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## Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: a nationwide study

M. F. J. Seesing,<sup>1,†</sup> A. van der Veen,<sup>1,†</sup> H. J. F. Brenkman <sup>1</sup>, H. B. A. C. Stockmann,<sup>2</sup> G. A. P. Nieuwenhuijzen,<sup>3</sup> C. Rosman,<sup>4</sup> F. J. H. van den Wildenberg,<sup>5</sup> M. I. van Berge Henegouwen,<sup>6</sup> P. van Duijvendijk,<sup>7</sup> B. P. L. Wijnhoven,<sup>8</sup> J. H. M. B. Stoot,<sup>9</sup> M. Lacle,<sup>10</sup> J. P. Ruurda,<sup>1</sup> R. van Hillegersberg,<sup>1</sup> and the Gastroesophageal Metastasectomy Group\*

<sup>1</sup> Department of Surgical Oncology, University Medical Center Utrecht, Utrecht, <sup>2</sup> Department of Surgery, Spaarne Gasthuis, Haarlem, <sup>3</sup> Department of Surgical Oncology, Catharina Hospital, Eindhoven, <sup>4</sup> Department of Surgical Oncology, Radboud University Medical Center, Nijmegen, <sup>5</sup> Department of Surgery, Canisius-Wilhelmina Hospital, Nijmegen, <sup>6</sup> Department of Surgery, Amsterdam University Medical Center, Amsterdam, <sup>7</sup> Department of Surgery, Gelre Ziekenhuizen, Apeldoorn, <sup>8</sup> Department of Surgical Oncology, Erasmus University Medical Center, Rotterdam, <sup>9</sup> Department of Surgery, Zuyderland Medical Center, Heerlen and Sittard-Geleen, and <sup>10</sup> Department of Pathology, University Medical Center Utrecht, Utrecht

**SUMMARY.** The standard of care for gastroesophageal cancer patients with hepatic or pulmonary metastases is best supportive care or palliative chemotherapy. Occasionally, patients can be selected for curative treatment instead. This study aimed to evaluate patients who underwent a resection of hepatic or pulmonary metastasis with curative intent. The Dutch national registry for histo- and cytopathology was used to identify these patients. Data were retrieved from the individual patient files. Kaplan–Meier survival analysis was performed. Between 1991 and 2016, 32,057 patients received a gastrectomy or esophagectomy for gastroesophageal cancer in the Netherlands. Of these patients, 34 selected patients received a resection of hepatic metastasis ( $n = 19$ ) or pulmonary metastasis ( $n = 15$ ) in 21 different hospitals. Only 4 patients received neoadjuvant therapy before metastasectomy. The majority of patients had solitary, metachronous metastases. After metastasectomy, grade 3 (Clavien–Dindo) complications occurred in 7 patients and mortality in 1 patient. After resection of hepatic metastases, the median potential follow-up time was 54 months. Median overall survival (OS) was 28 months and the 1-, 3-, and 5- year OS was 84%, 41%, and 31%, respectively. After pulmonary metastases resection, the median potential follow-up time was 80 months. The median OS was not reached and the 1-, 3-, and 5- year OS was 67%, 53%, and 53%, respectively. In selected patients with gastroesophageal cancer with hepatic or pulmonary metastases, metastasectomy was performed with limited morbidity and mortality and offered a 5-year OS of 31–53%. Further prospective studies are required.

**KEY WORDS:** esophageal and gastric cancer, esophageal and gastric surgery, hepatic surgery, metastasis, pulmonary surgery.

Address correspondence to: Richard van Hillegersberg, MD, PhD, Department of Surgical Oncology, University Medical Center Utrecht, Heidelberglaan 100 G04.228, 3508 GA, Utrecht, the Netherlands. Email: [R.vanHillegersberg@umcutrecht.nl](mailto:R.vanHillegersberg@umcutrecht.nl)

