

Conversion surgery for gastric cancer patients: A review

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Abstract

Gastric cancer (GC) is the third most common cancer-

related cause of death worldwide. In locally advanced tumors, neoadjuvant chemotherapy has recently been introduced in most international Western guidelines. For metastatic and unresectable disease, there is still debate regarding correct management and the role of surgery. The standard approach for stage IV GC is palliative chemotherapy. Over the last decade, an increasing number of M1 patients who responded to palliative regimens of induction chemotherapy have been subsequently undergone surgery with curative intent. The objective of the present review is to analyze the literature regarding this approach, known as "conversion surgery", which has become one of the most commonly adopted therapeutic options. It is defined as a treatment aiming at an R0 resection after chemotherapy in initially unresectable tumors. The 13 retrospective studies analyzed, with a total of 411 patients treated with conversion therapy, clearly show that even if standardization of unresectable and metastatic criteria, post-chemotherapy resectability evaluation and timing of surgery has not yet been established, an R0 surgery after induction chemotherapy with partial or complete response seems to offer superior survival results than chemotherapy alone. Additional larger sample-size randomized control trials are needed to identify subgroups of well-stratified patients who could benefit from this multimodal approach.

Key words: Metastatic gastric cancer; Gastric cancer; Conversion surgery; R0 resection; Stage IV gastric cancer; Palliative chemotherapy; Unresectable gastric cancer

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Core tip: Conversion surgery is defined as a surgical treatment with the goal of R0 resection in initially unresectable gastric cancer patients after response to chemotherapy. Although the heterogeneity of metastatic disease factors makes it difficult to identify true prognostic variables, a survival benefit has been

demonstrated in several reports. Further prospective large-scale studies seem to be necessary to improve patient selection and to validate this promising multimodal therapy.

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INTRODUCTION

Gastric cancer (GC) is known to be the third most common cancer-related cause of death worldwide^[1]. Surgical treatment with adequate extended lymphadenectomy is associated with good outcomes in early stages. However, in advanced GC, prognosis remains poor. Neoadjuvant chemotherapy (NAC) has been suggested for resectable, locally advanced GC based on well-known Randomized Controlled Trial (RCT)s^[2,3]. Despite many enrolled patients having lower esophagus or esophagogastric junction involvement and surgery not always including a standard extended lymphadenectomy, there was a survival advantage of NAC plus surgery compared to surgery alone. Therefore, NAC, or preferably preoperative chemotherapy, has been recently introduced as an option in most treatment guidelines^[4-9].

The SEER database shows that one third of Western patients with GC have unresectable disease, and different strategies have recently been adopted to manage advanced unresectable cancer^[10]. Generally, in these cases, surgery is upfront considered as a palliative treatment for obstruction or bleeding.

Palliative chemotherapy remains the main treatment strategy of IV stage GC patients^[11]. Although the median survival time (MST) of these patients has improved due to development of new chemotherapeutic agents, it is still unsatisfactory. Therefore, patients who demonstrated a response to chemotherapy have begun to be subsequently surgically treated with curative intent. This approach in stage IV patients, called "conversion surgery", is becoming one of the most common therapeutic options discussed in the literature over the last decades. The aim of the present review was to define the effective usefulness of this strategy, to identify its crucial aspects and to highlight critical issues and implications for future perspectives.

Literature search

We analyzed articles published in English from 1997 to 2017 using the following key words: Conversion surgery, conversion therapy, R0 resection stage IV GC, unresectable GC. We excluded case reports and case

series, ultimately obtaining 13 articles for 13 studies. We first analyzed stage IV factors singularly to define major current therapeutic strategies for any selected patient, and then, we considered oncological outcomes of palliative chemotherapy through experiences derived from several trials. Therefore, we focused on the emerging role of conversion therapy as a new treatment option for metastatic gastric cancer patients.

STAGE IV GC

Stage IV GC is a heterogeneous biological condition with a mixture of distant metastases, including hematologic, lymph nodal and/or peritoneal. To reduce this heterogeneity, the Japanese Gastric Cancer Association (JGCA) and the Union Internationale Contre le Cancer (UICC) minimized differences between their classifications and categorized similar groups^[12-16]. However, these systems do not seem sufficient to derive any significant clinical suggestions.

