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REVIEW ARTICLE

A systematic review of surgery for non-curative gastric cancer

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Abstract
Background Most gastric cancer patients present with advanced stage disease precluding curative surgical treatment. These patients may be considered for palliative resection or bypass in the presence of major symptoms; however, the utility of surgery for non-curative, asymptomatic advanced disease is debated and the appropriate treatment strategy unclear.
Purpose To evaluate the non-curative surgical literature to better understand the limitations and benefits of non-curative surgery for advanced gastric cancer.
Methods A literature search for non-curative surgical interventions in gastric cancer was conducted using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases from 1 January 1985 to 1 December 2009. All abstracts were independently rated for relevance by a minimum of two reviewers. Outcomes of interest were procedure-related morbidity, mortality, and survival.
Results Fifty-nine articles were included; the majority were retrospective, single institution case series. Definitions describing the treatment intent for gastrectomy were incomplete in most studies. Only five were truly performed with relief of symptoms as the primary indication for surgery, while the majority were considered non-curative or not otherwise specified. High rates of procedure-related morbidity and mortality were demonstrated for all surgeries across the majority of studies and treatment-intent categories. Median and 1-year survival were poor, and values ranged widely within surgical approaches and across studies.
Conclusions A lack of transparent documentation of disease burden and symptoms limits the surgical literature in non-curative gastric cancer. Improved survival is not evident for all patients receiving non-curative gastrectomy. Further prospective research is required to determine the optimal intervention for palliative gastric cancer patients.

Keywords Advanced disease · Non-curative · Palliative · Surgery

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Introduction

Less than 25% of gastric cancer cases are diagnosed when the tumor is still confined to the stomach and potentially

curable in North America and Europe [1–3]. Data from the Surveillance Epidemiology and End Results Database (SEER) report that in 31% of cases the tumor has already directly spread outside the stomach or regional lymph nodes, and in 34%, the tumor has metastasized to distant organs [3]. This translates into 5-year survival of 27.8% and 3.7% for regional and distant gastric cancer [1, 3]. Poor survival is credited to the late-stage presentation that precludes standard curative surgical resection and the lack of a durable response to chemotherapy [4–6]. While strides are being made in the detection and treatment of gastric cancer, questions regarding the optimal management of advanced gastric cancer remain unanswered. Advanced gastric cancer may present with significant life-threatening symptoms such as bleeding or obstruction; however, the majority of patients present with more insidious symptoms such as poor appetite, weight loss, early satiety, gas, bloating, pain or anemia [7–9]. While not immediately compromising the patient's life, the management of this local disease may significantly impact the patient's quality of life and overall survival.

The World Health Organization (WHO) defines palliation as 'interventions neither hastening death nor prolonging survival while providing relief from pain and other distressing symptoms' [10]. Therefore, palliative treatments are directed toward, and their success measured by, the ability to alleviate symptoms and improve quality of life. Non-surgical therapeutic options include chemotherapy, radiotherapy or stent placement. Surgery for symptoms may include gastrectomy or bypass [4–6].

While there is general agreement that surgery is indicated to provide palliation of the major symptoms such as bleeding and/or obstruction, the optimal surgical management of patients with minimal symptoms and non-curative disease is debated. Non-curative surgery for advanced gastric cancer cannot be considered truly palliative if performed in the absence of symptoms. The National Comprehensive Cancer Network (NCCN) recommends that patients with metastatic disease are not candidates for surgery unless they present with obstruction; however, the Japanese Gastric Cancer Association (JGCA) guidelines indicate that patients with metastases may be candidates for gastrectomy without major symptoms [5, 6]. Many authors advocate for non-curative resection of advanced gastric cancer, drawing attention to higher survival rates for patients treated with gastrectomy compared with those managed with bypass or with supportive care. The evidence supporting these arguments is derived from retrospective case series and also indicates high rates of procedure-related morbidity and mortality [11–13]. Significant selection bias exists as a result of the undocumented operative decision-making process based on the presence or absence of co-morbidities and the level of metastatic disease burden, affecting the estimates of procedure-related mortality and overall survival. Complicating matters further are the difficulties in retrospectively differentiating a truly palliative patient (treated for relief of symptoms) from one managed non-curatively and the inconsistent definitions of palliation utilized in the literature [14].

The burden of non-curative, advanced gastric cancer is large and the use of non-curative gastrectomy widespread; however, a clear consensus for the most favorable surgical treatment strategy is lacking. Given the high rates of procedure-related morbidity and mortality for surgery and proven improvements in survival with chemotherapy, it is not often clear which therapy would offer advanced patients the best improvement in quantity and quality of life. Without evidence from randomized controlled trials and the equivocal state of the surgical literature, the individual clinician must consider and weigh multiple factors such as age, co-morbidities and the extent of disease in devising a treatment plan for these advanced patients. Given the recent systematic review of the use of palliative stent placement in gastrointestinal cancers [15] and a Cochrane Review of chemotherapy for advanced gastric cancer [16], the need for a comprehensive review of the existing surgical literature for non-curative gastric cancer from both a methodological and clinical standpoint was warranted. Consequently, we performed a systematic literature search to determine outcomes associated with surgical interventions for non-curative gastric cancer.