\*P. C. Baas, Department of Surgery, Martini Hospital, Groningen; D. Boerma, Department of Surgery, St. Antonius Hospital, Nieuwegein; W. O. de Steur, Department of Surgical Oncology, Leiden University Medical Center, Leiden; J. W. D. de Waard, Department of Surgery, Westfriesgasthuis, Hoorn; J. Heisterkamp, Department of Surgery, Elizabeth-TweeSteden Hospital, Tilburg; M. van Hillo, Department of Surgery, Sionsberg, Dokkum; E. A. Kouwenhoven, Department of Surgery, ZGT Hospital Group Twente, Almelo; M. S. L. Liem, Department of Surgery, Medisch Spectrum Twente, Enschede; D. L. van der Peet, Department of Surgical Oncology, VU University Medical Center, Amsterdam; J. P. E. N. Pierie, Medical Center Leeuwarden, Leeuwarden; J. T. M. Plukker, Department of Surgical Oncology, University Medical Center Groningen, Groningen; R. M. H. Roumen, Department of Surgery, Máxima Medical Center, Eindhoven; G. W. M. Tetteroo, Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands; F. van Workum, Department of Surgery, Canisius-Wilhelmina Hospital, Nijmegen.

<sup>†</sup>M. F. J. Seesing and A. van der Veen contributed equally.

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## INTRODUCTION

Gastric cancer and esophageal cancer are the third (723,000 deaths annually) and sixth (400,000 deaths annually) most common causes of cancer-related deaths worldwide.<sup>1</sup> Neoadjuvant chemo(radio)therapy or perioperative chemotherapy followed by surgical resection is the cornerstone of curative care for gastroesophageal cancer.<sup>2–4</sup> However, up to 40% of patients with gastroesophageal cancer present with synchronous metastatic disease and are regarded incurable.<sup>5,6</sup> Approximately another 50% will develop metachronous metastases during follow-up after surgery.<sup>7–11</sup> The most common sites of metastases are the lung, liver, peritoneum, and bone.<sup>12,13</sup> Currently, the standard treatment for patients with hepatic or pulmonary metastases from gastroesophageal cancer consists of best supportive care or palliative chemotherapy. This leads to a median survival of 4–5 months for esophageal and 4–11 months for gastric cancer.<sup>14,15</sup> Resection of hepatic or pulmonary metastases has been established as a treatment option for other tumors, such as endocrine and colorectal cancer.<sup>16–22</sup> Several small retrospective studies suggest that resection of hepatic and pulmonary metastases from gastroesophageal cancer is also feasible and may increase survival in a selected group of patients.<sup>23–27</sup> Unfortunately, large series on metastasectomy are scarce for metastatic gastric cancer and even scarcer for esophageal cancer. According to a meta-analysis published in 2018,<sup>28</sup> no Western series exist that report on the resection of metachronous pulmonary metastasis.

The aim of this study was to identify and evaluate all patients in the Netherlands who underwent a resection of hepatic or pulmonary metastases from gastroesophageal cancer with curative intent. Primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes included surgical complications. Lastly, we wanted to describe the factors that may influence long-term survival.

## METHODS

### Patients and data

All patients who underwent a resection of hepatic or pulmonary metastases from gastroesophageal cancer between January 1991 and March 2016 were identified from the Dutch national registry for histo- and cytopathology (PALGA). The PALGA database collects every pathological report generated by pathology departments in the Netherlands since 1975.<sup>29</sup> The PALGA database was searched for '(stomach OR esophagus) AND (liver OR lung) AND metastases AND resection' and synonyms. Summaries of the pathology reports were supplied by PALGA and used for further patient selection. Patients treated

with curative intent, and of whom patient records were available, were included. Patient and treatment-related characteristics, as well as surgical outcome and histopathological data, were retrospectively collected from the individual patient files. The Netherlands Comprehensive Cancer Organisation supplied the total number of gastrectomies and esophagectomies performed for gastroesophageal cancer in the Netherlands between January 1991 and March 2016.

The primary tumor was staged according to the tumor node metastasis classification system of the International Union Against Cancer (UICC). Radicality was defined according to the UICC standards; R0: complete microscopic resection, R1: microscopic residual disease, or R2: local macroscopic residual disease or distant macroscopic residual disease. Curative intent was defined as patients for whom the intention of the surgery was to perform an R0 resection. Metastases were considered synchronous when they were diagnosed within 6 months after diagnosis of the primary tumor. Locations of hepatic metastases were defined according to Couinaud's liver segments.<sup>30</sup> Location of pulmonary metastases were defined according to the definition of the Thoracic Society.<sup>31</sup> Hepatic resections were divided into major and minor resections. Minor resections were defined as a resection of less than four segments; every other resection was defined as a major resection. This study received ethical approval (Institutional Review Board number 16–312/C) from the Medical Ethics Review Committee of the UMCU, and the need to obtain informed consent was waived.

