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Review Article

Outcomes of surgical treatment of non-metastatic gastric cancer in patients aged 70 and older: A systematic review and meta-analysis

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ABSTRACT

The optimal surgical treatment strategy for gastric cancer in older patients needs to be carefully evaluated due to increased vulnerability of older patients.

We performed a database search for randomized controlled trials (RCTs) and cohort studies that included patients ≥70 years with potentially resectable stage I-III gastric cancer. Postoperative and survival outcomes were compared between groups undergoing 1) gastrectomy vs conservative treatment (best supportive care or non-operative treatment), 2) minimally invasive (MIG) vs open gastrectomy (OG), or 3) extended vs limited lymphadenectomy. When possible, results were pooled using risk ratios (RR).

Thirty-one studies were included. Six retrospective studies compared overall survival (OS) between gastrectomy (N = 2332) and conservative treatment (N = 246). Longer OS was reported in the gastrectomy group in all studies, but study quality was low and meta-analysis was not feasible.

Eighteen cohort studies compared MIG (N = 3626) and OG (N = 5193). MIG was associated with fewer complications (pooled RR 0.68, 95% confidence interval 0.54–0.84). OS was not different between the groups.

Two RCTs and five cohort studies compared outcomes between extended (N = 709) and limited lymphadenectomy (N = 1323). Complication rates were comparable between the groups. Two cohort studies found longer OS or cancer-specific survival after extended lymphadenectomy.

No quality of life (QoL) or functional outcomes were reported.

In older patients with gastric cancer, there is low-quality evidence for better OS after gastrectomy vs conservative treatment. Compared to OG, MIG was associated with less postoperative morbidity. The evidence to support extended lymphadenectomy is limited. QoL and functional outcomes should be addressed in future studies.

1. Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide [1]. The highest incidence is found in East Asia which has led to the development of gastric cancer screening programs in Japan and South Korea. As a consequence, gastric cancer in these countries is often detected at an early stage, making endoscopic treatment often possible. Screening programs have not been implemented in Western countries, and therefore the incidence of advanced gastric cancer is higher [2]. If gastric cancer is diagnosed at a resectable stage and without distant metastases, surgical resection, preferably with perioperative chemotherapy, offers the only chance of cure [3].

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Gastric cancer is also a disease of older age; in North America, more than one third of patients are diagnosed at age 75 or older [4]. Older patients are at an increased risk of frailty which is defined as an age-related syndrome of physiological decline across multiple organ systems [5]. Frail individuals are vulnerable to stressors and have a limited ability to adapt to change (such as a surgical intervention). The benefits and harms of surgical treatment need to be weighed carefully in older patients. Besides survival, addressing quality of life (QoL) and functional outcomes is especially important for this patient group.

The surgical treatment options for gastric cancer vary with regard to invasiveness of surgery and the extent of lymphadenectomy performed. Currently, minimally invasive gastrectomy (MIG) is gaining ground over open gastrectomy (OG) as it is associated with better short- and long-term outcomes, including improved QoL [6–9]. Meta-analyses conducted in older Asian populations have shown that laparoscopic surgery is feasible and safe for patients 65 years and older [10,11]. Two Western RCTs have also shown similar morbidity and mortality rates after MIG and OG in adult patients [12,13]. Regarding lymph node dissection, survival after gastrectomy is proportional to the level of lymph node metastases [14]. The rationale behind a more extensive lymphadenectomy is therefore to improve diagnostic accuracy as well as decrease locoregional recurrence rates. For locally advanced cancers, D2 dissection is standard practice in Asian countries where it has been shown to be associated with better survival and lower recurrence rates, in part due to the surgeons' experience with extensive dissections as well as due to younger patients with less comorbidities and lower body fat. There is also increasing evidence supporting D2 dissections in the West provided that pancreaticosplenectomy can be avoided and that patients are treated in high-volume centers with the required expertise [15]. A specific case needs to be made for the older patients with a higher prevalence of frailty, which may limit the extent of surgery that can safely be performed. For the older patients, lower long-term locoregional recurrence rates after D2 dissection may not translate to improved survival rates due to the shorter life expectancy.

The optimal surgical treatment strategy for gastric cancer in older patients therefore remains a matter of debate. The aim of this review is to address the outcomes of different surgical options in the treatment of potentially resectable gastric cancer in the older patient population. The objectives of this review are threefold: first, to compare outcomes between gastrectomy and conservative treatment (including best supportive care (BSC), chemotherapy and/or radiotherapy) of potentially resectable gastric cancer; second, to assess the difference in outcomes between MIG and OG; and third, to determine whether postoperative and survival outcomes differ between extended and limited lymphadenectomy.

2. Methods

This review conforms to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The protocol of the review is available on Prospero (CRD42019126553).

