 % vs. 50.0 %, $p = 0.049$) and 5-year mortality (61.5 % vs. 75.7 %, $p = 0.031$) compared to the group who had gastrectomy only with no liver resection for liver metastases (GGNH group) (Table 3). These results are consistent with the Kaplan–Meier curves for survival for the matched groups, which showed that patients who had gastrectomy with additional hepatectomy for liver metastasis (GGH group) had similar survival to those who had gastrectomy

Table 1 Results of logistic regression analyzes for 30-day and 90-day mortality

Variable	30-day mortality			90-day mortality		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Age	1.05	1.04–1.06	<0.001	1.05	1.04–1.06	<0.001
Male gender	1.17	1.02–1.35	0.029	1.13	1.01–1.27	0.038
CCF	3.85	2.83–5.24	<0.001	3.34	2.50–4.46	<0.001
Hypertension	0.53	0.43–0.65	<0.001	0.49	0.42–0.59	<0.001
COPD	0.31	0.19–0.51	<0.001	0.28	0.18–0.44	<0.001
IHD	1.68	1.35–2.09	<0.001	1.39	1.15–1.69	0.001
Diabetes	0.80	0.32–1.98	0.623	1.29	0.70–2.38	0.421
Pulmonary disease	3.58	2.32–5.53	<0.001	3.45	2.33–5.10	<0.001
Renal failure	2.53	1.68–3.81	<0.001	2.45	1.70–3.55	<0.001
Liver failure	17.22	6.96–42.62	<0.001	10.18	4.15–25.0	<0.001

CCF congestive cardiac failure, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *OR* odds ratio, *95 % CI* 95 % confidence interval

Table 2 Comparative unmatched analysis of medical comorbidities for 30-day, 90-day, 1-year, and 5-year mortality rates across the four study groups

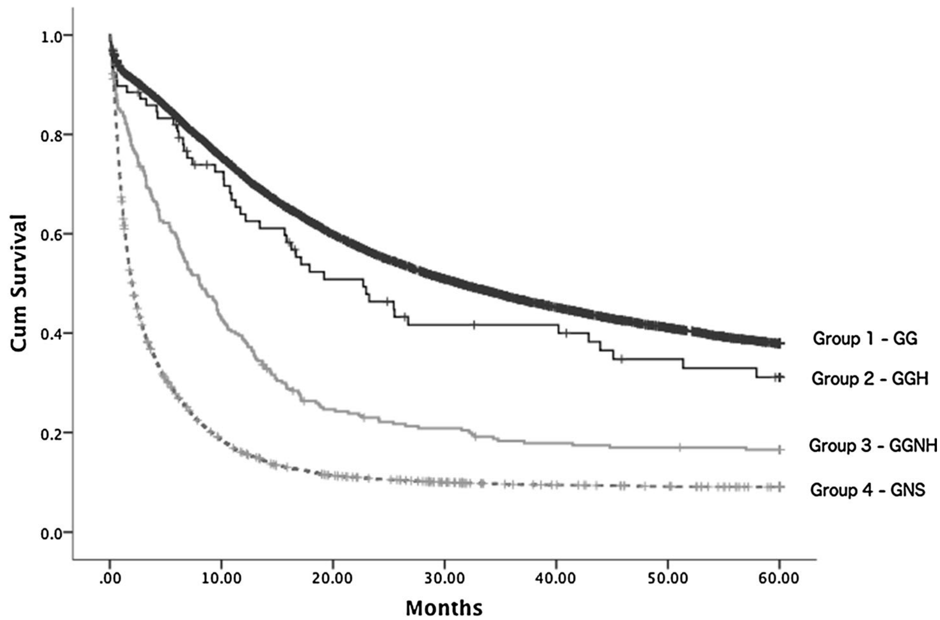
Variable	Gastrectomy (GG group 1)	*p* value (group 1 vs. group 2)	Gastrectomy plus hepatectomy (GGH group 2)	*p* value (group 2 vs. group 3)	Gastrectomy and no surgery for liver metastases (GGNH group 3)	*p* value (group 2 vs. group 4)	Gastric cancer and liver metastases and no operation (GNS group 4)
Total cases	13505	NA	78	NA	258	NA	7041
Age	69	0.001	65	0.001	70	<0.001	71
Male gender	8691 (64.4 %)	0.869	51 (65.4 %)	0.912	170 (65.9 %)	0.611	4938 (70.1 %)
Renal failure	186 (1.4 %)	0.946	0 (0 %)	0.339	4 (1.6 %)	0.137	157 (2.2 %)
Liver failure	42 (0.3 %)	0.643	0 (0 %)	0.582	2 (0.8 %)	0.766	9 (0.1 %)
Diabetes	113 (0.8 %)	0.550	1 (1.3 %)	0.677	2 (0.8 %)	0.495	56 (0.8 %)
IHD	1078 (8.0 %)	0.931	5 (6.4 %)	0.123	16 (6.2 %)	0.424	473 (6.7 %)
Pulmonary disease	995 (7.4 %)	0.160	9 (11.5 %)	0.421		0.222	537 (7.6 %)
COPD	1039 (7.7 %)	0.175	8 (10.3 %)	0.410	28 (10.9 %)	0.128	471 (6.7 %)
Hypertension	2782 (20.6 %)	0.598	12 (15.4 %)	0.235	34 (13.2 %)	0.342	1115 (15.8 %)
CCF	280 (2.1 %)	0.251	0 (0 %)	0.269	8 (3.1 %)	0.162	129 (1.8 %)
Lymph node disease	3545 (26.2 %)	0.517	23 (29.5 %)	0.567	85 (32.9 %)	<0.001	677 (9.6 %)
Peritoneal disease	336 (2.5 %)	0.495	1 (1.3 %)	0.002	35 (13.6 %)	0.045	501 (7.1 %)
30-day mortality	941 (7.0 %)	0.256	8 (10.3 %)	0.246	40 (15.5 %)	<0.001	2220 (31.5 %)
90-day mortality	1429 (10.6 %)	0.522	10 (12.8 %)	0.009	70 (27.1 %)	<0.001	4178 (59.3 %)
1-year mortality	3817 (28.3 %)	0.136	28 (35.9 %)	<0.001	159 (61.6 %)	<0.001	5916 (84.0 %)
5-year mortality	7793 (57.7 %)	0.494	48 (61.5 %)	<0.001	211 (81.8 %)	<0.001	6261 (90.3 %)
Reoperation	1359 (10.1 %)	0.995	8 (10.3 %)	0.396	36 (14.0 %)	NA	NA
Readmission	714 (5.3 %)	0.283	2 (2.6 %)	0.149	18 (7.0 %)	NA	NA
Pneumonia	703 (5.2 %)	0.139	2 (2.6 %)	0.176	14 (5.5 %)	NA	NA
Pleural effusion	541 (4.0 %)	0.517	2 (2.6 %)	0.688	9 (3.5 %)	NA	NA
Cardiac event	526 (3.9 %)	0.982	3 (3.8 %)	0.117	3 (1.2 %)	NA	NA
Thromboembolic event	121 (0.9 %)	0.430	1 (1.3 %)	0.545	4 (1.6 %)	NA	NA