### Outcomes

The primary outcomes were PFS and OS. 'PFS' was defined as the interval between metastasectomy and recurrence or progression of (residual) disease regardless of organ or tissue, or death from any cause. 'OS' was defined as the interval between metastasectomy and date of last follow-up or death.

Secondary outcome in this study was the safety of metastasectomy, expressed in terms of postoperative morbidity and 30-day mortality and in-hospital mortality. Postoperative complications were classified according to the Clavien–Dindo classification. Follow-up was not standardized.

### Statistical considerations

Data were analyzed using SPSS for windows, version 22.0 (IBM corp., Armonk, New York). All continuous data were presented as median (range) or mean ( $\pm$  standard deviation (SD)) based on their distribution; all categorical data were presented as a number (percentage). Patient and treatment-related characteristics in relation to the surgical procedure were studied using descriptive statistics. Potential

follow-up time was calculated with Kaplan–Meier estimate of potential follow-up (‘reverse Kaplan–Meier’).<sup>32</sup> Kaplan–Meier curves were used to assess PFS and OS. Nonoverlapping curves were compared with the log-rank test.

## RESULTS

### Patients

Between January 1991 and March 2016, a total of 32,057 patients received a gastrectomy or esophagectomy for gastroesophageal cancer in the Netherlands. Our initial PALGA search yielded summaries of 309 patients that could potentially be included in the current study. A total of 138 of these patients were excluded, because based upon the summaries of the pathology reports, it was clear that a biopsy was performed instead of a metastasectomy with curative intent. For the remaining 171 patients, the patient files (if available) were reviewed. Patients were excluded who did not receive a resection of gastroesophageal metastasis with curative intent (primary tumor left in situ, biopsy instead of resection, multiple other metastases left in situ, or metastasis not of gastroesophageal origin on definitive pathology) or who had unavailable patient files. The remaining 34 patients from 21 different hospitals were included. These patients were thus treated with a resection of hepatic or pulmonary metastasis from gastroesophageal origin with curative intent.

### Hepatic resection for metastases from gastroesophageal cancer

A resection of hepatic metastases was performed in 19 patients (Table 1). The (neo)adjuvant treatments are described in Tables 1 and 2. Extrahepatic metastasis prior to hepatic resection was present in 1 patient. This patient had a retrosternal metastasis that was treated with resection and radiotherapy. Metachronous metastases were diagnosed in 13 patients and synchronous metastases in 6 patients. The metastases were solitary in 16 patients and nonsolitary (2 metastases) in 3 patients.

The operative characteristics of the hepatic resections are displayed in Table 2a. Metastases were unilobar in 17 patients and confined to one liver segment in 12 patients. An R0 resection was achieved in 17 patients. After hepatic resection, complications were encountered in 6 patients. This led to a reintervention in 4 patients and death within 30 days in 1 patient. This patient had extensive cardiovascular comorbidities. He was readmitted after a postoperative hemorrhage. After a total intensive care unit stay of 26 days, this patient died due to ventricular fibrillation.

### Survival after hepatic resection

The median potential follow-up time was 54 months. Kaplan–Meier survival curves after hepatic resection for gastroesophageal cancer metastases are displayed in Fig. 1. The median progression-free survival was 16 months and the 1-, 3-, and 5-year PFS was 58%, 21%, and 21%, respectively. The median overall survival (OS) was 28 months and the 1-, 3-, and 5-year OS was 84%, 41%, and 31%, respectively.

A subgroup analysis of the 8 patients with gastric cancer hepatic metastasis showed a median OS of 23 months and the 1-, 3- and 5- year OS were 75%, 25% and 25% respectively. The 11 patients with esophageal cancer hepatic metastasis had a median OS of 52 months and the 1-, 3-, and 5-year OS was 91%, 55%, and 27%, respectively.

### Pulmonary resection for metastases from gastroesophageal cancer

A resection of pulmonary metastases was performed in 15 patients (Table 1). The (neo)adjuvant treatments are described in Tables 1 and 2. None of the patients had extrapulmonary metastases. Metachronous metastases were diagnosed in 14 patients and synchronous metastases in 1 patient. The metastases were solitary in 13 patients and nonsolitary (2 metastases) in 2 patients.