Methods

Data sources

Electronic literature searches were conducted in MEDLINE and EMBASE from 1 January 1985 to 1 December 2009 according to the search algorithm presented in the Appendix (Table 8). Search terms included: [exp Stomach Cancer/or (((gastric or stomach) adj1 cancer$) or ((gastric or stomach) adj1 carcinoma) or ((gastric or stomach) adj1 adenocarcinoma) or ((gastric or stomach) adj1 neoplasm$)).mp.] and [(exp palliative therapy/) or (exp terminal care/) OR (palliat$.mp.) or ("stage iv".mp.) OR (advanced disease.mp.)] and [clinical trial/or controlled clinical trial/or exp comparative study/or meta-analysis/or multicenter study/or exp practice guideline/or randomized controlled trial/] not [Case Report/or review]. A separate search of the Cochrane Central Register of Controlled Trials (1998–2009) was performed using the search term "gastric cancer." Searches were limited to English language and primary reports. No attempt was made to locate unpublished material.

Study selection and review process

To be eligible, studies had to meet the following criteria: (1) total sample size >30 patients and (2) report procedure-related morbidity, mortality, median survival or 1-year survival. Studies were excluded according to the following exclusion criteria: (1) reviews, meta-analyses, systematic reviews, abstracts, editorials or letters, case reports and guidelines, (2) 75% of data collection years <1985, (3) previously reported data or (4) mixed cancer types, with the inability to abstract outcomes for gastric cancer. All electronic search titles, selected abstracts and full-text articles were independently reviewed by a minimum of two individuals (NC, AM and LH). Reference lists from review papers and relevant articles were also examined for additional studies that met our inclusion criteria. Disagreements on study inclusion/exclusion were resolved with a consensus meeting. In the cases of repetitious reporting, the most comprehensive dataset from the most recent year was included from each institution.

Data extraction

A systematic approach to data extraction was used to produce a descriptive summary of participants, interventions and study findings. The following data points were collected during the review: study characteristics (country, study design, years of data collection), patient characteristics (age, description of population, cancer stage, number of patients, treatment strategy), procedure-related morbidity, mortality, median survival and 1-year survival. The first reviewer (AM) independently extracted the data, and a second reviewer (NC, LH) checked the data extraction. No attempt was made to contact authors for additional information.

Data analysis

The terminology "palliative" and "non-curative" are frequently used interchangeably and with variable definitions; therefore, definitions of gastrectomy intent were re-analyzed for each article and re-classified according to the following definitions: palliative (PAL)-referring specifically to the alleviation of symptoms or improvement of quality of life as the primary reason for performing the surgery; non-curative (NC)—referring to metastatic disease, lymph node involvement, positive resection margins or not specifically for the palliation of symptoms; not otherwise specified (NOS)—operative definition for palliative or non-curative not provided but surgery performed in patients with advanced disease. Ranges for each outcome (procedure-related morbidity, mortality, median survival and 1-year survival) are reported by treatment intent and surgical strategy.

Results

The systematic literature review process identified 1,939 unique abstracts from the Medline and Embase databases (Fig. 1). No articles were found searching the Cochrane Central Register of Controlled Trials database or from the manual search of bibliographies. Of the 1,939 abstracts, 201 articles were reviewed for inclusion in this review, and 59 articles were included in this review [11–14, 17–70]. One author reported complementary outcomes on a single patient population in two articles, so the results were included as one study [66, 67]. Due to the overall poor methodological quality of the data and heterogeneity of patient groups and definitions of palliation, quantitative analysis could not be completed.

Study and patient characteristics

The study and patient characteristics are described in detail in the Appendix (Tables 9, 10). The literature spanned 18 countries with 59% (34 studies) reporting on patients from Asia. The majority of the studies were single institution case series (50/58), while the remaining were multi-institution. None of the study designs were randomized controlled trials, and only three were prospectively designed to study the outcomes of an advanced gastric cancer population [52, 58, 59]. None of the studies discussed their sample size calculations, detectable effect sizes or study power.

The majority of the patients were described as having "incurable," "unresectable" or "advanced" disease, while a few reported outcomes for specific clinical subsets of these populations (e.g., liver metastasis, peritoneal dissemination). Intent of surgery for studies reporting outcomes for gastrectomy was re-defined according to the review criteria (Appendix Table 10). Only 9% of the studies reporting outcomes performed a truly palliative (PAL) resection per the definition that surgery was performed specifically for relief of symptoms [14, 26, 39, 46, 56] The correct definition for the intent of surgery for the rest of the articles was either non-curative (NC) [11, 12, 14, 19, 21, 23, 27, 32, 35–38, 40, 42, 47, 49, 51, 54, 57, 58, 61, 63, 66–68, 70, 71] or not otherwise specified (NOS) [13, 17, 18, 20, 24, 25, 28–31, 33, 39, 41, 43, 48, 50, 52, 53, 55, 59, 60, 69]. Mean patient age ranged from 51 to 76.4 years. Within the entire population of each study, the proportion of stage IV disease ranged from 12 to 100%. Stage distribution was rarely reported by palliative or non-curative treatment strategy. Studies reporting outcomes for palliative resection documented gastrointestinal bleeding, pain, obstruction and weight-loss as the most common symptoms at presentation [14, 26, 39, 46, 56].

