


## Current management of liver metastases from gastric cancer: what is common practice? New challenge of EORTC and JCOG

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**Abstract** The role of multidisciplinary treatment including surgery for liver metastases from gastric cancer (LMGC) is controversial. Studies to answer this clinical question are increasing in number, but all published data thus far are based on retrospective analyses with limited sample sizes. Thus, the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Group (GITCG) and the Japan Clinical Oncology Group (JCOG) Stomach Cancer Study Group (SCSG) initiated a collaboration to develop an optimal treatment strategy for LMG. Before planning a prospective study, a questionnaire was sent out to the network members of both groups in June 2016 to clarify current common practice in each region. Sixty-seven sites from 17 countries in the EORTC

network and 55 sites from Japan responded. According to the survey, for patients with resectable LMG without extrahepatic metastases, preoperative chemotherapy followed by resection of both primary (if still in place) and liver lesions was the preferred option for both the synchronous and the metachronous setting. For patients with unresectable LMG, most of the sites recommended chemotherapy only. In this article, the detailed results of this survey are reported, shedding light on current community practice, and a joint EORTC–JCOG strategy of investigation is delineated.

**Keywords** Gastric cancer · Liver metastases · Surgery · EORTC · JCOG

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## Introduction

Gastric cancer (GC) is the third leading cause of cancer-related death worldwide [1]. Surgery is the mainstay of multimodality treatment for localized GC, although, according to current guidelines, the standard for recurrent and metastatic GC is chemotherapy [2, 3]. The median overall survival (OS) for patients with unresectable GC remains 8–16 months [4–7]. Recently, in the reductive gastrectomy for advanced tumor in three Asian countries (REGATTA) trial conducted by the Japan Clinical Oncology Group (JCOG) and the Korean Gastric Cancer Association (KGCA), no survival benefit of reductive gastrectomy followed by chemotherapy compared with chemotherapy alone was reported for patients with advanced GC with a single noncurable factor [8], demonstrating that more effective treatment strategies are required to improve survival in this population [9, 10].

The liver is the most common site of hematogenous metastasis from GC. Liver metastases (LM) from GC (LMGC) are diagnosed synchronously in 3–14% of patients with GC and metachronously in as many as 37% after curative gastrectomy [11, 12]. In contrast to LM from colorectal cancer, patients with LMGC have not been recommended to be candidates for surgery because of a high rate of simultaneous peritoneal seeding or extensive lymph node metastases [13].

However, a potential benefit of hepatectomy for a subpopulation of patients with LMGC has been reported in several studies within the past decade (Table 1). Even though almost all studies were small retrospective series, a limited number and small size of LM were favorable prognostic factors in patients who undergo hepatectomy. One multicenter retrospective analysis of 256 patients reported a promising median OS of 31.1 months [14]. A propensity-matched analysis using a national database in the United Kingdom showed that the prognosis of patients who underwent both gastrectomy and hepatectomy was better than of those who received no surgery [15]. The pooled analysis of nine retrospective studies in 679 patients indicated a potential survival benefit of surgery compared with chemotherapy alone (HR = 0.50; 95% CI, 0.41–0.61) [16]. Although the retrospective nature of these studies limits their value for clinical recommendations, it appears that there is a potential benefit of surgery for subpopulations of patients with LMGC. However, there are several unresolved clinical questions, such as the optimal indication for surgery and the role of preoperative or postoperative chemotherapy. The clinical outcome after hepatectomy alone is still poor, with a 5-year survival rate as low as 15–30%. In view of the dismal prognosis of patients with LMGC, there is an urgent medical need to develop more efficient treatment strategies.

For this reason, the EORTC GITCG and JCOG SCSG have decided to work together to develop a joint treatment strategy for LMGC. As an initial step, a center survey was conducted to establish what represents the standard or most commonly applied clinical practice in Europe and Japan. This article presents the results of this survey and delineates the vision to develop a joint treatment strategy for LMGC.