In the recent classification introduced by Yoshida *et al*^[17] with the proposal to identify objective principles for conversion surgery, stage IV patients were subdivided into 4 new categories (Figure 1). Initially, the presence of macroscopic peritoneal dissemination is considered as a different biological and prognostic finding compared with hematological metastases. Patients without peritoneal involvement belong to category 1 (potentially resectable metastases) and category 2 (marginally resectable metastases). Patients with macroscopic peritoneal metastases are stratified into category 3 (unresectable except certain situations) and category 4 (incurable metastases). Below we highlight different critical aspects in terms of staging, treatment and prognosis of different potential metastatic patterns in stage IV GC.

Peritoneal metastases

Synchronous peritoneal carcinomatosis (PC) is the most frequent site of metastasis in stage IV GC. PC occurs in 14%-43% of GC patients and represents 35% of all synchronous metastases^[18,19]. The prognosis of PC in GC is worse than that for other metastatic sites^[20,21]. Peritoneal dissemination of GC is a dynamic multistep process that involves several molecules acting in a coordinated way. As reported in a recent review by Kanda *et al*^[22], there are 4 steps in peritoneal dissemination: (1) migration to the abdominal cavity after detachment of cells from the tumor; (2) adaptation to the abdominal microenvironment; (3) adhesion to mesothelial cells and invasion of the baseline membrane; and (4) growth and angiogenesis of the tumor. These molecular mechanisms are very challenging because identification of a single pathway is not necessarily correlated with disease prognosis.

Survival of patients with PC is poor, despite the progress of chemotherapy. Hence, PC is often considered a determinant for a "real" curative treatment possibility,