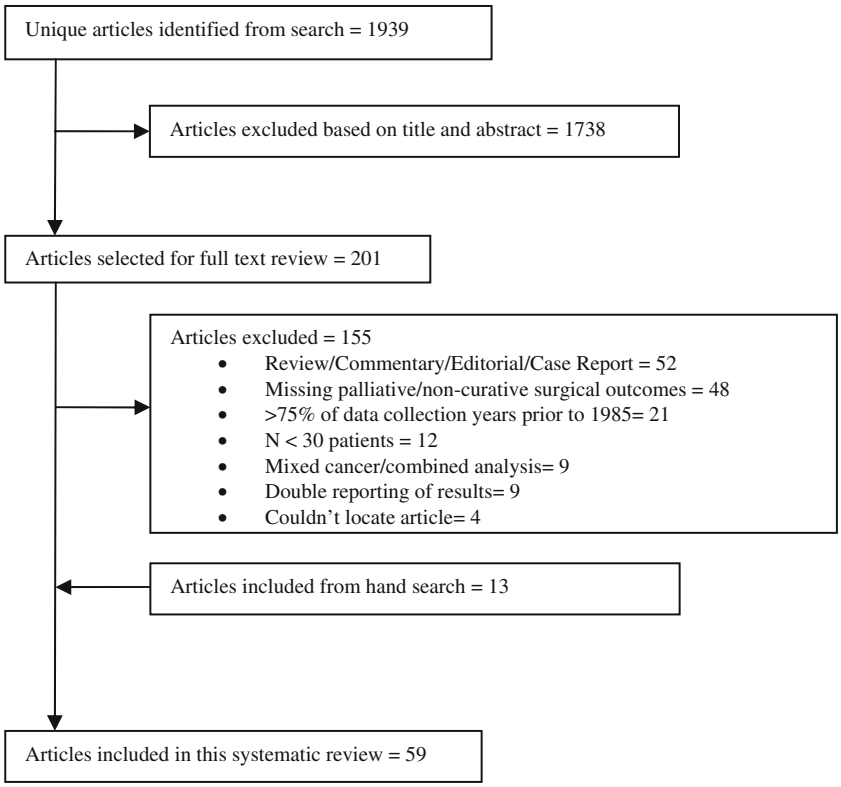

Fig. 1 Literature review selection process

Procedure-related morbidity and mortality

Authors recorded procedure-related morbidity in 12 articles (Table 1) [12, 13, 18, 26, 27, 31, 45, 56–58, 65–67]. Morbidity was generally defined as those complications, excluding death, occurring during the hospital stay that related to the operation performed. The list of complications covered by the definition varied by study, and complications were often defined for collection post hoc. It was not possible to determine if all potential complications related to a procedure were measured or recorded. Substantial procedure-related morbidity appeared to occur alongside all surgical interventions, whether a resection was performed or not, and irrespective of the intent of the resection. Morbidity for gastrectomy ranged from 3.8% (NOS gastrectomy) to 49% (NC total gastrectomy) (Table 1). For non-resectional interventions, procedure-related morbidity ranged from 14 to 21% (Table 1).

Procedure-related mortality was reported by 37 studies for gastrectomy (Table 2) and by 19 studies for surgical bypass or exploratory laparotomy (Table 3). Procedure-related mortality was most commonly defined as occurring within 30 days of the operation and/or prior to hospital discharge. Mortality ranged from 0 to 21% for gastrectomy (any intent) (Table 2). Palliative resections reported lower mortality (0–7%) compared with the NOS (0–20.4%) and NC (0–21%) resections (Table 2). Procedure-related mortality was high for non-resectional surgery: surgical bypass (0–33% and exploratory laparotomy (8–39%) (Table 3).

Long-term survival

Median survival for gastrectomy was reported in 32 studies (Table 4) and 1-year survival reported in 20 studies (Table 5). Median survival was reported in 21 studies for non-resectional surgery (Table 6) and 1-year survival in 10 studies (Table 7). The range for median survival was tightly contained for PAL gastrectomy (9–13 months) and less precise in the NC (5–24 months) and NOS (3–20.6 months) treatment-intent groups (Table 4). The extent of resection did not appear to confer or diminish any additional survival benefit. One-year survival was not reported in any PAL gastrectomy series, and ranged from 12 to 66.7% for NC and 26.6–80.3% for NOS resections (Table 5). Median survival for patients receiving surgical bypass or exploratory laparotomy was low (3–12 months) (Table 6). Overall 1-year survival for surgical bypass or exploratory laparotomy was also poor, ranging from 3 to 37.5% (Table 7).

Discussion

Procedure-related morbidity, mortality and long-term survival are extremely poor for non-curative gastric cancer.