The operative characteristics of the pulmonary resections are displayed in Table 2b. An R0 resection was achieved in 12 patients, an R1–2 resection in 2 patients, and data on the radicality were missing in 1 patient. After pulmonary resection, complications were encountered in 6 patients, though data on complications were missing in 2 patients. The complication led to a reintervention in 4 patients and there was no 30-day mortality or in-hospital mortality. The median hospital stay was 7 days.

### Survival after pulmonary resection

The median potential follow-up time was 80 months. Kaplan–Meier survival curves after pulmonary resection for gastroesophageal cancer metastases are displayed in Fig. 1. The median PFS was 12 months and the 1-, 3-, and 5- year PFS was 40%, 40%, and 33%, respectively. The median OS was not reached and the 1-, 3-, and 5-year OS was 67%, 53%, and 53%, respectively.

A subgroup analysis of the 4 patients with gastric cancer pulmonary metastasis showed a median OS of 7 months. The 1-, 3-, and 5-year OS was 25%. The 11 patients with esophageal cancer did not reach the median OS and the 1-, 3-, and 5-year OS was 82%, 64%, and 64%, respectively.

**Table 1** Gastroesophageal cancer: patient and treatment-related characteristics in relation to surgical procedure

Characteristic		Hepatic resection (N = 19)		Pulmonary resection (N = 15)	
Gender	Female	4	21.1%	5	33.3%
	Male	15	78.9%	10	66.7%
Mean age (years)		±12.2	63.5	±8.79	
Mean BMI (kg/m <sup>2</sup> )	20.6	±3.49	24.5	±2.85	
	Missing	7	36.8%	3	20.0%
ASA score	I	3	15.8%	1	6.67%
	II	10	52.6%	6	40.0%
	III	2	10.5%	4	26.7%
	Missing	4	21.1%	4	26.7%
Organ of primary tumor	Stomach	8	42.1%	4	26.7%
Location of primary tumor	Esophagus	11	57.9%	11	73.3%
	Middle esophagus	0		2	13.3%
	Distal esophagus	7	36.8%	8	53.3%
	Cardia (esophagectomy)	3	15.8%	1	6.67%
	Cardia (gastrectomy)	1	5.26%	4	26.7%
	Corpus	2	10.5%	0	
	Antrum	4	21.1%	0	
	Pars pylori	1	5.26%	0	
	Missing	1	5.26%	0	
	Stage of primary tumor	0	1	5.26%	0
Histology of primary tumor	IA	3	15.8%	3	20.0%
	IB	1	5.26%	0	
	IIA	4	21.1%	6	40.0%
	IIB	2	10.5%	1	6.67%
	IIIA	5	26.3%	5	33.3%
	IIIB	1	5.26%	0	
	IV	2	10.5%	0	
	Adenocarcinoma	17	89.5%	9	60.0%
Differentiation of primary tumor	Squamous cell carcinoma	1	5.26%	4	26.7%
	Neuroendocrine carcinoma <sup>‡</sup>	1	5.26%	1	6.67%
	Undifferentiated	0		1	6.67%
	Moderately	8	42.1%	5	33.3%
	Poorly	4	21.1%	4	26.7%
(Neo)adjuvant therapy of primary tumor	Undifferentiated	0		1	6.67%
	Missing	7	36.8%	5	33.3%
	Neoadjuvant CRT	6	31.6%	4	26.7%
	Neoadjuvant CT	0		1	6.67%
History of extrahepatic or extrapulmonary metastasis prior to metastasectomy	Neoadjuvant and adjuvant CT	2	10.5%	3	20.0%
	None	11	57.9%	7	46.7%
	Yes	1	5.26%	0	
Interval diagnoses primary tumor and metastases	No	18	94.7%	15	100.0%
	Synchronous	6	31.6%	1	6.7%
Median interval (months) between diagnosis of primary tumor and diagnosis of metastases <sup>†</sup>	Metachronous	13	68.4%	14	93.3%
		20	11–27	30	18–39
	Missing	2	10.5%	1	6.67%
Number of metastases	1	16	84.2%	13	86.7%
	2	3	15.8%	2	13.3%

Data are *n* (%), mean (±SD), and median (IQR).

<sup>†</sup>For the metachronous tumors.