## The survey

The survey was sent to the network of the EORTC GITCG and JCOG SCSG. The respondents were instructed to provide answers based on their institutional policies. Seven questions were posed, covering the following topics:

1. The treatment of patients with cT3N0 GC with synchronous 2-cm solitary LM in a lateral liver segment.
2. The timing of surgery when both primary tumor and LM are present (this was asked for the sites that selected surgery in question 1).
3. The role of staging laparotomy/laparoscopy in synchronous LM.
4. The treatment of patients with two resectable metachronous LMGC in both lobes 2 years after curative gastrectomy.
5. The treatment of patients with ten unresectable metachronous LMGC in both liver lobes 2 years after curative gastrectomy.
6. Preferred first-line chemotherapy regimens for HER2-negative metastatic GC.
7. The number of GC patients with liver-limited metastases in 2015.

The survey was initiated on 14 June 2016, and the date of data collection cutoff was 13 July 2016. All responses were collected and analyzed by K.K. and S.S. (staff at EORTC headquarters).

## Results

Answers were collected from 67 sites (17 countries) in Europe and 55 sites in Japan (Supplemental Fig. 1). The answers are presented in Figs. 1, 2, and 3.

### Clinical practice for the treatment of synchronous resectable LMGC (questions 1–3)

Figure 1a shows that 47.5% of the sites perform preoperative chemotherapy followed by gastrectomy and hepatectomy whereas only 16.4% of sites perform chemotherapy

**Table 1** Previous studies to evaluate hepatectomy for liver metastases from gastric cancer (LMGC)

Author (journal, year)	Retro/prospective	Period	Single/multi center	n	Synchronous/metachronous	Neoadjuvant/adjuvant CTX (%)	5 years OS (%)	MST (months)	Prognostic factor
Miyazaki et al. [23] (Am J Gastroenterol, 1997)	Retro	1980–1994	Single	21	11/10	0/76	23.8	11	Solitary, RM $\geq$ 10 mm
Okano et al. [24] (Ann Surg, 2002)	Retro	1986–1999	Single	19	13/6	0/31	34	NA	Solitary, metachronous, well-differentiated, capsule formation
Shirabe et al. [25] (Hepatogastroenterology, 2003)	Retro	1979–2001	Single	36	16/20	NA/NA	26	NA	No. of metastases $\leq$ 3, no lymphovascular invasion
Adam et al. [26] (Ann Surg, 2006)	Retro	1983–2004	Multi	64	NA	13/42	27	15	
Sakamoto et al. [27] (J Surg Oncol, 2007)	Retro	1990–2005	Single	37	16/21	0/16	11	31	Unilobar, diameter $\leq$ 40 mm
Cheon et al. [28] (Ann Oncol, 2008)	Retro	1995–2005	Single	41	30/11	NA/88	21	17	Solitary, R0 resection
Thelen et al. [29] (Eur J Surg Oncol, 2008)	Retro	1988–2002	Single	24	15/9	NA/NA	10	9	RM0
Garancini et al. [30] (HPB, 2012)	Retro	1998–2007	Single	21	12/9	NA/5	19	11	Solitary, R0 resection, capsule formation
Takemura et al. [31] (Langenbecks Arch Surg, 2012)	Retro	1993–2011	Single	64	34/30	28/41	37	34	No serosal invasion, diameter $\leq$ 50 mm
Wang et al. [32] (BMC Surg, 2012)	Retro	2003–2008	Single	30	30/0	0/100	16.7	11	Solitary, no peritoneal dissemination
Schildberg et al. [33] (World J Surg, 2012)	Retro	1972–2008	Single	31	17/14	7/29	13	NA	Solitary, synchronous
Vigano et al. [19] (Hepatogastroenterology, 2013)	Retro	1997–2008	Single	20	9/11	40/NR	33.2	52.3	Solitary
Chen et al. [17] (World J Gastroenterol, 2013)	Retro	2007–2012	Single	20	20/0	100/100	15	22.3	
Wang et al. [34] (Med Oncol, 2014)	Retro	1996–2008	Single	39	39/0	0/100	10.3	14	Solitary, pN status
Aizawa et al. [35] (Hepatogastroenterology, 2014)	Retro	1997–2010	Single	53	53/0	0/77	18.6	27.4	Solitary
Kameda et al. [18] (World J Surg, 2014)	Retro	2000–2012	Multi	24	1/23	43/63	40.1	22.3	$\leq$ 50 mm GCLM diameter
Kinoshita et al. [14] (Br J Surg, 2015)	Retro	1990–2010	Multi	256	106/150	NA/67	31.1	31.1	No serosal invasion, no. of metastasis $\leq$ 3, diameter $\leq$ 50 mm