Table 1 Procedure-related morbidity rates in palliative gastric cancer procedures (for studies that reported this outcome)

Study	Treatment group (*N*)	Morbidity (%)
Total gastrectomy		
Floris et al. [27]	NC (7)	42.9
Hartgrink et al. [12]	NC (63)	49
Wang et al. [66, 67]	NC (142)	8.5
Pacelli et al. [56]	PAL (88)	37.5
Proximal gastrectomy		
Floris et al. [27]	NC (1)	0
Subtotal gastrectomy		
Floris et al. [27]	NC (11)	45.4
Hartgrink et al. [12]	NC (93)	30
Distal gastrectomy		
Wang et al. [66, 67]	NC (219)	2
Gastrectomy		
Ti [65]	NC (60)	10
Piso et al. [58]	NC (64)	34.4
Floris et al. [27]	NC (19)	42.1
Hartgrink et al. [12]	NC (156)	38
Wang et al. [66, 67]	NC (525)	23.3
Park[a] et al. [57]	NC (72)	12.5
Chow[a] et al. [13]	NOS (25)	32
Heemskerk et al. [31]	NOS (51)	39
An et al. [18]	NOS (1,056)	3.8
Du et al. [26]	PAL LG (43)	9
Surgical bypass		
Floris et al. [27]	BP (52)	21.1
Hartgrink et al. [12]	BP (51)	14
Maetani et al. [45]	BP (22)	18.2
Exploratory laparotomy		
Hartgrink et al. [12]	EL (78)	12
Combined non-resectional		
Heemskerk et al. [31]	BP/EL (66)	21
Park[a] et al. [57]	BP/EL (56)	1.8

N number of patients, *NC* non-curative, *PAL* palliative, *NOS* not otherwise specified, *LG* laparosopic gastrectomy, *BP* surgical bypass, *EL* exploratory laparotomy

[a] Complication types determined prospectively

The utility of performing non-curative and palliative gastrectomy has been much debated in the surgical literature with conflicting conclusions. The guidelines from the NCCN and the JGCA differ in recommendations for the treatment of patients with metastatic disease [5, 6]. Differences in disease biology and the more aggressive surgical approach to the disease advocated by Eastern surgeons may explain this discordance [72, 73]. Within this review, patients with advanced disease who were offered aggressive surgical resection had better survival than those treated conservatively. Improvements in survival likely

Table 2 Procedure-related mortality rates for gastrectomy

Study	Treatment groups (*N*)	Mortality (%)
Total gastrectomy		
Monson et al. [49]	NC (53)	8[a]
Floris et al. [27]	NC (7)	14.3[b]
Hartgrink et al. [12]	NC (63)	11[a]
Wang et al. [66, 67]	NC (141)	8.5[c]
Saidi et al. [59]	NOS (70)	10[d]
Medina-Franco et al. [46]	PAL (24)	4.2[d]
Pacelli et al. [56]	PAL (88)	6.8[c]
Proximal gastrectomy		
Floris et al. [27]	NC (1)	0[b]
Subtotal gastrectomy		
Floris et al. [27]	NC (11)	0[b]
Hartgrink et al. [12]	NC (93)	13[a]
Medina-Franco et al. [46]	PAL (16)	0[d]
Distal gastrectomy		
Wang [66, 67]	NC (220)	3.6[c]
Gastrectomy		
Crookes et al. [23]	NC (32)	3[c]
Ti [65]	NC (60)	12[d]
Piso et al. [58]	NC (64)	6.2[a]
Floris et al. [27]	NC (19)	5.3[b]
Borch et al. [19]	NC (177)	12.4[b]
Hansson et al. [11]	NC (19)	21[a]
Wang et al. [66, 67]	NC (361)	5.5[c]
Miner et al. [14]	NC (160)	4[d]
Kotan et al. [38]	NC (83)	9.6[c]
Lello et al. [42]	NC (41)	14.6[a]
Onate-Ocana et al. [54]	NC (71)	8.5[c]
Park et al. [57]	NC (72)	0[c]
Chow et al. [13]	NOS (25)	20[a]
Damhuis and Tilanus [24]	NOS (176)	9.7[d]
Ouchi et al. [55]	NOS (64)	1.6[a]
Doglietto et al. [25]	NOS (93)	11.8[a]
Hanazaki et al. [30]	NOS (84)	0[d]
Yoshikawa et al. [69]	NOS (87)	3.4[c]
	NOS (87)	13.8[a]
Moriwaki et al. [50]	NOS (206)	3.4[a]
Saidi et al. [60]	NOS (24)	8.3[a]
Heemskerk et al. [31]	NOS (51)	16[d]
Nazli [53]	NOS (29)	13.3[e]
Kunisaki et al. [41]	NOS (164)	4[c]
Budisin [20]	NOS (108)	20.4[d]
Miner et al. [14]	PAL (147)	7[d]
Du et al. [26]	PAL LG (43)	0[c]
Kunisaki et al. [39]	PAL (141)	11.3[a]

[a] In-hospital, [b] not reported/necessary information not provided, [c] operative, [d] 30-day, [e] early

Table 3 Procedure-related mortality rates for surgical bypass and/or exploratory laparotomy