<sup>‡</sup>Both patients had a high-grade neuroendocrine neoplasm with a Ki-index of >20% or >20 mitoses per 10 high power fields, which were thus classified as neuroendocrine carcinoma.<sup>40</sup>

ASA, American Society of Anesthesiologists; BMI, body mass index; CRT, chemoradiotherapy; CT, chemotherapy.

### Disease-free interval subgroup analysis

Two further subgroup analyses were performed comparing OS for patients with a disease-free interval (DFI) of <24 months versus >24 months and comparing OS for patients with synchronous versus metachronous metastasis. These analyses are displayed in Online Supplementary Material 1.

### DISCUSSION

This study reports on patients who underwent a resection of hepatic and pulmonary metastases from gastroesophageal cancer. According to a meta-analysis published in 2018,<sup>28</sup> this is the first Western series on the resection of predominantly metachronous

**Table 2a** Hepatic resection: perioperative and histological outcomes

Outcomes		N = 19	
Neoadjuvant therapy prior to hepatic resection	Chemoradiotherapy <sup>†</sup>	2	10.5%
	Chemotherapy <sup>‡</sup>	1	5.3%
	Chemoradiation, followed by chemoimmunotherapy <sup>§</sup>	1	5.3%
	None	14	73.7%
Timing of hepatic resection	Missing	1	5.3%
	Before resection of primary tumor	1	5.3%
	Combined resection (of primary and metastasis)	3	15.8%
Year of hepatic resection	After resection of primary tumor	15	78.9%
	1995–2000	3	15.8%
	2001–2005	2	10.5%
	2006–2010	4	21.1%
Distribution	2011–2014	10	52.6%
	Unilobar	17	89.5%
Segments	Bilobar	2	10.5%
	1	12	63.2%
Mean diameter (in mm) of metastasis <sup>¶</sup>	>2	7	36.8%
	34.5		±37.5
Type of hepatic resection	Missing	2	10.5%
	Minor	16	84.2%
Radicality	Major	3	15.8%
	R0	17	89.5%
Complications	R1–2	2	10.5%
	Total	6	31.6%
	CD1	0	0.0%
	CD2	2	10.5%
	CD3	3	15.8%
Reintervention	CD4	0	0.0%
	CD5	1	5.3%
	4		21.1%
In-hospital or 30 day postoperative mortality	1		5.3%
Median hospital stay (days)	7		1–76
	Missing	3	

Data are *n* (%), mean (±SD), or median (range).

<sup>†</sup> Combined resection of primary tumor and metastasis; neoadjuvant therapy was aimed at the primary tumor.

<sup>‡</sup> Metastasis was initially too large for resection; however, after induction chemotherapy, resection could be performed.

<sup>§</sup> Metastasectomy was performed before resection of primary tumor.

<sup>¶</sup> Metastasis with largest diameter, as based upon pathology in 11 cases and computed tomography scan in 2 cases.

CD, Clavien–Dindo classification.

pulmonary metastasis from esophageal cancer. Metastasectomy was performed in selected patients with low postoperative morbidity and mortality rates, leading to a 5-year OS of 31–53%. The median OS was 28 months in the hepatic resection group and the median OS was not reached in the pulmonary resection group. The survival rates in these selected patients are favorable compared to the current standard treatment of best supportive care or palliative chemotherapy, which leads to a median survival of 4–11 months.<sup>14,15</sup>

Previous retrospective studies on patients with hepatic metastases from gastric cancer demonstrated a favorable survival after a hepatic resection.<sup>23,24</sup> Only 2 series with over 5 patients exist on hepatic metachronous metastases from esophageal cancer that were treated with esophagectomy and hepatic resection.<sup>28</sup> Liu *et al.* reported a 2-year OS of 21.2% in 26 patients and Adam *et al.* reported a 3-year OS of 12–32%.<sup>33,34</sup> The current study demonstrates a 3-year and 5-year OS of 55% and 27%, respectively, in 11 patients after hepatic resection.

Data on pulmonary resections for gastroesophageal pulmonary metastasis are also scarce. A recent systematic review on pulmonary resections for gastric cancer pulmonary metastasis found only 44 patients reported in the literature thus far and reported a median survival of 45 months.<sup>25</sup> In 3 small retrospective cohort series, all Japanese with predominantly squamous cell carcinoma, pulmonary resections for esophageal cancer pulmonary metastasis were found to be feasible and leading to a 5-year OS of 30–44%. They conclude that pulmonary resection could be considered in selected patients.<sup>27,35,36</sup> The current study, which included 15 Western patients with mostly gastroesophageal adenocarcinoma, also supports this conclusion.