2.1. Database search

A search was conducted in MEDLINE, Embase, Web of Science and CINAHL databases for titles and abstracts with the following search terms and related terms: elderly, gastric cancer, surgery, and treatment outcomes on April 23rd, 2020. The search was restricted to English language only and for articles published after December 31st, 1999. The full search for MEDLINE is included in Appendix A.

2.2. Inclusion and exclusion criteria

Articles were considered eligible if they were relevant to one of the three review topics. Randomized controlled trials (RCTs) or cohort studies were considered if the included patients were 70 years or older or if subgroup analysis was available in patients 70 years or older. The patients had to have potentially resectable gastric cancer without distant metastases at diagnosis and reported outcome data had to include at least one of the following: overall survival (OS), cancer-specific survival (CSS), postoperative complications, QoL, hospital length of stay (LOS), or physical/functional outcomes (e.g., ability to live independently, walking distance, muscle strength). Studies that reported on survival were eligible for inclusion provided that cancer stage was controlled for at the level of study design or analysis. For the first review topic, studies were eligible if they compared patients undergoing partial or total gastrectomy to patients receiving conservative treatment (e.g., only chemotherapy, radiotherapy or BSC). For the second research question, studies were eligible if they compared MIG (e.g., laparoscopic or laparoscopy-assisted surgery) and OG. For the third review topic, studies were eligible if they compared extended lymphadenectomy with limited lymphadenectomy (e.g., D2 vs D1, >15 lymph nodes vs < 15 lymph nodes) in patients undergoing gastrectomy.

Studies with fewer than ten participants per treatment arm were not eligible. Studies that reported specifically on palliative resections, metastasectomies or additional resections after non-curative endoscopic resections were excluded.

2.3. Study selection

After removing duplicates, title and abstract screening was performed by one review author (TA) using Rayyan web-based software (https://rayyan.qcri.org [17]). Unclear cases were discussed with other review authors. Following, two authors (TA and SF) independently screened the full texts of potentially eligible articles according to the inclusion and exclusion criteria. Any disagreement between the authors was solved by discussion with other review authors when necessary. Whenever multiple reports of the same study were identified, the report with most complete outcome information was retained, provided that data from all outcomes of interest was available. The reference lists of the included articles and relevant review articles were hand searched for potentially missed articles.

2.4. Data extraction

Data was extracted on: 1) study identifying information, 2) study design, 3) baseline characteristics of participants including comorbidities, American Society of Anesthesiologist (ASA)-classification, performance status (PS), and geriatric parameters (e.g., any assessment of frailty, mobility problems, cognitive functioning) 4) description of intervention and control groups; 5) relevant study outcomes; 6) information on risk of bias (ROB). One review author (TA) performed data extraction, and 10% of the data was checked randomly by a second review author (HvdZ).

2.5. Risk of bias

ROB was assessed independently for each study by three review authors (TA and SF or HvdZ). RCTs were rated using the Cochrane ROB tool where each source of bias was reported as high, low or unclear risk for the main study outcome. For cohort studies, ROB in non-randomized studies of interventions (ROBINS-I) tool was used where each source of bias was reported as low, moderate, serious,

critical or unknown risk for the main study outcome. Any disagreement between the authors was solved by discussion.

2.6. Data synthesis

Meta-analysis was considered feasible if studies were sufficiently similar with regard to design, population, intervention/comparison and outcomes. Summaries of intervention effects were provided by calculating risk ratios (RR) for dichotomous outcomes (complications, mortality) and standardized mean differences (SMD) for LOS. Whenever only median and (interquartile) range (IQR) were reported, we estimated the mean and standard deviation (SD) according to Wan et al., 2014 [18]. The results were pooled using a fixed-effects or random-effects meta-analysis and 95% confidence intervals (CI). Fixed-effects meta-analysis was conducted if the I^2 (statistical heterogeneity) was <50%, otherwise random-effects pooling was performed. A two-sided p-value <0.05 was considered statistically significant. All analyses were performed with Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

2.7. Subgroup analyses

When possible, subgroup analyses for study outcomes were performed for different age categories, cancer stages and total/subtotal (distal) gastrectomies.

3. Results

A flow diagram of study selection is depicted in Fig. 1. The database search resulted in 21776 citations of which 13607 remained after removing duplicates. After title and abstract screening, 321 records remained for full text assessment. Of these, 289 publications were excluded mostly due the age of study participants being too low or not addressing the questions in our study aim. Thirty-two publications on 31 separate studies were included in the review. For the first review topic comparing gastrectomy and conservative treatment, six retrospective cohort studies were included [19–24]. For the second review topic comparing MIG and OG, eighteen studies were included (one randomized study [25], one prospective study [26], and seventeen retrospective studies [25,27–42]). For the third review topic comparing extended and limited lymphadenectomies, eight publications reporting results from seven individual studies were included (an RCT from Italy (two separate publications on short- and long-term outcomes) [43,44] and the Netherlands [45], one prospective cohort study [46], and four retrospective studies [47–50]).