Study	Treatment groups (*N*)	Mortality (%)
Surgical bypass		
Lo et al. [44]	BP (51)	22[d]
Ouchi et al. [55]	BP (15)	33.3[a]
Floris et al. [27]	BP (52)	19.2[b]
Doglietto et al. [25]	BP (78)	10.2[a]
Choi [22]	OBP (38)	0[f]
Choi [22]	LBP (30)	0[f]
Hartgrink et al. [12]	BP (51)	10[a]
Wang et al. [66, 67]	BP(64)	10.9[c]
Yoshikawa et al. [69]	BP (13)	15.4[c]
Yoshikawa et al. [69]	BP (13)	30.8[a]
Medina-Franco et al. [46]	BP (10)	0[d]
Maetani et al. [45]	BP (22)	0[c]
Stupart et al. [64]	BP (67)	6[c]
Lello et al. [42]	BP (16)	25[a]
Onate-Ocana et al. [54]	BP (40)	2.5[c]
Budisin et al. [20]	BP (84)	23.8[d]
Exploratory laparotomy		
Ouchi et al. [55]	EL (16)	31.3[a]
Doglietto et al. [25]	EL (72)	8.3[a]
Hartgrink et al. [12]	EL (78)	10[a]
Wang et al. [66, 67]	EL (26)	11.5[c]
Lello et al. [42]	EL (31)	39[a]
Budisin et al. [20]	EL (138)	23.2[d]
Combined non-resectional		
Kunisaki et al. [39]	BP/EL (75)	34.5[a]
Saidi et al. [60]	BP/EL (35)	8.5[a]
Heemskerk et al. [31]	BP/EL (66)	20[d]
Nazli et al. [53]	BP/EL[g] (45)	27.6[e]
Park et al. [57]	BP[h] (56)	0[c]

BP Surgical bypass, *OBP* open surgical bypass, *LBP* laparoscopic surgical bypass

[a–e] See Table 2 footnote for mortality definitions, [f] perioperative, [g] gastrostomy, internal biliary derivation or suture of gastric perforation, [h] and/or biospy only

reflect treatment selection bias; however, this implies that properly selected subsets of advanced cancer patients may benefit from gastrectomy. A clear set of selection criteria is not evident, leaving little to guide clinicians when faced with this common scenario.

The most commonly reported outcomes in the surgical literature for the assessment of non-curative gastric cancer procedures are procedure-related morbidity, mortality and long-term survival, and were summarized in this systematic review. The procedure-related morbidity and mortality results provide insight into the high complication rates and limited life expectancy related to each available surgical option for advanced gastric cancer patients. Evaluation of these measures allows the surgeon to create a risk ratio of harm and benefit to help determine the optimal strategy [74]. For patients with non-curative gastric cancer, measures of physiological response must be considered in parallel with quality of life outcomes and the end-of-life preferences of each patient. Convincing evidence to recommend guidelines for the most appropriate surgical management strategy for advanced gastric cancer did not emerge from the literature; however, much may be learned from the available literature and applied to future research addressing the advanced gastric cancer population.

Definitions of palliation and study design

Prospectively defining and differentiating those patients who were surgically managed for active symptoms (bleeding, obstruction), those approached with curative intent but who had positive margins after resection, and those who were asymptomatic and underwent non-curative resection are important. For these three distinct subgroups of patients, there should be different management strategies, goals of surgery and outcome measurements. While improvement in survival is sometimes an added benefit to addressing symptoms in the advanced cancer population, it should not be the primary focus of palliative interventions [10, 75]. Heterogeneity in defining palliative intent surgery created a lack of clarity in the literature. "Non-curative," "advanced" and "palliative" are dissimilar groups of patients that cannot be combined to assess outcomes for interventions. Re-defining the studies in this review left only five as being truly palliative [14, 26, 39, 46, 56]. When the intent of surgery is unclear, the results are not easily analyzed.

Retrospective case series are not the optimal method of investigating palliative interventions, as the intent of surgery and process of patient selection for different treatment modalities are difficult to determine. With few prospective series and an absence of randomized controlled trials, the majority of studies describing non-curative surgical management strategies for advanced, non-curative gastric cancer fall into this category. Therefore, although the results of these case series may be useful for describing the delivery of care and procedural outcomes, they must be considered in the context of selection bias, confounding and chance. The sample size of the study design also plays a role in interpreting results. None of the included studies reported conducting sample size, minimal detectable effect size differences or study power for their statistical comparisons. Even if adequate sample sizes for comparison were obtained, treatment selection bias prohibits drawing conclusions on the superiority of treatment strategy.