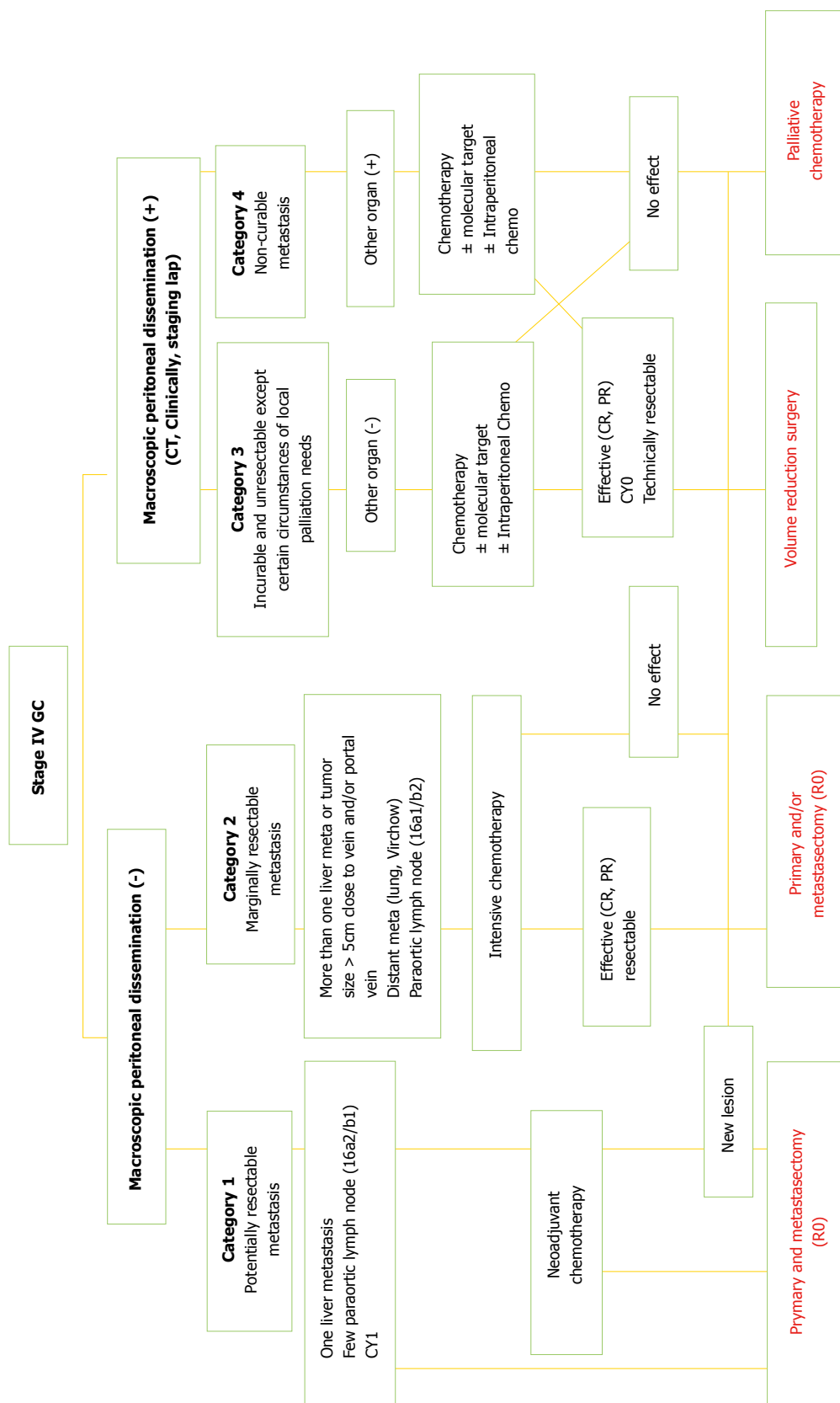


Figure 1 Biological categories proposed by Yoshida *et al.*^[17], GC: Gastric cancer.

and several scoring systems on extension of PC have been validated to accurately discriminate treatment options, stratify patients prognosis, and, consequently, correct statistical analyses^[23-25]. Okabe *et al.*^[26] noted that in curatively (R0) resected patients, after disappearance of limited peritoneal dissemination treated with induction therapy (S-1 plus cisplatin), MST was significantly longer (43.2 mo) than in patients who underwent non-curative resection (12.6 m), as well as in patients without surgery (10.3 m). To increase chemotherapy efficacy for PC, the literature suggests an additional benefit of hyperthermic intraperitoneal administration of drugs (hyperthermic intraperitoneal chemotherapy, HIPEC)^[27-31].

Recent advances in multimodal treatment for patients with peritoneal dissemination are highlighted by Ishigami *et al.*^[32] in the PHOENIX-GC trial that, although failing to show statistical superiority for intraperitoneal paclitaxel plus systemic chemotherapy, suggested possible clinical benefit for this treatment option. In a systematic review of 10 studies considering 441 patients treated with cytoreductive surgery plus HIPEC, a median overall survival of 15 mo after radical (R0) cytoreduction was shown by Gill *et al.*^[33]. Consistently, the phase III randomized trial by Yang *et al.*^[34] and the GYMSSA trial reported improved survival rates with surgery plus HIPEC compared with surgery alone^[35].

Distant metastasis

Many patients with stage IV GC have multiple metastatic sites. Usually, the first site of metastasis occurring through the hematogenous pathway is the liver. Systemic chemotherapy is a standard treatment approach for GC patients with liver metastases^[36], recommended by both the National Comprehensive Cancer Network (NCCN) Guidelines and the Japanese Guidelines^[37,38]. Surgical resection has been recently reported to prolong survival in highly selected patients^[39-41]. Li *et al.*^[42] reported a 100% response rate after chemotherapy with weekly DCF regimen before curative gastrectomy in 8 patients. A multidisciplinary approach, including surgery in selected GC patients when the liver is the only site of metastasis, is associated with interesting results^[43]. However, treatment of synchronous or metachronous hepatic metastases is not well standardized in GC patients. Once combined with gastrectomy and extended lymphadenectomy, there are no differences in 5-year survival after resection of synchronous and metachronous liver metastases^[44]. Considering metachronous metastases, patients submitted to surgery benefit from better selection and exhibit good survival over short and medium terms^[45]. Surgical treatment of the best subgroups of candidates can achieve good results that should encourage surgeons and medical oncologists^[41,46].