Although hepatic and pulmonary metastasectomies may be performed rather safely, they do carry a certain risk. This is illustrated by 1 postoperative death and 7 postoperative reinterventions in 34 patients in the current study. In the selected patient group in this study, the risk for postoperative complications and death seems acceptable as relatively favorable OS rates

**Table 2b** Pulmonary resection: perioperative and histological outcomes

Outcomes		N = 15	
Neoadjuvant therapy prior to pulmonary resection	None	15	100.0%
Timing of pulmonary resection	Before resection of primary tumor	0	
	Combined resection (of primary and metastasis)	0	
Year of pulmonary resection	After resection of primary tumor	15	100.0%
	1991–1995	2	13.3%
	1996–2000	0	
	2001–2005	1	6.7%
	2006–2010	6	40.0%
	2011–2015	6	40.0%
Distribution	Left, superior lobe	2	13.3%
	Left, inferior lobe	4	26.7%
	Right, superior lobe	8	53.3%
	Right, inferior lobe	0	
	Middle lobe	0	
	Missing	1	6.7%
Mean diameter (in mm) of metastasis <sup>†</sup>		17.3	±12.6
Operative methods	Missing	2	13.3%
	Wedge resection	11	73.3%
	Segmentectomy	0	
Radicality	Lobectomy	4	26.7%
	R0	12	80.0%
	R1–2	2	13.3%
	Missing	1	6.7%
	Complications	Total	6
CD1		2	13.3%
CD2		0	
CD3		4	26.7%
CD4		0	
CD5		0	
Missing		2	13.3%
Reintervention		4	26.7%
In-hospital or 30 day postoperative mortality		0	
Median hospital stay (days)		12	3–41
	Missing	1	6.67%

Data are *n* (%), mean ( $\pm$ SD), or median (IQR).

<sup>†</sup>Metastasis with largest diameter, as based upon pathology in 11 cases and computed tomography scan in 2 cases. CD, Clavien–Dindo classification.

were achieved. In patients with metastatic gastroesophageal cancer, quality of life must be taken into account as well. Unfortunately, data on quality of life after resection of gastroesophageal metastases are lacking.

Metastasectomy of gastroesophageal hepatic or pulmonary metastases is not the standard of care in the Netherlands. The patients described in this study are highly selected. Most patients had metachronous metastasis with long intervals between diagnosis of the primary tumor and the metastasis. The metachronous presentation could be indicative of a more favorable cancer biology, as is the case for metachronous hepatic metastases from colorectal cancer.<sup>37</sup> Furthermore, except for one patient, all patients had oligometastatic disease. The majority of metastases were solitary and radically resected and a slight majority of the primary tumors were moderately differentiated. Comparable characteristics were also reported as favorable prognostic factors in the study by Kobayashi *et al.* on patients who underwent pulmonary metastasectomy of esophageal cancer metastases.<sup>27</sup> It is possible that

these factors contributed to the favorable survival in the current study and these factors could be used as a means of selecting physically fit patients for curative therapy, ideally within the context of a prospective study.

Only 7 patients in this study had synchronous oligometastasis and it is thus difficult to use the data in the current study to discuss a procedure to select these patients for curative therapy. For these patients, a tailored approach is required, which could include any combination of systemic therapy, resection of the primary tumor, and local treatment of the metastasis by resection or (stereotactic body) radiotherapy. Recently, the AIO-FLOT3 trial also demonstrated favorable results: a median OS of 31 months with perioperative chemotherapy and combined resection of the primary tumor and oligometastasis in patients with limited synchronous metastatic diseases.<sup>38</sup> The AIO-FLOT5 trial is currently investigating this approach in a randomized setting.<sup>39</sup>

A strength of this study is the use of the Dutch national registry for histo- and cytopathology, which