Table 4 Median survival for non-curative and palliative gastrectomy

Study	Treatment groups (*N*)	MST (mo)	Follow-up
Total gastrectomy			
Monson et al. [49]	NC (53)	19	100%
Wang et al. [66, 67]	NC (107)	7.1	42.8 months[a]
Kunisaki et al. [40]	NC (51)	5	NR
Samarasam et al. [61]	NC (39)	20	Min 6 months
Kunisaki et al. [41]	NOS (92)	9	15.0 months[b]
Kunisaki et al. [39]	PAL (74)	9	7.8 months[a]
Subtotal gastrectomy			
Kunisaki et al. [40]	NC (15)	7	NR
Samarasam et al. [61]	NC (68)	24	Min 6 months
Kunisaki et al. [41]	NOS (72)	9	15.0 months[b]
Kunisaki et al. [39]	PAL (67)	9	7.8 months[a]
Distal gastrectomy			
Wang et al. [66, 67]	NC (150)	11.3	42.8 months[a]
Gastrectomy			
Crookes et al. [23]	NC (32)	21	NR
Piso et al. [58]	NC (64)	10	NR
Floris et al. [27]	NC (19)	14	NR
Shiraishi et al. [63]	NC (17)	7	65 months[b]
Hartgrink et al. [12]	NC (156)	8.1	NR
Miner et al. [14]	NC (160)	13.5	Min 1 year
Zhang et al. [70]	NC (891)	15	NR
Kunisaki et al. [41]	NC (66)	7	NR
Samarasam et al. [61]	NC (107)	24	Min 6 months
Onate-Ocana et al. [54]	NC (71)	12.4	NR
Shiraishi et al. [63]	NC (38)	8.9	63.5 months[b]
Miyagaki et al. [47]	NC (52)	11.5	Min 2 years
Cheon et al. [21]	NC (17)	8.1	15.5 months[a]
Park et al. [57]	NC (72)	12	12.1 months[b]
Saito et al. [71]	NC (202)	9	NR
Yoshikawa et al. [68]	NC (117)	8.9	NR
Murata et al. [51]	NC (116)	8	Min 4 years
Chow et al. [13]	NOS (25)	3	NR
Nakajima et al. [52]	NOS (10)	7	NR
Kikuchi et al. [33]	NOS (63)	12.2	Until death[c]
Yoshikawa et al. [69]	NOS (87)	8.5	NR
Doglietto et al. [25]	NOS (93)	16.3	Min 5 years[d]
Hanazaki et al. [30]	NOS (84)	20.6	NR
Alici et al. [17]	NOS (9)	9.8	NR
Gretschel et al. [29]	NOS (27)	7.1	Until progression or death
Nazli et al. [53]	NOS (29)	8	NR
Mizutani et al. [48]	NOS (13)	11.8	NR
Kunisaki et al. [41]	NOS (164)	9	15.0 months[b]
An et al. [18]	NOS (1,056)	18.8	13.5 months[a]
Kunisaki et al. [39]	PAL (141)	9	7.8 months[a]
Miner et al. [14]	PAL (147)	8.3	Min 1 year
Medina-Franco et al. [46]	PAL (40)	13	Min 1 year

NR Not reported/necessary information not provided, *Gastrectomy* gastrectomy (total or partial)

[a] Median, [b] mean, [c] two lost to follow-up after mean 2 months, [d] 83% followed

Table 5 One-year survival for non-curative and palliative gastrectomy

Study	Treatment groups (*N*)	1-year survival (%)	Follow-up
Total gastrectomy			
Kunisaki et al. [41]	NOS (92)	32.90	15.0 months[a]
Subtotal gastrectomy			
Kunisaki et al. [41]	NOS (72)	46.70	15.0 months[a]
Gastrectomy			
Kim et al. [35]	NC (146)	50.00	80%
Murata et al. [51]	NC (NR)	22.00	Min 4 years
Borch et al. [19]	NC (177)	12	Min 6 years
Kim et al. [36]	NC (193)	25.5	NR
Miyagaki et al. [47]	NC (52)	48.10	Min 2 years
Cheon et al. [21]	NC (19)	29.40	15.5 months[b]
Kim et al. [37]	NC (466)	40	4.3% lost to follow-up
Park et al. [57]	NC (72)	48.60	12.1 months[a]
Jeong et al. [32]	NC (24)	66.70	17.6 months
Yoshikawa et al. [68]	NC (117)	39.30	NR
Kikuchi et al. [33]	NOS (63)	30	Until death[c]
Ouchi et al. [55]	NOS (64)	48.20	NR
Fujisaki et al. [28]	NOS (29)	31.70	NR
Hanazaki et al. [30]	NOS (84)	63	NR
Alici et al. [17]	NOS (9)	26.6	NR
Heemskerk et al. [31]	NOS (51)	43	11.9 months[b]
Kunisaki et al. [41]	NOS (164)	37.70	15.0 months[a]
Lin et al. [43]	NOS (183)	80.30	NR
An et al. [18]	NOS (1056)	69.10	13.5 months[b]
Budisin et al. [20]	NOS (108)	54.30	NR