3.1. Gastrectomy compared to conservative treatment for potentially resectable gastric cancer

3.1.1. Study quality

The overall quality of the studies comparing gastrectomy and conservative treatment was poor, mainly due to presence of baseline confounding and selection bias (Table 1).

3.1.2. Characteristics of included studies

Table 2 shows the characteristics of the studies comparing gastrectomy and conservative treatment for gastric cancer [19–24]. Two studies from Japan [21,22] reported on partially overlapping patient populations; the most recent study [22] had a longer inclusion period and included only patients with distal gastrectomy into the analyses. All studies reported on OS. No study reported on QoL or functional outcomes.

The intervention group consisted of patients who underwent total or distal gastrectomy [19–21,24], distal gastrectomy only [22], and gastrectomy (including total or subtotal gastrectomy and local excision) for proximal tumors [23]. Radical resection (R0) rate was 100% in two studies [21,22], >90% in one study [20] and 89% in one study [24]. Two studies did not report on R0 rates [19,23]. Adjuvant chemotherapy was administered to 18% of the surgical patients in one study [19] whereas no patients received adjuvant chemotherapy in three studies [21,22,24]. In a North American study [23], 6.2% and 12.4% of surgical patients received (neo)adjuvant chemotherapy or chemoradiation, respectively. The conservative treatment group consisted of patients who received BSC (not further specified) in four studies [20–22,24], patients who underwent bypass, chemotherapy or observation in one study [19], and

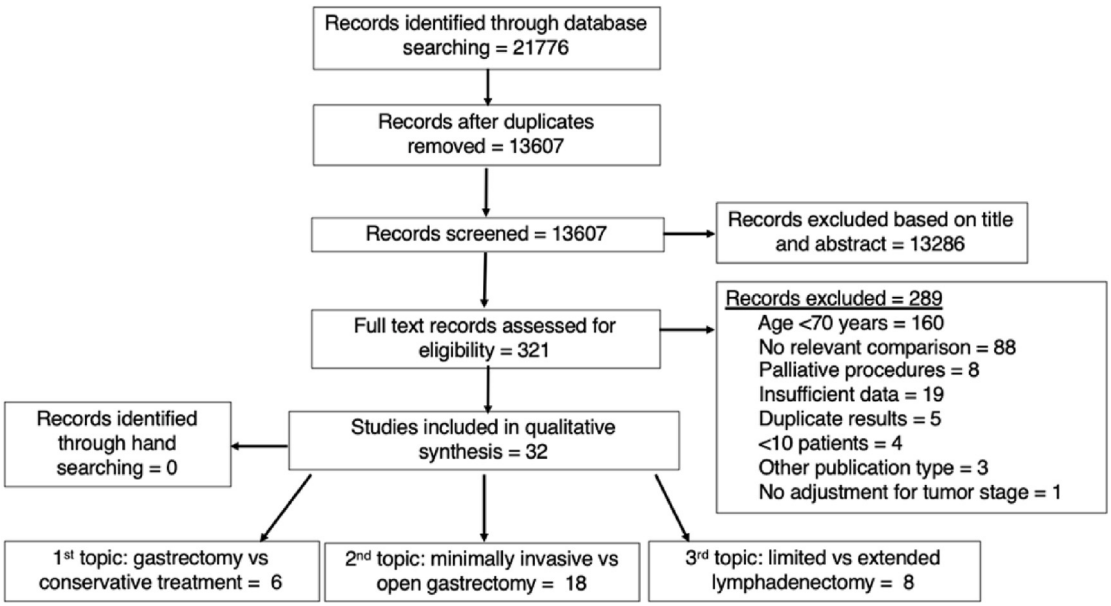

Fig. 1. Flow chart of study inclusion.

Table 1
Quality assessment of included studies.