Lymph node metastases

A proper lymphadenectomy during surgical resection is a milestone for GC treatment. Patients with para-aortic lymph node (PAN) metastases, or bulky nodes around the hepatic, splenic, or celiac arteries are considered unresectable. Some retrospective studies demonstrated the presence of PAN metastases in greater than 20% of patients undergoing D2 + PAN dissection, and 5-year survival rates of patients with PAN metastases do not exceed 20%^[47,48]. Furthermore, a phase III trial JCOG9501 comparing D2 nodal dissection with or without PAN dissection for GC concluded that prophylactic PAN dissection does not improve survival rates^[49]. Interestingly, patients with macroscopic metastases in

these nodes were excluded from analysis, resulting in a low incidence of metastatic n° 16 nodes in patients receiving PAN dissection. This "selection bias" left open the issue of prognostic efficacy of removal of PAN station in PAN metastatic patients^[50]. On the other hand, since 2000, three phase II trials (JCOG0001, JCOG0405 and JCOG1002) have explored preoperative/induction chemotherapy and PAND gastrectomy for bulky N2/N3 gastric cancer^[51-54]. The JCOG0001 study reported a low 3-year survival rate (27%) after 2-3 cycles of irinotecan and cisplatin followed by surgery. Conversely, the JCOG0405 trial demonstrated an excellent response rate (up to 64.7%) with 3-year survival of 58.8% in patients who received 2-3 cycles of cisplatin and S-1 before surgery. Similarly, in the JCOG1002 study, among 52 eligible patients, 48 underwent surgery, 44 with R0 resection (84.6%), after 2-3 cycles of docetaxel, cisplatin and S-1 with a pathological response rate of 50%.

PALLIATIVE CHEMOTHERAPY

As specified above, according to current guidelines, palliative chemotherapy is the main strategy for treatment of stage IV GC patients. These cases have always represented the ideal setting for use of many new combinations of chemotherapeutic agents, both in Japan and in Western countries^[55-67]. The median overall survival observed in these studies varies between 3 and 17 mo. In the SPIRIT trial, an overall survival of 13 mo was reported using S-1 plus cisplatin, which is defined as the standard treatment for metastatic GC in Japan^[56]. In Western countries, the treatment most commonly used for metastatic GC is a combination of chemotherapy regimens, including fluoropyrimidine plus a platinum agent, though epirubicin or docetaxel can also be combined^[64,66]. Recent developments in chemotherapeutic and molecular targeted agents have added new clinical issues in the management of incurable GC. As reported in the ToGA trial, Trastuzumab plus chemotherapy in HER2-positive patients improved overall median survival from 11.1 to 13.8 mo^[60]. In addition, histological biomarkers have been identified to predict survival among GC patients^[68]. Recently, palliative chemotherapy seemed further validated compared with palliative surgery by results of the REGATTA trial. In fact, although some authors emphasized the beneficial role of palliative gastrectomy^[69,70], in this RCT, Fujitani *et al.*^[71] demonstrated no survival benefit for palliative gastrectomy prior to chemotherapy in advanced GC patients with a single non-curative factor. However, the methodological biases of the REGATTA trial negatively affect reliability of its results and weaken its potential clinical implications^[72]. Therefore, at the moment, for stage IV GC patients, we have no strong evidence to consider the results of palliative chemotherapy satisfactory. On the other hand, we also have no reliable data to suggest definitely abandoning surgery.

FROM SALVAGE SURGERY TO CONVERSION THERAPY

The heterogeneous presentation of stage IV GC characteristics makes it difficult to identify the best therapeutic strategy for these tumors due to their different biological behaviors. On the other hand, given the poor results achieved with chemotherapy alone, in order to further improve survival of these patients, new therapeutic approaches have been considered. Based on experiences of the multidisciplinary treatment of metastatic colorectal cancer, in the last 2 decades, many studies have been conducted to evaluate efficacy of the combination of chemotherapy and surgery for stage IV GC. Surgical resection for advanced tumors has historically been called "radical", "salvage", "adjuvant" or "secondary" gastrectomy. More specifically, the concept of conversion surgery has been recently treated by Yoshida^[17] to define a treatment aiming to R0 resection after chemotherapy in initially unresectable patients.