NA not applicable

in the absence of liver metastasis (GG group) ($p = 0.128$) but improved survival compared to patients who had gastrectomy with no liver resection for liver metastases (GGNH group) ($p = 0.037$) (Fig. 2). Again, consistent with the unmatched analysis, the matched group who did not have an operation (GNS group) had the highest mortality at every stage and the worst survival ($p < 0.001$). There were no significant difference in unmatched and matched comparisons between GG, GGH, and GGNH groups in the incidence of readmission or reoperation.

Discussion

The results of the study showed that additional surgical resection of hepatic metastases in a selected group of patients who underwent gastrectomy may be associated with survival benefits, as reflected by a reduction in 1- and 5-year mortality when compared to patients with hepatic metastases who did not have any surgery or underwent gastrectomy without resection of the metastases. Propensity matching for patient comorbidities and lymph node or peritoneal disease distribution has maintained the survival benefit seen in the gastrectomy with hepatectomy group. However, we were unable to adjust for the number, size, and distribution of hepatic metastases, which are also determinants of long-term survival. This administrative dataset shows that patients who underwent gastrectomy and hepatectomy were young and had a low level of medical comorbidities. Our previous meta-analysis demonstrated patients with single unilobar hepatic metastases have significantly improved prognosis compared with multiple or bilobar hepatic metastases [12]. The equality in survival between the group who had gastrectomy in the absence of liver metastases and the group who had gastrectomy and hepatectomy for liver metastases should be viewed with extreme caution because patient selection, low volume of liver metastasis, and sample size may account for this



Group 1 - GG	13505	9771	7387	5978	4981	4233	3594
Group 2 - GGH	78	49	34	26	24	19	16
Group 3 - GGNH	258	108	57	48	40	38	36
Group 4 - GNS	7041	1266	769	647	591	561	534

Fig. 1 Kaplan–Meier survival analysis of the four unmatched study groups: (1) gastric cancer without liver metastases treated by gastrectomy (*GG*); (2) gastric cancer with liver metastases treated by gastrectomy and hepatectomy (*GGH*); (3) gastric cancer with liver metastases treated by gastrectomy without hepatectomy (*GGNH*); (4) gastric cancer with liver metastases treated with no surgery (*GNS*). *Cum* cumulative

result. Most of the patients had minor hepatectomy, indicating a low metastatic volume in the liver. Only one patient had right hepatectomy, and no patients had extended hepatectomy.