Study	Domain (Robins Risk of Bias for cohort studies)						
	Confounding	Selection	Classification	Deviations	Missing data	Outcomes	Reporting
Gastrectomy vs conservative treatmentt							
Choo 2017 [20]	High	High	Low	Low	No information	No information	Low
Endo 2013 [21]	High	High	Low	Low	Low	Low	Low
Endo 2017 [22]	High	High	Low	Low	High	No information	High
Gong 2016 [19]	High	High	Low	Low	High	High	High
Wang 2019 [23]	High	Low	Low	Low	Low	Low	Low
Zhao 2018 [24]	High	Low	Low	Low	Low	High	Low
Minimally invasive vs open surgery							
Honda 2019 [26]	High	Low	Low	Low	Low	Low	Low
Inokuchi 2017 [27]	High	Low	Low	High	Low	High	Low
Kim 2018 [35]	High	No information	Low	Low	No information	High	High
Kinoshita 2019 [36]	Moderate	Low	Low	Low	Low	Low	Low
Liu 2017 [37]	High	Low	Low	Low	Low	High	Low
Mochiki 2005 [38]	High	High	Low	Low	No information	High	Low
Mohri 2015 [39]	High	No information	Low	No information	No information	High	Low
Pak 2019 [40]	High	Low	Low	Low	Low	Low	Low
Pan 2018 [41]	Low	High	Low	Low	High	Low	Low
Qiu 2014 [42]	High	Low	Low	No information	Low	High	Low
Suzuki 2015 [28]	High	Low	Low	Low	No information	High	Low
Tsuchiya 2018 [29]	High	High	Low	No information	Low	High	Low
Ushimaru 2020 [30]	High	Low	Low	Low	Low	Low	Low
Wu 2016 [31]	Low	Low	Low	No information	No information	High	Low
Yamamoto 2019 [32]	Low	Low	Low	No information	No information	Low	Low
Yasuda 2004 [33]	High	Low	Low	Low	Low	High	Low
Zheng 2016 [34]	High	Low	Low	Low	Low	High	Low
Extended vs limited lymphadenectomy							
Brenkman 2018 [47]	High	Low	Low	Low	Low	Low	Low
Edwards 2004 [46]	High	Low	Low	Low	High	Low	Low
Mikami 2016 [50]	High	Low	High	No information	Low	Low	Low
Passot 2016 [49]	High	High	Low	High	Low	Low	Low
Seo 2017 [48]	High	Low	Low	No information	Low	Low	Low

	Domain (Cochrane Risk of Bias for randomized controlled trials)						
	Sequence	Allocation	Blinding	Detection	Attrition	Reporting	Other (non-compliance and contamination)
Minimally invasive vs open surgery							
Li 2014 [25]	High	High	High	High	Low	Low	N/A
Extended vs limited lymphadenectomy							
Degiuli 2010 & 2014 [43,44]	Low	Low	High	Low	Low	Low	High
Songun 2010 [45]	Low	Low	High	Low	Low	Low	High

patients who either received BSC or chemotherapy and/or radiotherapy in one study [23].

Regarding baseline physical status, half of the studies reported significant baseline differences between the groups. In a South Korean study [20], patients receiving conservative treatment had worse PS (PS 3–4: 48% vs 13%, $p = 0.002$) and higher ASA-scores (ASA III-IV: 52% vs 13%, $p = 0.001$). In a Chinese cohort [24], patients undergoing conservative treatment had significantly worse PS (PS 3: 32% vs 13%, $p = 0.018$) whereas no difference was found in comorbidity level. In a Japanese cohort [21], patients with conservative treatment had worse PS (PS 3: 22% vs 14%). Two studies [19,23] reported no significant baseline differences regarding comorbidity burden between the surgical and conservative treatment groups. In a propensity-matched cohort study from Japan, no baseline differences in PS were observed [22]. No other frailty measures (e.g., mobility problems, cognitive problems, or results from a geriatric assessment) were presented in the included studies.

3.1.3. Overall survival

All six studies reported on OS. Meta-analysis was not feasible due to significant clinical and methodological heterogeneity between the studies. OS outcomes per study are summarized in Table 2.

In a South Korean cohort [19], mean survival was better in patients who underwent gastrectomy regardless of cancer stage (stage I: 52 vs 37 months ($p < 0.05$), stage II: 42 vs 22 months ($p = 0.004$), stage III: 32 vs 11 months ($p = 0.049$)). In another South Korean study [20], the study population was divided into two groups (80–85 years and ≥86 years). In univariable analyses, gastrectomy was associated with better OS in both groups (80–85 years: median 34 vs 9 months, $p < 0.001$; ≥86 years: median 31 vs 12 months, $p = 0.028$). In multivariable analyses adjusted for patient characteristics (ASA-score, comorbidities) and tumor characteristics, only the younger patient group benefited from gastrectomy (HR 0.3, 95% CI 0.1–0.6, $p = 0.003$). In a Japanese cohort [21], better median survival was reported in patients who underwent gastrectomy than those who received BSC (3.2 vs 1.5 years, $p = 0.001$). In subgroup analysis, patients with stage IB-IIIC cancer benefited from gastrectomy (HR 0.3, 95% CI 0.1–0.6) whereas patients with stage IA cancer did not (HR 0.5, 95% CI 0.2–1.3). In a propensity-matched cohort in Japanese patients [22], patients undergoing distal gastrectomy had better OS compared to patients who received BSC (median 57 vs 16 months, $p = 0.002$). In multivariable analysis adjusted for sex and comorbidities, BSC was associated with worse OS (HR 2.9, 95% CI 1.5–5.8). In a North American cohort [23], better 5-year OS was reported for stage 0-I patients undergoing gastrectomy compared to conservative treatment (37% vs 14%, $p < 0.001$) whereas OS was not significantly different for stage II (18% vs 18%, $p = 0.11$) or stage III patients (11% vs 0%, $p = 0.08$). In multivariable analysis adjusted for age, sex, comorbidities and tumor characteristics, gastrectomy was associated with significantly better OS (HR 0.66, 95% CI 0.51–0.86, $p = 0.002$). A

Table 2
Characteristics and survival outcomes of studies comparing gastrectomy with conservative treatment for potentially resectable gastric cancer in patients 70 years and older.