Tables 1 and 2 show patient characteristics and treatment options analyzed in the considered studies, as well as survival results. Below, we discuss in chronological order the main results of these studies, with particular focus on potential prognostic factors in conversion surgery strategy.

Examined studies

Probably, the first report of conversion surgery was in 1997 by Nakajima *et al*^[73]. Thirty patients with incurable GC were treated with combined chemotherapy and radical surgery. Survival of patients with curative resection was 55.6% at 5 years. Long-term survivors were exclusively found among patients with distant metastatic lymph nodes. PC and extra-abdominal lesions did not respond to chemotherapy and, hence, did not reach surgery^[73].

Yano *et al*^[74] analyzed 34 patients with inoperable GC who underwent NAC. Eight patients among 14 who received salvage surgery exhibited curative resection. Histological type, T4 as non-curative factors, clinical response, and salvage surgery were significant prognostic factors. T4 unresectable lesions and para-aortic node metastases showed high dissolution rates after chemotherapy, whereas peritoneal and distant metastases did not^[74]. A study on combined treatment with S-1 plus cisplatin followed by gastrectomy and post-operative S-1 for stage IV GC was conducted by Satoh *et al*^[75]. Their results showed that 26 patients among 44 who received preoperative chemotherapy underwent R0 surgical resection. Interestingly, all 12 patients with pre-cy1 as a single pre-stage IV factor achieved R0 resection with a 2-year OS of 75%^[75].

In 2012, Kanda *et al*^[76] reported a good response rate to S-1 chemotherapy in patients with incurable GC who were submitted to secondary surgery. Twenty-

six patients of 28 underwent R0 resection. The results showed that 1-, 3- and 5-year survival were 82.1, 45.9 and 34.4%, respectively. Multivariate analysis revealed histological lesion length to be the only significant prognostic factor^[76]. According to reports from Han *et al*^[77], 22/34 M1 patients with one initial metastatic site who responded to induction chemotherapy exhibited good survival outcomes after R0 resection, with resection rates of 88% and 44% for one and two metastatic sites, respectively. MST of R0 was 22.9 mo, with a 3-year overall survival of 41.4%. Concerning gastric cancer patients with peritoneal seeding, Kim *et al*^[78] published results of 18 conversion patients in which 10 received R0 resection after chemotherapy. MST and 3-year OS of R0 patients were 37 mo and 50%, respectively. Unexpectedly, 8 patients who received non-curative resection had longer survival rates than did other patients who continued chemotherapy^[78].

Fukuchi *et al*^[79] reported a series of 40 out of 151 patients who underwent conversion surgery. In 32 of them, it was possible to perform R0 resection with a 5-year OS of 49% (MST: 62 mo). By multivariate analysis, the presence of just one non-curative factor and R0 resection were significant independent predictors for good OS^[79].

Kinoshita *et al*^[80] analyzed the effects of conversion gastrectomy after docetaxel, cisplatin and S-1 (DCS) combined chemotherapy. Of 57 patients, 42 were categorized as unresectable, while 15 patients were potentially resectable cases, with a single incurable factor (16 a2-b1 metastases or < 3 peripheral liver metastases). The 3-year OS rate of potentially resectable cases was 92.9%, compared with 35.1% of unresectable cases^[80].

In a multi-institutional retrospective study, Sato *et al*^[81] highlighted pathological response as a significant independent predictor for OS. He determined that 33/100 patients were able to undergo conversion therapy. Almost eighty-five of them received an R0 resection after DCS chemotherapy with a pathological response rate of 78.8%. Five-year OS in R0 patients was 48.6%^[81].

Ten patients with one incurable factor were retrospectively analyzed by Einama *et al*^[82]. All cases were considered resectable after chemotherapy, achieving R0 resection. The authors reported a longer survival of surgical patients compared with those who received chemo alone (MST 29 mo). Non-invasive macroscopic type, higher differentiation, and absence of peritoneal dissemination were all favorable survival predictors^[82].