The study also showed that the surgical resection of hepatic metastases in addition to gastrectomy did not significantly increase postoperative mortality in selected patients. It is important to acknowledge that there is positive selection bias toward the group treated with gastrectomy and hepatectomy who were younger (median age, 65 years) and had no incidence of renal, cardiac, or liver failure and a very low level of other medical comorbidities. Those results were maintained after propensity matching for the differences between groups. Other publications from the Far East [4–7], and some Western centers [14–17], have also suggested the safety of hepatectomy for gastric cancer liver metastases in selected patients. The results of this study also parallel the outcomes of hepatectomy for colorectal cancer liver metastases, where surgical resection is more common and is considered the standard of care for isolated hepatic metastases [11]. However, data regarding the distribution of hepatic metastases and the extent of hepatectomy were not available for the matching process for short-term outcomes. These gaps along with other confounding factors are important in terms of procedure-associated mortality and long-term survival following hepatectomy for metastases [18, 19]. Nevertheless, in general across this national dataset and as expected, important patient-related factors that were significantly associated with 30-day mortality included increasing age, male gender, congestive cardiac failure, ischemic heart disease, pulmonary disease, and renal and liver failure. Of these factors, liver failure was the most prognostically important, with an odds ratio (OR) of 17.22 associated with 30-day mortality.

It is important to acknowledge the limitations that must be taken into account in the interpretation of the results presented. There is a selection bias toward the group who underwent hepatectomy and gastrectomy. As highlighted previously, the dataset used for this study does not include data regarding number, size, anatomical location, or distribution of hepatic metastases, which are important factors that can affect the survival results presented in this study. Furthermore, the dataset used is administrative in nature, and therefore it was not possible to analyze other oncological factors that may affect survival including

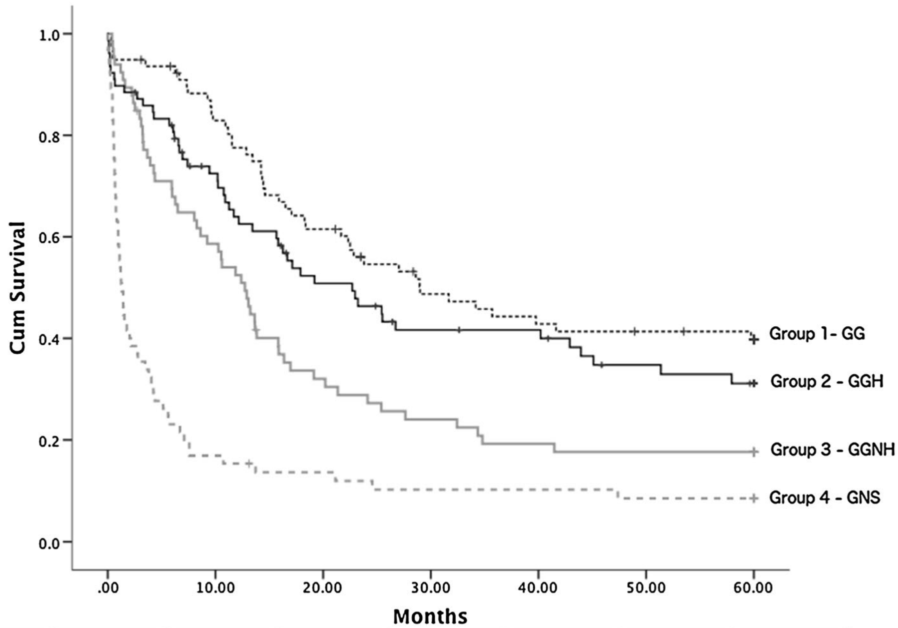
Table 3 Comparative propensity-matched analysis of medical comorbidities for 30-day, 90-day, 1-year, and 5-year mortality rates across the four study groups