Ref	Type of study Country	Inclusion period	Comparison (N)	Age	Performance status/ comorbidities	Resectability/ type GC	Cancer stage	Survival (univariable)	Survival (multivariable)
Choo 2017 [20]	Retrospective South Korea	2001 –2015	Gastrectomy (group 1: 38, group 2: 25) vs BSC (group 1: 11, group 2: 25)	Group 1: 80 –85 years Group 2: ≥86 years	Group 1: PS 3 –4 13% vs 48% Group 2: PS 3 –4 36% vs 64%	Potentially resectable stage IB-IIIC GC	Group 1: stage III 61% vs 76% Group 2: stage III 73% vs 44%	Group 1: median 34 (95% CI 24–44) vs 9 (95% CI 5 –13) months, p < 0.001 Group 2: median 31 (95% CI 14–48) vs 12 (95% CI 6 –18) months, p = 0.028	Group 1: HR 0.3, 95% CI 0.1 –0.6, p = 0.003 Group 2: HR 0.5, 95% CI 0.2 –1.1, p = 0.1
Endo 2013 [21]	Retrospective Japan	1998 –2011	Gastrectomy (58) vs BSC (32)	>85 years	PS 3: 14% vs 22%	Potentially resectable stage IA-IIIC GC	Stage I: 45% vs 56% Stage II: 33% vs 34% Stage III: 22% vs 9%	Median 3.2 vs 1.5 years, p = 0.001 Stage IA: HR 0.5 (95% CI 0.2–1.3) Stage IB-IIIC: HR 0.3 (95% CI 0.1–0.6)	NR
Endo 2017 [22]	Retrospective propensity-matched Japan	1996 –2015	Distal gastrectomy (30) vs BSC (30)	>85 years	PS 3: 17% vs 23%	Potentially resectable stage IA-IIIC GC	Stage I: 43% vs 53% Stage II: 40% vs 33% Stage III: 17% vs 13%	Median 57 vs 16 months, p = 0.002	HR 2.9, 95% CI 1.5–5.8 (favoring gastrectomy)
Gong 2016 [19]	Retrospective South Korea	2009 –2011	Gastrectomy (61) vs conservative treatment (bypass, chemotherapy or observation) (39)	>80 years	Mean CCI 0.34 vs 0.48	Potentially resectable stage IA-IIIC GC	Stage I: 62% vs 33% Stage II: 26% vs 33% Stage III: 11% vs 33%	Stage I: mean 52 ± 3 vs 37 ± 5 months, p < 0.05 Stage II: mean 42 ± 5 vs 22 ± 6 months, p = 0.004 Stage III: mean 32 ± 9 vs 11 ± 2 months, p = 0.049	NR
Wang 2019 [23]	Retrospective (National Cancer Database) United States	2004 –2013	Gastrectomy ±(neo)adjuvant therapy (2134) vs conservative treatment (chemo-/radiotherapy or BSC) (350)	>80 years	CCI 0 67% vs 62% CCI 1 23% vs 25% CCI≥2 10% vs 13%	Potentially resectable proximal stage I-III GC	Stage 0-I: 52% vs 47% Stage II: 22% vs 25% Stage III: 27% vs 28%	5-year OS; stage 0–1: 37% vs 14%, p < 0.001 5-year OS; stage II: 18% vs 18%, p = 0.11 5-year OS; stage III: 11% vs 0%, p = 0.08	HR 0.66, 95% CI 0.51–0.86, p = 0.002
Zhao 2018 [24]	Retrospective China	2004 –2015	Gastrectomy (224) vs BSC (60)	>75 years	PS 3: 13% vs 32% CCI≥2 36% vs 38%	Potentially resectable stage I-III GC	Stage I: 12% vs 10% Stage II: 32% vs 38% Stage III: 56% vs 52%	5-year OS: 28% vs 0%, p < 0.001 Median: 29 vs 10 months	NR

Abbreviations: BSC *best supportive care;* CCI *Charlson Comorbidity Index*; CI *confidence interval*; GC *gastric cancer;* HR *hazard ratio*; NR *not reported*; OS *overall survival;* PS *performance status*.

Chinese study [24] also found significantly better survival in patients undergoing gastrectomy (5-year OS 28% vs 0%, p < 0.001; median survival 29 vs 10 months).