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Table 1 continued

Author (journal, year)	Retro/prospective	Period	Single/multi center	<i>n</i>	Synchronous/metachronous	Neoadjuvant/adjuvant CTx (%)	5 years OS (%)	MST (months)	Prognostic factor
Oki et al. [36] (Gastric Cancer, 2016)	Retro	2000–2010	Multi	94	37/57	NA/69	42.3	40.8	Solitary diameter <30 mm pN0/1
Tatsubayashi et al. [37] (Gastric Cancer, 2016)	Retro	2000–2014	Single	28	15/13	NA/NA	59	49	Age ≥70 years, synchronous liver metastases, presence of postoperative complications
Marker et al. [15] (Gastric Cancer, 2016)	Retro	1997–2012	National survey	78	78/0	NA/NA	38.5	NA	
Tiberio et al. [38] (Ann Surg Oncol, 2015)	Retro	1997–2011	Multi	53	53/0	NA/53	9.3	13	T stage, H3 hepatic involvement

CTx: chemotherapy, *n* number, OS overall survival, MST median survival time

one. Twenty-two percent of the sites perform upfront gastrectomy and hepatectomy. Looking at differences between Europe and Japan (Fig. 1b), there is a tendency that European sites prefer chemotherapy alone compared to surgery alone (26.9% vs. 7.5%) whereas the Japanese sites prefer upfront surgery compared to chemotherapy alone (40.0% vs. 3.6%). Regarding the timing of resection of the primary and LM, 89% of the sites perform gastrectomy and hepatectomy at the same time. Staging laparoscopy/laparotomy is performed at only half the sites for this situation.

#### Clinical practice for the treatment of metachronous resectable LMGC (question 4)

As with synchronous disease, preoperative chemotherapy followed by surgery is the preferred option in cases of metachronous LMGC. Figure 2a shows that 50.4% of the sites are treating patients with preoperative chemotherapy followed by hepatectomy, and 24% of the sites prefer chemotherapy alone. Radiofrequency ablation (RFA) is performed in 10% of the sites if the maximal diameter of the liver metastasis is less than 3 cm. When focusing on European sites, 33.3% and 30.3% choose preoperative chemotherapy followed by surgery and chemotherapy alone, respectively. For the Japanese sites, 70.9% and 16.4% choose preoperative chemotherapy followed by surgery and chemotherapy alone, respectively (Fig. 2b).

#### Clinical practice for the treatment of unresectable LMGC (question 5)

For unresectable LMGC, 85% of the sites perform chemotherapy alone (Supplemental Fig. 2). Conversion to resectable disease is not intended in most sites. No difference was seen between European and Japanese sites.

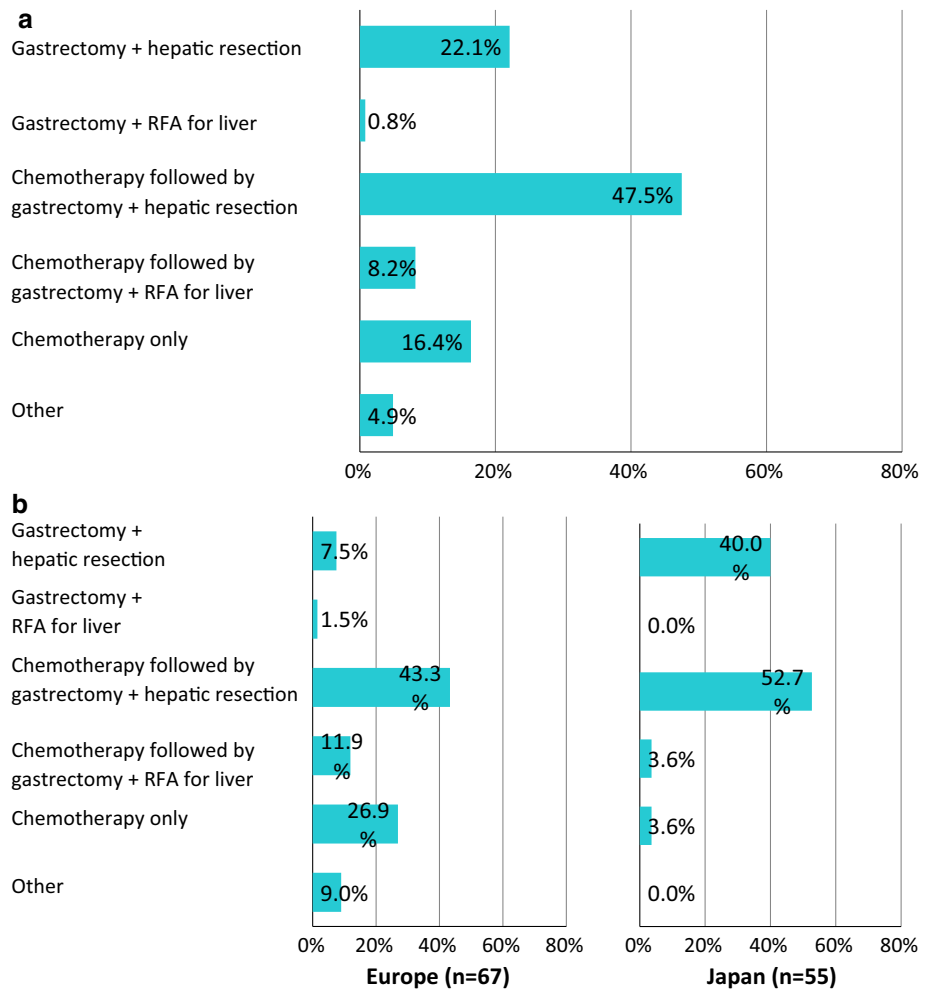
#### Chemotherapy regimen (question 6)