Another study concerning conversion surgery after combination chemotherapy of docetaxel, cisplatin, and S-1 from Mieno *et al*^[83] reported that 74.2% of the study population (23/31) underwent R0 resection in patients with stage IV GC initially deemed unresectable. Fifty-eight point one percent of patients had extra regional

Table 1 Patient characteristics and onco-surgical treatments

Reference	Period	Population (conversion surgery)	Median - age	Unresectable criteria				Chemotherapy	Surgery	Lymphadenectomy (D2 or more)	Ro	
				P1	H1	Cy1	PAN/N3					T4
Nakajima <i>et al</i> ^[73] , 1997	1989-1995	30 (19)	53	9 (30%)	11 (37%)	23 (77%)	8 (27%)	3 (10%)	FLEP	NS	NS	9 (30%)
Yano <i>et al</i> ^[74] , 2002	May 1994-Dec 1999	34 (14)	54.4 (31-73)	26 (76%)	4 (12%)	10 (3.4%)	12 (35%)	1 (0.3%)	FEMTXP or THP-FLPM	NS	NS	8 (24%)
Satoh <i>et al</i> ^[75] , 2012	May 2003-Mar 2008	51 (44)	63 (35-79)	24 (49%)	3 (6%)	12 (23%)	7 (14%)	5 (10%)	S1 + Cisplatin	TG (58%) DG (21.5%)	82%	26 (51%)
Kanda <i>et al</i> ^[76] , 2012	Apr 2000-Mar 2008	31(28)	65.5 (49-79)	7 (25%)	4 (14.3%)	15 (54%)	9 (32%)		S1 + Cisplatin or Paclitaxel or Irinotecan	TG (42.89%) DG (57.1%)	96.30%	26 (93%)
Han <i>et al</i> ^[77] , 2014	Jan 2000+Dec 2009	34 (34)	56 (28-71)	7 (14%)	5 (10%)	15 (29.4%)	7 (14%)		5-FU + Platinum or 5-FU + Platinum + Taxane	NS	NS	26 (76.5%)
Kim <i>et al</i> ^[78] , 2014	Jan 2003-Dec 2012	43 (18)	52.8 (32-72)	43 (100%)					5-FU + Cisplatin or S1 + Cisplatin	TG (72.2%) DG (27.7%)	100%	10 (55%)
Fukuchi <i>et al</i> ^[79] , 2015	Feb 2003-Dec 2013	151 (40)	66 (31-79)	11 (28%)	5 (13%)	3 (8%)	6 (15%)	26 (65%)	S1 + Cisplatin or S1 + Paclitaxel	TG (72.5%) DG (27.5%)	NS	32 (80%)
Kinoshita <i>et al</i> ^[80] , 2015	Apr 2006-Mar 2012	57 (34)	65 (30-78)	15 (26%)	18 (32%)	23 (40%)	2 (3.5%)		DCS	TG (64.7%) DG (26.5%)	50%	27 (79%)
Sato <i>et al</i> ^[81] , 2017	Dec 2002-Apr 2014	100 (33)	63 (26-78)	33 (33%)	29 (29%)	61 (61%)	14 (14%)	11 (11%)	DCS I line, CPT-11 II line	TG (84.8%) DG (12.1%)	100%	28 (85%)
Einama <i>et al</i> ^[82] , 2017	Jan 2009-Dec 2015	10	70.5 (59-86)	3 (30%)	1 (10%)	4 (40%)	1 (10%)		S1 + CDDP or DOC	TG (40%) DG (30%)	100%	10 (100%)
Mieno <i>et al</i> ^[83] , 2017	Oct 2006-Dec 2012	31 (31)	63 (35-78)	25%	16%	58%	26%		DCS + DS (Docetaxel-S1) in responder patients	TG (74.2%) DG (22.6%)	77%	23 (74%)
Yamaguchi <i>et al</i> ^[84] , 2017	2001-2013	259 (84)	61.7 (21-78)	35 (41%)		37 (44%)	34 (40%)		DCS or S1 or S1 + Cisplatin or S1 + Taxane	TG (82.1%) DG (17.9%)	NS	43 (51%)
Morgagni <i>et al</i> ^[85] , 2018	Apr 2005-Aug 2016	73 (22)	69 (59-74)						Epirubicin + Cisplatin + 5-FU or Oxaliplatin + 5-FU or Docetaxel + Oxaliplatin + 5-FU or Other	TG (72.7%) DG (22.7%)	91.90%	22 (100%)