3.2. Minimally invasive gastrectomy compared to open gastrectomy for gastric cancer

3.2.1. Study quality

The overall quality of studies comparing MIG and OG was poor to moderate. Most studies had a high ROB regarding confounding and outcome assessment (Table 1).

3.2.2. Characteristics of included studies

Table 3 shows the characteristics of studies comparing MIG and OG. The procedure of MIG was described in detail in nine studies (MIG with extracorporeal anastomosis via minilaparotomy) [27–29,31,33,34,38,39,42]. The remaining studies did not provide further details on the procedure [25,26,30,32,35–37,40,41]. Four studies only included patients with early gastric cancer [33,38,39,41]. In five studies, tumor stage was significantly higher in patients who underwent OG [26,27,35,37,42]. Five studies excluded patients who underwent total gastrectomy [27,28,33,34,38]. Three studies reported more total gastrectomies

in the OG group [26,35,37], one study [39] did not report on total gastrectomy rates and one study [40] reported the rate on the whole group level. Of the nine studies reporting on the level of lymphadenectomy, four of them reported significantly more D2 resections in the OG group [26–28,35]. Most studies reported on comorbidities or PS; these were generally well balanced between the groups.

3.2.3. Postoperative outcomes

Results on postoperative outcomes are shown in Supplementary Table S1 and meta-analyses of pooled data in Fig. 2a–h.

3.2.3.1. Overall complications. Fixed-effects meta-analysis including data from nine retrospective cohort studies [27,29,31,32,34,35,38,39,42] showed that patients undergoing MIG had a significantly lower complication rate (pooled RR 0.71, 95% CI 0.55–0.90, p = 0.005) (Fig. 2a). A randomized study [25] also found a lower complication rate in the MIG group (15% vs 30%, p = 0.04).

In three studies that included patients >80 years [27,29,35], there was no difference in complication rates between MIG and OG (pooled RR 0.77, 95% CI 0.53–1.11, p = 0.16) (Fig. 2b). In three studies focusing on distal gastrectomy [27,34,38], the complication rate was not significantly different between the groups (pooled RR 0.64, 95% CI 0.40–1.05, p = 0.08) (Fig. 2c).

3.2.3.2. Severe complications. Severe complications were defined as Clavien-Dindo grade ≥ III [51] in all studies. A fixed-effects meta-analysis analysis of five retrospective studies [29,31,34,39,41] revealed no significant difference in severe complication rates between MIG and OG (pooled RR 0.88, 95% CI 0.72–1.08, p = 0.23) (Fig. 2d). The results of a prospective cohort study [26] were comparable to the pooled risk found in the retrospective studies (adjusted OR 0.81, 95% CI 0.60–1.09).

3.2.3.3. Surgical and medical complications. In a fixed-effects meta-analysis of four studies [28,30,33,37], there was no statistically significant difference in the surgical complication rates between MIG and OG groups (pooled RR 0.81, 95% CI 0.53–1.22, p = 0.31). In two studies [28,33], MIG was associated with a lower medical complication rate (pooled RR 0.23, 95% CI 0.09–0.59, p = 0.002).

3.2.3.4. Postoperative mortality. Four studies reported no postoperative deaths [28,30,31,34]. In the other studies [25–27,29,32,33,35,37,40], the mortality rates were generally low (0–7% after MIG and 1–7% after OG). A fixed-effects meta-analysis of the retrospective cohort studies [27,29,32,33,35,37,40] showed that there was no difference in the mortality rates between MIG and OG (pooled RR 0.90, 95% CI 0.61–1.32, p = 0.58) (Fig. 2g). In a prospective cohort study [26], higher 30-day mortality in the OG group was found (2% vs 1%, p = 0.04). In a randomized study [25], only one postoperative death was reported.

3.2.3.5. Length of stay. In a random-effects meta-analysis of retrospective studies [24,27–29,31,33,34,37,40,41], LOS was significantly shorter in patients undergoing MIG (SMD −3.21, 95% CI −4.78, −1.64, p < 0.00001) (Fig. 2h). In a randomized study [25] and a prospective study [26], LOS was also shorter in the MIG groups (mean 7.0 vs 9.4 days, p < 0.001 and median 12 vs 16 days, p < 0.001, respectively).

3.2.3.6. Overall survival. OS was reported three months to five years after surgery. None of the studies found a difference in the OS rates between MIG and OG [24,27–29,31,33,34,40,41]. Meta-analysis was precluded due to methodological heterogeneity between the studies.

3.3. Extended vs limited lymphadenectomy for gastric cancer

3.3.1. Study quality

The overall quality of the studies comparing extended and limited lymphadenectomy was moderate. In the two RCTs, blinding was not possible and significant contamination and non-compliance were reported. Serious baseline confounding was found in all cohort studies, but ROB was generally low in the remaining domains (Table 1).