Platinum-based regimens are used at almost all sites, but the combinations vary among sites. Although regimens vary considerably among European countries, S-1 combined with oxaliplatin or cisplatin is preferred in almost all Japanese sites (Fig. 3).

#### Number of LMGC patients treated per year (question 7)

The median number of LMGC patients (without extrahepatic disease) treated in each site is 5 (range, 0–50). About 75% of the sites treat at most 5 LMGC patients per year.

**Fig. 1** Clinical practice for a patient with gastric cancer with synchronous solitary liver-limited metastasis: all sites (a) and sites in Europe and Japan (b)



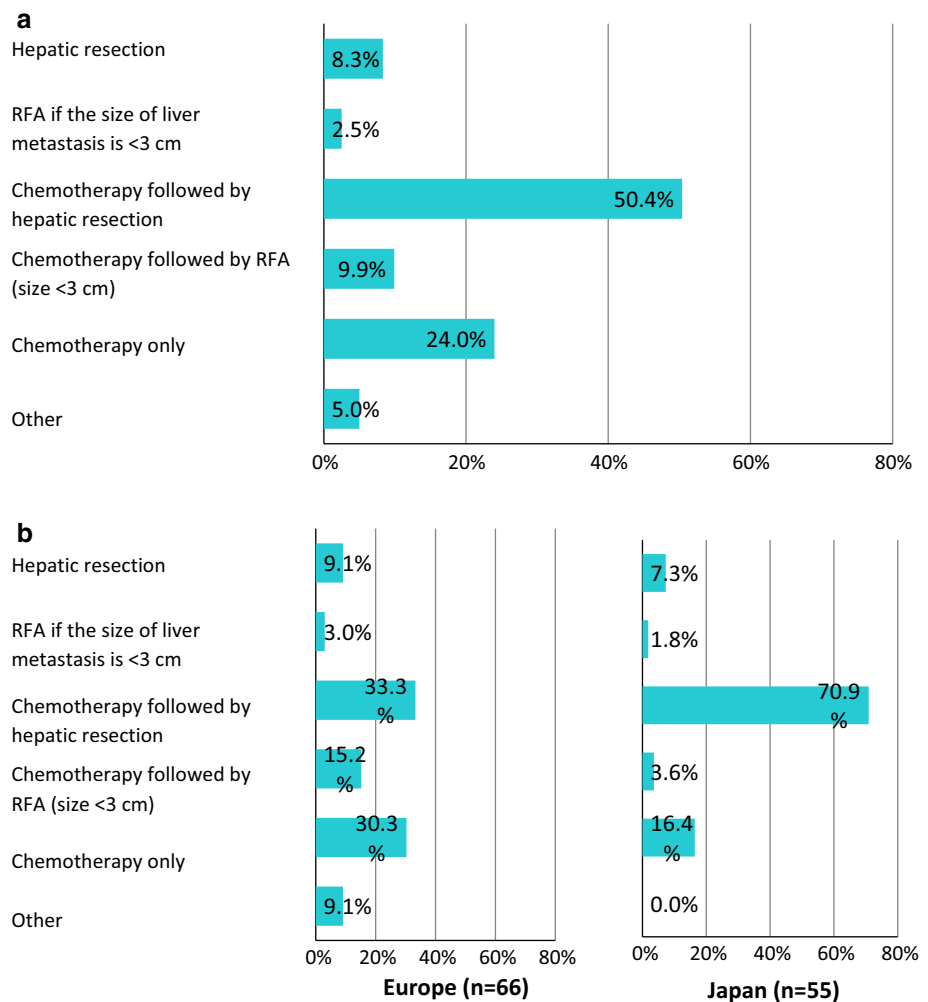
### What is the next step?