P1: Peritoneal carcinomatosis; H1: Hepatic metastases; Cy1: Positive cytology; PAN: Para-aortic node metastases; TG: Total gastrectomy; DG: Distal gastrectomy; DCS/DS: Docetaxel-Cisplatin-S1/Docetaxel-Cisplatin; FEMTXP: Fluorouracil, epirubicin, methotrexate, cisplatin; THP-FLPM: Pirarubicin, 5-FU, Leucovorin, Cisplatin, mitomycin C; FLEP: 5-FU + Leucovorin + Etoposide; CDDP: Cisplatin; DOC: Docetaxel; NS: Not specified.

lymph node as unresectable factor^[83].

In a study by Yamaguchi *et al*^[84], 84 patients among 259 with stage IV GC received conversion surgery after chemotherapy. Patients were classified into four categories

Table 2 Overall survival and median survival time

Reference	Years	OS (rate)			MST (mo)		
		CHT	CHT + surgery		CHT	CHT + surgery	
			R1/R2	R0		R1/R2	R0
Nakajima <i>et al</i> ^[73] , 1997	2/3-yr 5-yr			55.6	4.7	6.5	
Yano <i>et al</i> ^[74] , 2002 ²	2/3-yr 5-yr						
Satoh <i>et al</i> ^[75] , 2012	2/3-yr 5-yr		43	75 ¹			19.2
Kanda <i>et al</i> ^[76] , 2012	2/3-yr 5-yr		0	45.9 34.4			29
Han <i>et al</i> ^[77] , 2014	2/3-yr 5-yr			41.4		7.8	22.9
Kim <i>et al</i> ^[78] , 2014	2/3-yr 5-yr	0	0	50	8	18	37
Fukuchi <i>et al</i> ^[79] , 2015	2/3-yr 5-yr				14	30	62
Kinoshita <i>et al</i> ^[80] , 2015	2/3-yr 5-yr	1	15	49	9.6	29.9	
Sato <i>et al</i> ^[81] , 2017	2/3-yr 5-yr	18.7	0	48.6	15.7	21.7	47.9
Einama <i>et al</i> ^[82] , 2017	2/3-yr 5-yr						29
Mieno <i>et al</i> ^[83] , 2017	2/3-yr 5-yr	56.9		73.1		56.1	
Yamaguchi <i>et al</i> ^[84] , 2017	2/3-yr 5-yr				11.3	21.2	41.3
Morgagni <i>et al</i> ^[85] , 2018	2/3 yr 5 yr	0		39.4	14		38 ³

¹R0 in only pre-Cy1 patients; ²No data are specified but a *P* value < 0.0003 is shown between resected and not-resected 5-years OS rate; ³Patients who had cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy had an MST of 50 mo. OS: Overall survival; MST: Median survival time; CHT: Chemotherapy.

previously published by the same authors^[17]. Survival results of this series rose from 24.7 to 31.0 of MST. Patients who underwent R0 resection had an MST of 41.3 mo^[84]. Recently, Morgagni *et al*^[85] reported a Western series of 22 patients among 73 unresectable subjects who underwent R0 resection after induction chemotherapy. Gastrectomy plus HIPEC was performed in 9 patients. The 1- and 3-year survival rates were 63.6% and 39.4%, respectively^[85].