3.3.2. Characteristics of included studies

Table 4 shows the characteristics of studies investigating extended versus limited lymphadenectomy. The definition of extended and limited lymphadenectomy varied between the studies. Four studies [43–46,48] compared outcomes between D2 and D1 dissections where D1 dissections indicated a limited lymphadenectomy. The definitions of D2 or D1 dissections were not uniform between the studies as lymph nodes were removed according to the specific location of the lymph node station [45,46], according to tumor location [43,44] or according to whether total or distal gastrectomy was performed [48]. One study [50] compared outcomes between standard and limited lymphadenectomy where standard lymphadenectomy was defined according to the 2010 Japanese Gastric Cancer Guidelines (version 3) [52], and anything less was considered a limited lymphadenectomy. Finally, two studies [47,49] used lymph node yield (LNY) as a surrogate for the extent of lymphadenectomy; both compared outcomes between low (<15 nodes), intermediate (15–25 nodes) and high (>25 nodes) LNY. The reported number of removed lymph nodes during D1 lymphadenectomy in the two Asian studies [48,50] was comparable to that of D2 dissections [43–46] or high LNY [47,49] in the European studies.

In the two RCTs [43–45] and the prospective cohort study [46], baseline characteristics were not available for the subgroup of older patients. In three of the four studies that reported on the patients' preoperative physical status (comorbidities, ASA-score and/or PS), patients undergoing extended lymphadenectomy had better preoperative scores or less comorbidities [46,49,50]. The Italian RCT reported significantly more patients with early gastric cancer (stage IA tumors) in the D1 group [43,44]. In the Dutch RCT, significantly more patients in the D2 group underwent multiorgan resections (as was necessitated by the protocol) [45]. In the prospective cohort study [46], stage I-II cancers were more prevalent in the D1 group and total gastrectomies were performed more often in the D2 group. Total gastrectomies were performed more often in the high LNY group in the two cohort studies from The Netherlands and Italy [47,49].

3.3.3. Postoperative outcomes

3.3.3.1. Postoperative complications. The complication rates between groups did not differ in the Italian RCT comparing D2 and D1 lymphadenectomy [41] (26% vs 13%, p = 0.16), in the cohort study comparing standard and limited lymphadenectomy [48] (15% vs 19%, p = 0.49) or in the cohort study comparing high vs low LNY [47] (48% vs 41%, p = 0.59). Meta-analysis was precluded due to clinical and methodological heterogeneity between the studies.

3.3.3.2. Postoperative mortality. In the Italian RCT [41], no difference was found in mortality rates between D2 and D1 groups (3% vs 4%, p = 1.00). In a Japanese cohort study [48], no difference was found in mortality between standard and limited lymphadenectomy groups (0.6% vs 2.1%, p = 0.30). A pooled analysis of the cohort studies reporting on 90-day mortality after high LNY vs low LNY [47,49] revealed no between-group difference (pooled RR 0.76, 95% CI 0.46–1.86, p = 0.26). Similarly, no difference was found between

Table 3
Characteristics of studies comparing minimally invasive and open gastrectomy for gastric cancer in patients 70 years and older.