Three treatment options are mainly considered for resectable LMGC according to the survey: (1) chemotherapy alone, (2) upfront surgery, and (3) preoperative chemotherapy followed by surgery. Preoperative chemotherapy followed by surgery is the preferred option for both synchronous and metachronous resectable LMGC. Although chemotherapy alone is the recommended standard of care for LMGC patients in the guidelines [2, 3], the strategy of preoperative chemotherapy followed by surgery should be further explored for resectable LMGC. Regarding unresectable LMGC, most of the sites perform chemotherapy only. However, with the future introduction of more effective chemotherapy, conversion strategies might occur. Thus, prospective data should be collected to build a basis for developing more effective treatment strategies for this population.

Several questions arise from the results of our survey. First, the efficacy and safety data of preoperative

chemotherapy followed by surgery are still quite limited. The meta-analysis included only a few series investigating preoperative chemotherapy followed by surgery [17–19]. Evaluation of this approach by prospectively collected data is required because patients with disease progression during chemotherapy might have been excluded from the retrospective data analyses, biasing the reported study results. Second, it is not clarified whether we should differentiate the therapeutic approach between synchronous and metachronous LMGC. In the answers received from European sites, the treatment strategy is similar in synchronous and metachronous LMGC whereas upfront surgery is preferred in synchronous LMGC in Japan. As outlined in Table 1, some reports showed that synchronous disease is a prognostic factor, but this was not consistent. Because the condition is rare, we have to think carefully about whether the development of novel treatment strategies should be separated between synchronous and metachronous LMGC. The third question is the role of RFA, which is performed in about 10% of

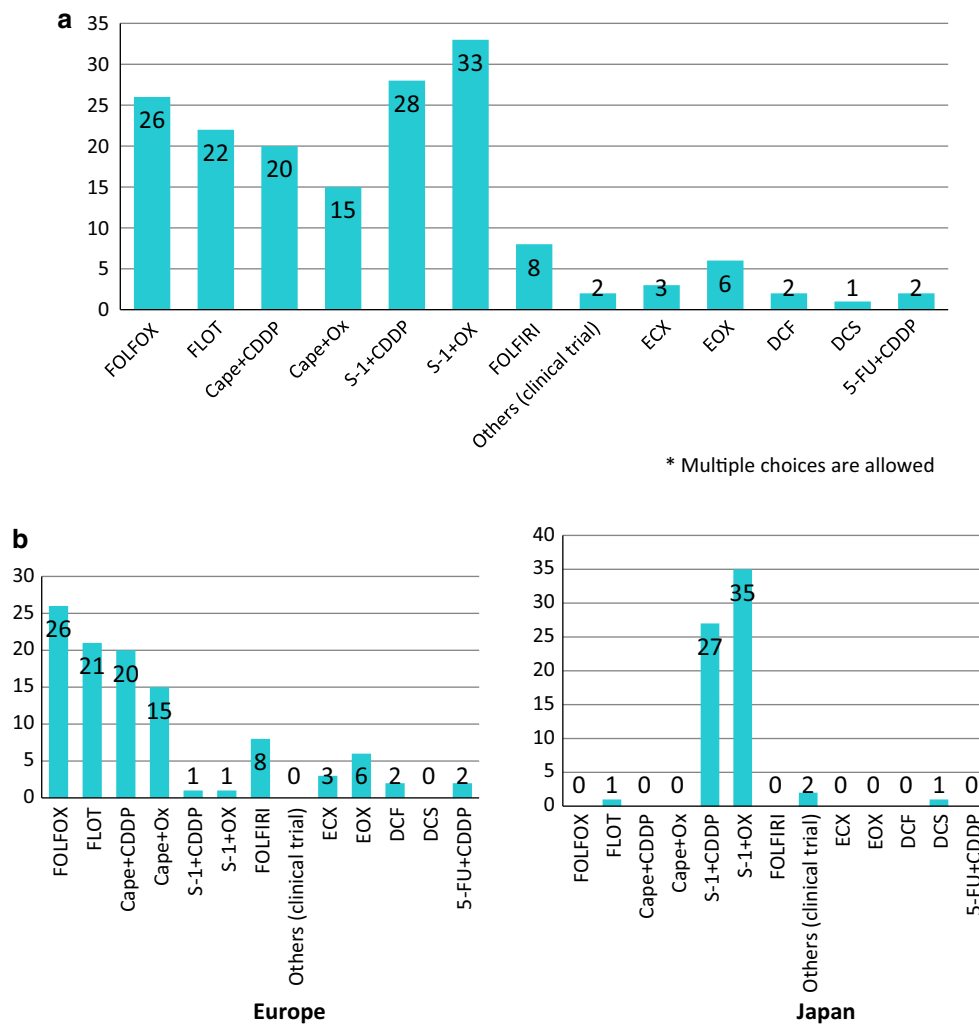
**Fig. 2** Clinical practice for a patient with metachronous resectable liver metastasis after curative resection of the primary tumor: all sites (a) and sites in Europe and Japan (b)