[a] Mean, [b] median, [c] two lost to follow-up after mean 2 months

Patient characteristics and treatment selection

Underlying differences in the health of patients selected for specific treatment strategies are important considerations when interpreting outcomes from retrospective data [76, 77]. As the management strategy was not assigned at random, patients receiving different options are likely significantly different from one another with respect to clinically important factors related to both the indication for treatment strategy choice and the treatment outcome. The majority of patients considered palliative, non-curative or advanced were classified as having unresectable or incurable disease, and included patients with locally advanced disease, peritoneal disseminated disease and solid organ metastasis. In the studies that compared patient characteristics among treatment strategies, differences in prognostic factors such as age, stage, number of metastatic sites, prevalence of invasive disease, invasion into adjacent organs and other markers of disease progression were noted. Additionally, the proportion of stage IV disease in the study populations ranged from 12 to 100%, and a description of stage or any other clinical prognostic factors by treatment strategy was rarely provided. Imbalances in patient characteristics may be addressed when calculating procedure-related mortality and overall survival to estimate a more accurate effect size using multivariate modeling. Uncontrolled confounding by variables that are not measured or included in the statistical analysis may still influence survival. Socioeconomic status, institution volume, pre- or postoperative chemotherapy, and patient preference were neither included in the analysis by many studies when assessing outcomes nor discussed as limitations to the observational data.

In addition to restricting patient populations to homogenous levels of disease burden and controlling for other disease and demographic factors, randomized controlled trials and prospectively designed studies are able to account for treatment selection. Patients with advanced disease who receive a gastrectomy, compared with those who receive surgical bypass, exploratory laparotomy or no surgical intervention, are likely healthier and have a lower burden of disease [76]. These carefully selected patients may already have a better prognosis before receiving the treatment strategy, making them more likely to receive invasive surgery and more likely to have a positive outcome. This bias may result in overestimating the benefit of

Table 6 Median survival for surgical bypass and/or exploratory laparotomy

Study	Treatment groups (*N*)	MST (mo)	Follow-up
Surgical bypass			
Lo et al. [44]	BP (51)	3.22	Until death
Floris et al. [27]	BP (52)	4.5	NR
Doglietto et al. [25]	BP (78)	7.1	Min 5 years
Kikuchi et al. [34]	BP (52)	5	Until death
Wang et al. [66, 67]	BP (64)	6.2	42.8 months[a]
Yoshikawa et al. [69]	BP (13)	5.7	NR
Medina-Franco et al. [46]	BP (10)	5	Min 1 year
Zhang et al. [70]	BP (130)	6.4	NR
Kunisaki et al. [40]	BP (11)	3	NR
Maetani et al. [45]	BP (22)	3	121 days[b]
Stupart et al. [64]	BP (67)	9.1	NR
Onate-Ocana et al. [54]	BP (40)	6.4	NR
Exploratory laparotomy			
Doglietto et al. [25]	EL (72)	4.4	Min 5 years[c]
Wang et al. [66, 67]	EL (26)	6.6	42.8 months[a]
Yoshikawa et al. [69]	EL (28)	3.6	NR
Zhang et al. [70]	EL (196)	5.2	NR
Kunisaki et al. [41]	EL (26)	5	NR
Hartgrink et al. [12]	BP/EL (129)	5.4	NR
Kunisaki et al. [39]	BP/EL (75)	3	7.8 months[a]
Combined nonresectional			
Samarasam et al. [61]	BP/EL (44)	12	Min 6 months
Mizutani et al. [48]	BP/EL (13)	5.7	NR
Crookes et al. [23]	BP[a] (39)	12	NR
Kikuchi et al. [33]	BP[b] (59)	5.5	Until death[d]
Hanazaki et al. [30]	BP/EL (100)	5.7	NR
Nazli et al. [53]	BP/EL[c] (45)	3.45	NR
Park et al. [57]	BP[d] (56)	4.8	12.1 months[b]

MST median survival time, *mo* months

[a] Median, [b] mean, [c] 83% followed, [d] two lost to follow-up after mean 2 months

non-curative gastrectomy when in fact the procedure itself was not responsible for conferring the survival benefit [76, 77]. Instrumental variable analysis and propensity scores have been proposed as methods to overcome this limitation of retrospective, observational data and to decrease the effect of treatment selection bias; however, they have been demonstrated to do so incompletely [76, 77].

Outcomes

Procedure-related morbidity, mortality, median survival and 1-year survival varied by surgical strategy and treatment intent. Only two studies reported procedure-related morbidity rates in the PAL resections, and they ranged from 9% (laparoscopic gastrectomy) to 37% (open gastrectomy). Procedure-related mortality was lower for PAL resection than NC or NOS resections, and this may reflect more conservative patient selection for PAL procedures. Patients who received gastrectomy purely for palliation of symptoms (PAL) had a narrow survival range among studies, suggesting a relatively homogenous set of patients with a similar burden of advanced disease and symptoms. Atlhough survival in the PAL patients was poor, survival is not the most important outcome in these cases. Few of these studies reported information on changes in quality of life or symptom relief, which are the most appropriate primary outcomes in these patients. A detailed summary of quality of life and surgical palliation for surgically managed, advanced gastric cancer patients is reported elsewhere [78].