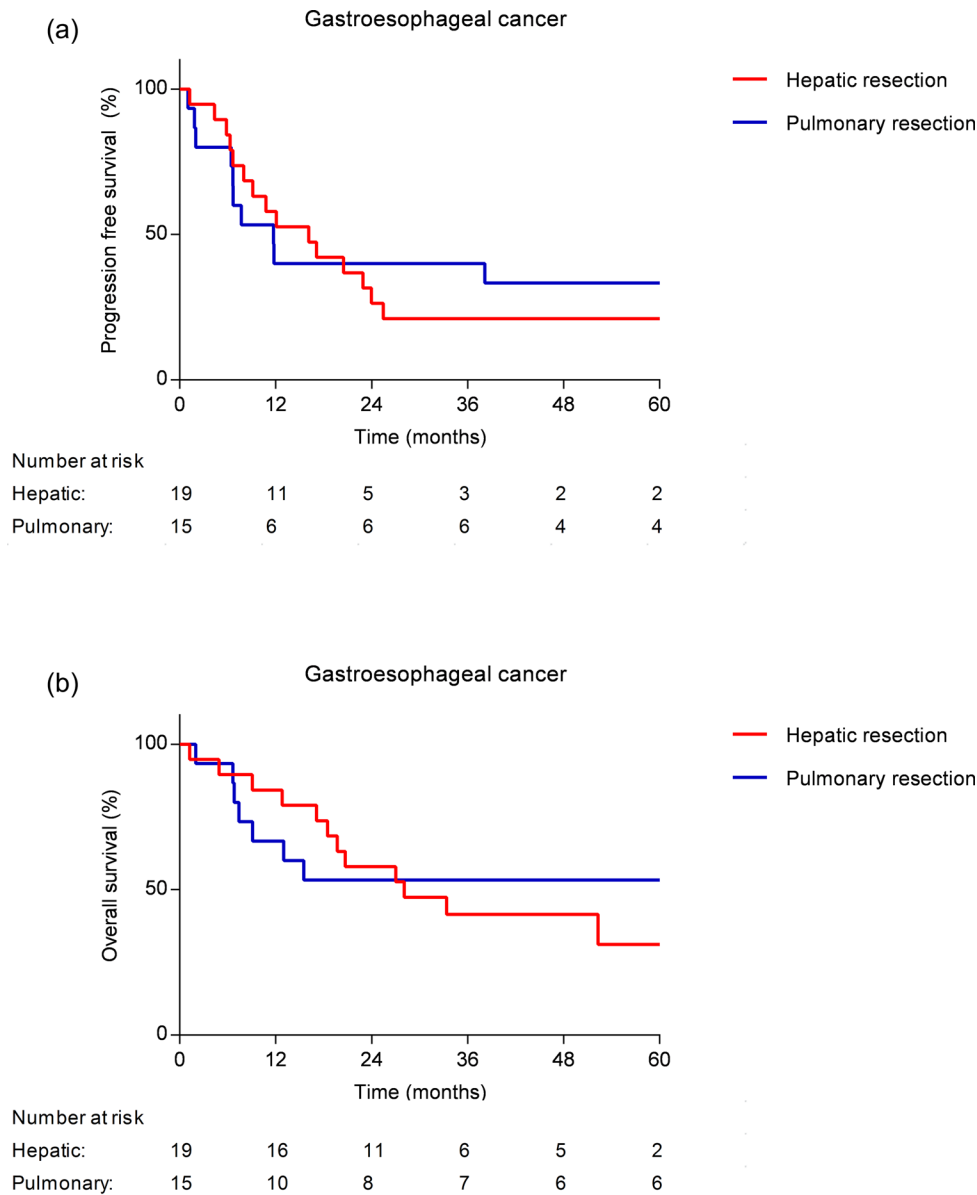


Fig. 1 Kaplan–Meier survival curves after hepatic or pulmonary resection, displaying PFS (a) and OS (b).

guaranteed the inclusion of all patients who underwent a hepatic or pulmonary resection with curative intent for metastatic gastroesophageal cancer (with available patient files) in the Netherlands within a time frame of 25 years. A limitation of this study is its retrospective nature. Especially in old patient files, some variables were missing and the reason why a resection was or was not performed was not always explicitly mentioned. The main limitation of this study is selection bias. Nevertheless, one could speculate that the favorable survival is unlikely to be the result of selection alone, but rather of selection in combination with metastasectomy.

In conclusion, in selected patients with gastroesophageal cancer with hepatic or pulmonary metastasis, metastasectomy was performed with limited morbidity and mortality and offered a 5-year OS of 31–53%. These results justify the conduction of

prospective studies with strict inclusion criteria, which can evaluate whether or not more patients can be selected for a metastasectomy and if an improvement in survival and quality of life is observed in a randomized setting.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

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