metachronous LMGC patients according to our survey. In addition, limited retrospective series indicate a potential benefit of RFA for LMGC [20, 21]. Taking into account that RFA is less invasive than surgery and that the treatment indication of RFA for colorectal LM has been expanding [22], treatment strategies including RFA should also be investigated.

So far, only one randomized controlled study is currently addressing the role of surgery for patients with metastatic GC. The *FLOT 5* study is now investigating the superiority of chemotherapy plus surgery compared with chemotherapy alone for patients with limited metastatic GC or esophagogastric junction (NCT02578368). Of note, this trial allows metastatic lesions aside from LMGC. In REGATTA [8], only 9% of the metastatic GC patients presented with LM only. EORTC GITCG and JCOG SCSG are now working together to develop a more efficacious multidisciplinary treatment strategy for LMGC. The exact design of the new collaboration project

is still under discussion. Although this survey showed some difference in preferred treatment strategies, and some difficulties in harmonizing scientific aspects such as the diagnostic procedure, chemotherapy regimen, and surgical procedures are anticipated, we agree to collaborate to improve the outcome of LMGC patients because the prognosis is still not sufficient. Currently, we are discussing the initiation of an interventional study on perioperative chemotherapy and hepatectomy with additional use of an investigational compound that may enhance the anti-tumor activity of perioperative treatment for LMGC patients. In parallel, an observational cohort in the form of a registry trial is planned to allow for better insights about what is done in clinical practice. Taking into account the need for international cooperation in this important field, this study should be led by large cancer research organizations such as EORTC and JCOG [39] to enable faster recruitment and wider generalizability of findings.



**Fig. 3** Preferred first-line chemotherapy regimens for HER2-negative gastric cancer in the metastatic setting: all sites (a) and sites in Europe and Japan (b)

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#### Compliance with ethical standards

**Conflict of interest** Florian Lordick is an advisory for BioNTech, Bristol-Myers-Squibb, Eli Lilly, GANYMED Pharmaceuticals, Merck Sharp & Dohme, Roche Pharma AG. He received lecture honoraria from Amgen, Astra Zeneca, Eli Lilly, Merck Sharp & Dohme, Roche Pharma AG. He has research grants from Boehringer Ingelheim, Fresenius Biotech and received travel grants from Amgen, Bayer, Merck Sharp & Dohme, Roche Pharma AG, Taiho Pharmaceutical. Anna Dorothea Wagner is a consultant for Eli Lilly, Roche, Merck, Celgene, Bayer, Taiho. She receives lecture fees from Lilly and Celgene, travel grants from MSD, Lilly, Bayer, Janssen, and

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**Human rights statement and informed consent** All the questions asked in this survey were about the preference of the clinical practice of each investigator. Any patient information such as names, initials, addresses, admission dates, hospital numbers, or any other data that might identify patients were not asked or included in this survey.

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