Variable	Gastrectomy (GG group 1)	*p* value (group 1 vs. group 2)	Gastrectomy plus hepatectomy (GGH group 2)	*p* value (group 2 vs. group 3)	Gastrectomy and no surgery for liver metastases (GGNH group 3)	*p* value (group 2 vs. group 4)	Gastric cancer and liver metastases and no operation (GNS group 4)
Total number of cases	78		78		74		65
Age (years)	64	0.647	65	0.805	65	0.820	65
Male gender	27 (34.6 %)	1.0	27 (34.6 %)	0.782	25 (33.8 %)	0.194	16 (24.6 %)
Renal failure	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)
Liver failure	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)
Diabetes	1 (1.3 %)	1.0	1 (1.3 %)	0.970	1 (1.4 %)	0.360	0 (0 %)
IHD	5 (6.4 %)	1.0	5 (6.4 %)	0.276	2 (2.7 %)	0.358	2 (3.1 %)
Pulmonary disease	9 (11.5 %)	1.0	9 (11.5 %)	0.308	5 (6.8 %)	0.441	5 (7.7 %)
COPD	8 (10.3 %)	1.0	8 (10.3 %)	0.441	5 (6.8 %)	0.378	4 (6.2 %)
Hypertension	12 (15.4 %)	1.0	12 (15.4 %)	0.270	7 (9.5 %)	0.796	9 (13.8 %)
CCF	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)	NA	0 (0 %)
Lymph node disease	23 (29.5 %)	1.0	23 (29.5 %)	0.569	25 (33.8 %)	0.388	15 (23.1 %)
Peritoneal disease	1 (1.3 %)	1.0	1 (1.3 %)	0.529	2 (2.7 %)	0.897	1 (1.5 %)
30-day mortality	4 (5.1 %)	0.229	8 (10.3 %)	0.869	7 (9.5 %)	<0.001	28 (43.1 %)
90-day mortality	4 (5.1 %)	0.093	10 (12.8 %)	0.303	14 (18.9 %)	<0.001	42 (64.6 %)
1-year mortality	17 (21.8 %)	0.052	28 (35.9 %)	0.049	37 (50.0 %)	<0.001	55 (84.6 %)
5-year mortality	44 (56.4 %)	0.077	48 (61.5 %)	0.031	56 (75.7 %)	<0.001	59 (90.8 %)
Reoperation	12 (15.4 %)	0.338	8 (10.3 %)	0.257	11 (16.7 %)	NA	NA
Readmission	5 (6.4 %)	0.246	2 (2.6 %)	0.088	6 (9.1 %)	NA	NA
Pneumonia	6 (7.7 %)	0.117	2 (2.6 %)	0.297	3 (4.5 %)	NA	NA
Pleural effusion	5 (6.4 %)	0.246	2 (2.6 %)	0.518	3 (4.5 %)	NA	NA
Cardiac event	4 (5.1 %)	0.699	3 (3.8 %)	0.396	1 (1.5 %)	NA	NA
Thromboembolic event	0 (0 %)	0.316	1 (1.3 %)	0.356	0 (0 %)	NA	NA

NA not applicable

neoadjuvant chemotherapy, extent of lymphadenectomy, pathological TNM stage, and resection margin status. Given the retrospective nature of this study, data are not available regarding the decision-making process in the allocation of treatment in these patients. National databases such as HES are dependent to some extent upon the accuracy of data entry, which can vary, but this is a recognized constraint of any national database [20]. The study also did not address the quality of life, which is a critical issue that has been commonly overlooked in previous single-institutional publications.

The authors are not presenting these data as evidence to operate on unselected patients with gastric cancer and hepatic metastases. The study should not be regarded as a rationale to change current clinical practice, but rather as a stimulus to prospectively study the role of surgery in a selected group of patients who are currently treated with palliative chemotherapy [9]. The selection bias in this article has resulted in survival benefits comparable to those patients who had gastrectomy in the absence of liver metastasis. The role of the surgical and oncology community is to identify those selection factors to recreate and formalize what is regarded as a selection bias in this study. We believe there is a need for a large-scale prospective study in Western centers to formally address the survival benefits of surgical resection of gastric cancer hepatic metastases in selected patients, with focused assessment of prognostic factors, patient selection, and quality of life. The marked reduction in postoperative mortality from gastrectomy and hepatectomy in England



Group 1 - GG	78	62	46	33	29	27	25
Group 2 - GGH	78	49	34	26	24	19	16
Group 3 - GGNH	74	38	20	14	12	11	11
Group 4 - GNS	65	11	8	6	6	5	5

Fig. 2 Kaplan–Meier survival analysis of the four propensity-matched study groups: (1) gastric cancer without liver metastases treated by gastrectomy (*GG*); (2) gastric cancer with liver metastases treated by gastrectomy and hepatectomy (*GGH*); (3) gastric cancer with liver metastases treated by gastrectomy without hepatectomy (*GGNH*); (4) gastric cancer with liver metastases treated with no surgery (*GNS*)

during the past few years paves the way for such study [2].

Acknowledgments Dr. Melody Ni, Statistician, Department Surgery and Cancer, Imperial College London.

Compliance with ethical standards

Conflicts of interests The authors declare they have no conflict of interests.

Ethical statement This article does not contain any studies with human or animal subjects performed by any of the authors.

Funding Sheraz R. Markar is supported by the National Institute for Health Research (Grant Number: DRF-201-07-088).

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