Procedure-related morbidity, mortality and long-term survival were more variable for patients in whom gastrectomy was not clearly performed for palliation of symptoms. A wide range of disease burden, differences in baseline patient characteristics and indications for the procedures falling under the non-curative and NOS categories are likely responsible for the variation. Despite assumptions of a higher degree of patient selection, the complication rate for NC and NOS resections was as high as 49%, the procedure-related mortality as high as 21% and the median survival 3–24 months. The inclusion of patients

Table 7 One-year survival for surgical bypass and/or exploratory laparotomy

Study	Treatment groups (*N*)	1-year survival (%)	Follow-up
Surgical bypass			
Ouchi et al. [55]	BP (15)	20.40	NR
Kim et al. [37]	BP (NR)	8.00	4.3% lost
Budisin et al. [20]	BP (83)	12.20	NR
Kim et al. [37]	BP (352)	30.00	80%
Exploratory laparotomy			
Ouchi et al. [55]	EL (16)	37.50	NR
Kim et al. [37]	EL (NR)	12.00	4.3% lost
Budisin et al. [20]	EL (138)	8.40	NR
Combined nonresectional			
Kikuchi et al. [33]	BP/EL[a] (59)	20	Until death[b]
Borch et al. [19]	EL[c] (846)	7	Min 6 years
Fujisaki et al. [28]	BP/EL (14)	16.20	NR
Hanazaki et al. [30]	BP/EL[d] (100)	9.30	NR
Heemskerk et al. [31]	BP/EL (28)	3.00	11.9 months[e]
Lin et al. [43]	BP/EL (206)	33.50	NR
Park et al. [57][g]	BP[d] (56)	14.30	12.1 months[f]

[a] Or gastrostomy, jejunostomy, [b] two lost to follow-up after mean 2 months, [c] ± additional non-resectional procedure, [d] or intubation, [e] median, [f] and/or open biopsy, [g] mean

classified as non-curative following a positive margin resection or positive peritoneal washings detected in an initially curative-intent surgery may contribute to the apparent survival benefit of gastrectomy in these patient groups.

Outcomes for patients undergoing surgical bypass for relief of obstruction were dismal. Procedure-related morbidity rates were as high as 21% and mortality as high as 33%. Median survival ranged from 3 to 9.1 months. These poor results possibly reflect a high burden of metastatic disease and/or significant co-morbidities. For patients with an already limited life span, non-surgical, less invasive options such as stent placement may be encouraged [79]. A recent RCT of patients with malignant gastric outlet obstruction was forced to end recruitment early due to an overwhelming number of patients who preferred stent placement over surgical bypass and thus low accrual [79]. This variation in preference is an excellent example of how unaccounted for patient factors may confound the comparison of two very different treatment strategies.

Patients who underwent exploratory laparotomy only fared the worst. Procedure-related morbidity rates were reported as high as 21%, with procedure-related mortality reaching 39% and median survival only 3.6–6 months. Exploratory laparotomy has been associated with increased mortality [80]. This non-therapeutic surgical intervention may be avoidable with improved preoperative radiological staging or the utilization of diagnostic laparoscopy, both of which are thought to explain decreases in resection rates for stage IV metastatic gastric cancer and increases in R0 resection rates for curative-intent surgeries [80].

Chemotherapy may be a less risky non-surgical approach for patients with unresectable or metastatic disease, and may offer a comparable survival benefit, although the indication for chemotherapy is strictly to improve survival and not to alleviate symptoms. A recent Cochrane review performed a meta-analysis of randomized controlled trials comparing chemotherapy and best supportive care for advanced gastric cancer patients with technically inoperable $T_4N_XM_0$ or $T_xN_xM_1$ disease. The study concluded that chemotherapy provided improved survival in comparison with best supportive care (HR 0.37 95% CI 0.24–0.55), and patients survived a median of 11 months [16]. This survival is the midpoint in the reported median survival range for NC and NOS gastrectomy.

The medical oncology trials evaluated in the Cochrane review were randomized controlled trials [16]. The same level of evidence should be expected in the surgical oncology literature for palliation of gastric cancer. Recently, the GYMSSA (GastrectomY and Metastectomy plus Systemic therapy vs. Systemic therapy Alone) and REGATTA (REductive Gastrectomy for Advanced Tumor in Two Asian countries) trials have been initiated to evaluate the survival benefit and adverse events associated with gastrectomy with metastectomy and systemic therapy versus systemic therapy alone in metastatic gastric cancer patients [81, 82]. The GYMSSA and REGATTA trials aim to identify patient selection factors for gastrectomy in the presence of limited metastatic disease and will help to fill a gap in knowledge and level of evidence missing in the surgical non-curative literature for gastric cancer [81, 82]. Recruitment and accrual in these surgical trials may prove

difficult given patient preferences and biases of individual clinicians; however, these trials are crucial for determining the actual survival benefit provided by non-curative gastrectomy and are supported by the clinical equipoise in the literature.

Conclusion

Many retrospective series investigating the effectiveness of surgical management for advanced gastric cancer patients exist. Variation in the definitions of palliative and non-curative intent among studies makes patient groups difficult to compare. Treatment selection bias and confounding potentially inflate the effectiveness of gastrectomy. Prospectively designed research with clear, preoperatively standardized definitions of palliation that incorporate assessment of quality of life is essential to aid decision-makers and patients in choosing the optimal surgical strategy for advanced gastric cancer.

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