DISCUSSION

Gastric cancer is known to be a heterogeneous disease. Dissemination may occur directly to the peritoneum, through the hematogenous and lymphatic systems. Moreover, the method whereby cancer cells enter into the portal circulation varies, resulting in significant variability of metastatic patients both for the site and the amount of tumor. Consequently, few metastatic patients are eligible for conversion surgery. Moreover, frequent coexistence of different factors of incurability make it difficult to identify true prognostic variables, as well as the rate of response to chemotherapeutic treatments. Despite progress in chemotherapy providing significant hope with new drug agents, the response rates of metastatic GC patients remain unsatisfactory

with non-optimal patient compliance. The definition of initial unresectable criteria and post-chemotherapy resectability has yet to be established. In many cases, the line between neoadjuvant and induction chemotherapy remains unclear. Therefore, analysis of experiences on conversion surgery in stage IV GC is very challenging due to the heterogeneity of series, makes it very difficult to compare results from different studies. Furthermore, the majority of analyzed studies have been performed in Eastern Asia (only one in Italy). As such, this could represent a potential bias for reliable evaluation independent of differences in chemotherapy schedules, quality of surgery, and patient biology, for example. Undoubtedly, the Regatta trial taught us that even a palliative gastrectomy increases patient morbidity compared with chemotherapy alone. Hence, a strict selection of patients who could potentially benefit from conversion surgery seems mandatory. Yoshida *et al*^[17] proposed a biological classification to stratify all stage IV GC patients to respond to this need (Figure 1). Probably, long-term survivors can be found mostly in the first three categories, though the small number of patients in the first category can be explained by this unusual condition. Actually, these patients are likely to benefit from NAC.

Although analyzed studies were retrospective and

limited with respect to number of patients enrolled, the possibility of curative resection seems a crucial aspect. The literature reports R0 resection rates ranging from 24%-100% (Table 1), and these numbers are closely correlated with prognosis (Table 2). Thus, the survival benefit derived from R0 resections might justify a predictable increase in morbidity compared with survival from medical therapy alone. Interestingly, even non-curative resection often results in superior survival compared to chemotherapy alone. Consistent with this suggestion from the literature, quality of life (QOL) after conversion (even if non curative) surgery remains an intriguing issue to be analyzed. In this regard, a meta-analysis conducted by Lasithiotakis *et al*^[86] underlined the relevant role of QOL outcomes after palliative gastrectomy.

Consistent with considerations by Yoshida *et al*^[17], the presence of only one-site of metastasis is one of the most important prognostic factors according to most analyzed studies. In this literature review, lymph node metastases and positive cytology on peritoneal washing as unresectable factors are also related to better prognoses after conversion surgery when partial or complete response to chemo was observed. In this regard, while the more reliable (and later) evaluation of pathological response was demonstrated to be correlated with survival after conversion therapy, we have no unquestionable prognostic data and no objective criteria for clinical response assessment. Indeed, another determining factor is the detection of the best timing to operate (or to decide to not operate). Generally, surgery occurs when the tumor decreases in sizes and before it develops any drug resistance. For this determinant decision making step, cooperation between oncologists and surgeons is mandatory for general management of patients (and not the tumor alone). Regarding type of surgery and extension of lymphadenectomy, total or distal gastrectomy (also with multivisceral approach) aiming at R0 resection was generally associated with D2 or more extended lymphadenectomy. We believe that a proper and standardized D2 lymphadenectomy could achieve optimal results with acceptable morbidity/mortality. Finally, whether chemotherapy is required after an R0 resection is an issue that needs clarification.

In conclusion, the survival efficacy of conversion surgery may dramatically improve when combined with targeted chemotherapy. Perhaps new cytotoxic and molecular targeted agents and progress in sensitive molecular biomarker development could shift treatment from standardized to personalized, leading to further improved outcomes. The promising results of this multimodal therapy are increasingly gaining the attention of medical and surgical oncologists in planning further studies. Although it seems hard to design a valuable trial due to the difficulty of enrolling patients, it appears mandatory to demonstrate the effectiveness of this strategy in stage IV GC patients, or at least in well-

selected and stratified stage IV patient subgroups. On the other hand, given that long-time survivors exist, we are convinced that the multidisciplinary discussion should always be recommended on a case-by-case basis. In conclusion, it is well known that some decades ago patients affected by unresectable GC represented a large population on whom medical oncologists applied new and promising therapies without great success. Today, the strategy of conversion surgery induces oncologists to consider that surgery could still have a role, even after almost "hopeless" systemic therapy.

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