Reference	Type of study Country	Inclusion period	Comparison (N)	Age % males	Neoadjuvant therapy	Preoperative comorbidities	Total gastrectomy	D2 resection	Tumor stage
Honda 2019 [26]	Prospective Japan	2014 –2015	Laparoscopic (1366) vs open (1471)	>75 67% vs 71%	Chemotherapy: 1.2% vs 3.8%	Ischemic heart disease: 1.0% vs 2.4% Diabetes: 2.6% vs 3.5% Pulmonary: 12.9% vs 12.6	24% vs 40%	31.9% vs 56.5%	I: 67% vs 34% II: 14% vs 25% III: 12% vs 36%
Inokuchi 2017 [27]	Retrospective China	2004 –2016	Laparoscopy-assisted (45) vs open (25)	>80 64% vs 60%	0% vs 0%	≥3 comorbidities: 29% vs 36%	0% vs 0%	13% vs 28%	I: 73% vs 28% II: 16% vs 24% III: 11% vs 48%
Kim 2018 [35]	Retrospective South Korea	2010 –2016	Laparoscopic (59) vs open (183)	>80 61% vs 67%	NR	Comorbidity index ≥2: 24% vs 20%	5% vs 22%	50.8% vs 91.3%	Early GC: 64% vs 32% Advanced GC: 36% vs 68%
Kinoshita 2019[36*]	Retrospective propensity-matched Japan	2008 –2014	Laparoscopic (90) vs open (87)	>75 71% vs 70%	Chemotherapy: 9.8% vs 11.5%	Ischemic heart disease: 7% vs 6% Diabetes: 14% vs 14% Pulmonary: 7% vs 5%	42% vs 44%	NR	I: 10% vs 9% II: 31% vs 34% III: 51% vs 50% IV: 8% vs 8%
Li 2014 [25]	Randomized study (retrospective) China	2008 –2009	Laparoscopic (54) vs open (54)	>70 67% vs 56%	0% vs 0%	Cardiovascular: 61% vs 63% Diabetes: 22% vs 30% Pulmonary: 43% vs 35%	57% vs 61%	100% vs 100%	I/II: 44% vs 39% III/IV: 56% vs 61%
Liu 2017 [37]	Retrospective Taiwan	2011 –2015	Laparoscopic/robotic (27) vs open (53)	>80 70% vs 77%	NR	≥2 comorbidities: 59% vs 42%	4% vs 26%	92.6% vs 88.7%	I: 67% vs 42% II: 22% vs 25% III: 11% vs 34%
Mochiki 2005 [38]	Retrospective Japan	1998 –2004	Laparoscopy-assisted (30) vs open (16)	>75 67% vs 88%	NR	Cardiovascular: 23% vs 13% Diabetes: 10% vs 6% Pulmonary: 10% vs 0%	0% vs 0%	NR	Early GC 100% vs 100%
Mohri 2015 [39]	Retrospective matched Japan	1992 –2011	Laparoscopy-assisted (30) vs open (30)	>70 73% vs 67%	NR	NR	NR	NR	Early GC: 100% vs 100%
Pak 2019 [40]	Retrospective (database) United States	2010 –2014	Laparoscopic (381) vs open (1759)	>80 55% (whole group)	Chemotherapy: 7.2% (whole group) Radiotherapy: 2.4% (whole group)	Comorbidity index 2: 13% (whole group)	15% (whole group)	NR	Ib: 16% (whole group) II: 38% (whole group) III: 46% (whole group)
Pan 2017 [41]	Retrospective propensity-matched China	2001 –2008	Laparoscopic (1180) vs open (1180)	>70 60% vs 59%	0% vs 0%	NR	9% vs 10%	NR	Early GC: 100% vs 100%
Qiu 2014 [42]	Retrospective China	2012 –2013	Laparoscopy-assisted (30) vs open (34)	>70 83% vs 65%	NR	Diabetes: 10% vs 15% Pulmonary: 20% vs 18%	47% vs 65%	100% vs 100%	II: 53% vs 29% III: 47% vs 71%
Suzuki 2015 [28]	Retrospective Japan	2000 –2011	Laparoscopy-assisted (38) vs open (28)	>75 74% vs 64%	NR	Cardiovascular: 26% vs 32% Diabetes: 16% vs 29% Pulmonary: 5% vs 11%	0% vs 0%	5.3% vs 14.3%	I: 93% vs 97% II: 7% vs 3%
Tsuchiya 2018 [29]	Retrospective propensity-matched Japan	1997 –2013	Laparoscopy-assisted (39) vs open (39)	>80 77% vs 77%	NR	Cardiovascular: 59% vs 46% Diabetes: 18% vs 15% Pulmonary: 10% vs 8%	26% vs 18%	10% vs 16%	I: 67% vs 64% II: 33% vs 36%
Ushimaru 2020 [30]	Retrospective propensity-matched Japan	2001 –2015	Laparoscopic (56) vs open (46)	>70 77% vs 74%	Chemotherapy: 7.1% vs 8.7%	NR	30% vs 30%	69.6% vs 71.7%	I: 9% vs 24% II: 55% vs 50% III: 36% vs 26%
Wu 2016 [31]	Retrospective matched China	2008 –2015	Laparoscopic (64) vs open (64)	>70 64% vs 60%	NR	Diabetes: 9% vs 11%	28% vs 30%	NR	I: 6% vs 5% II: 64% vs 70% III: 19% vs 16%
Yamamoto 2019 [32]	Retrospective propensity-matched Japan	2003 –2014	Laparoscopic/laparoscopy-assisted (69) vs open (69)	>70 61% vs 68%	NR	NR	30% vs 33%	NR	I: 68% vs 68% II: 15% vs 15% III: 17% vs 17%
Yasuda 2004 [33]	Retrospective Japan	1994 –2003	Laparoscopy-assisted (45) vs open (28)	>70 58% vs 61%	NR	Cardiovascular: 36% vs 50% Diabetes: 11% vs 18% Pulmonary: 0% vs 4%	0% vs 0%	NR	Early GC: 100% vs 100%
Zheng 2016 [34]	Retrospective China	2013 –2014	Laparoscopy-assisted (23) vs open (27)	>70 74% vs 56%	NR	Comorbidity index ≥2: 39% vs 38%	0% vs 0%	NR	I: 17% vs 15% II: 9% vs 19% III: 74% vs 67%

Abbreviations: ASA *American Society of Anesthesiologists*; GC *gastric cancer*; NR *not reported*.
*Baseline data on the whole group level, no subgroup data reported.

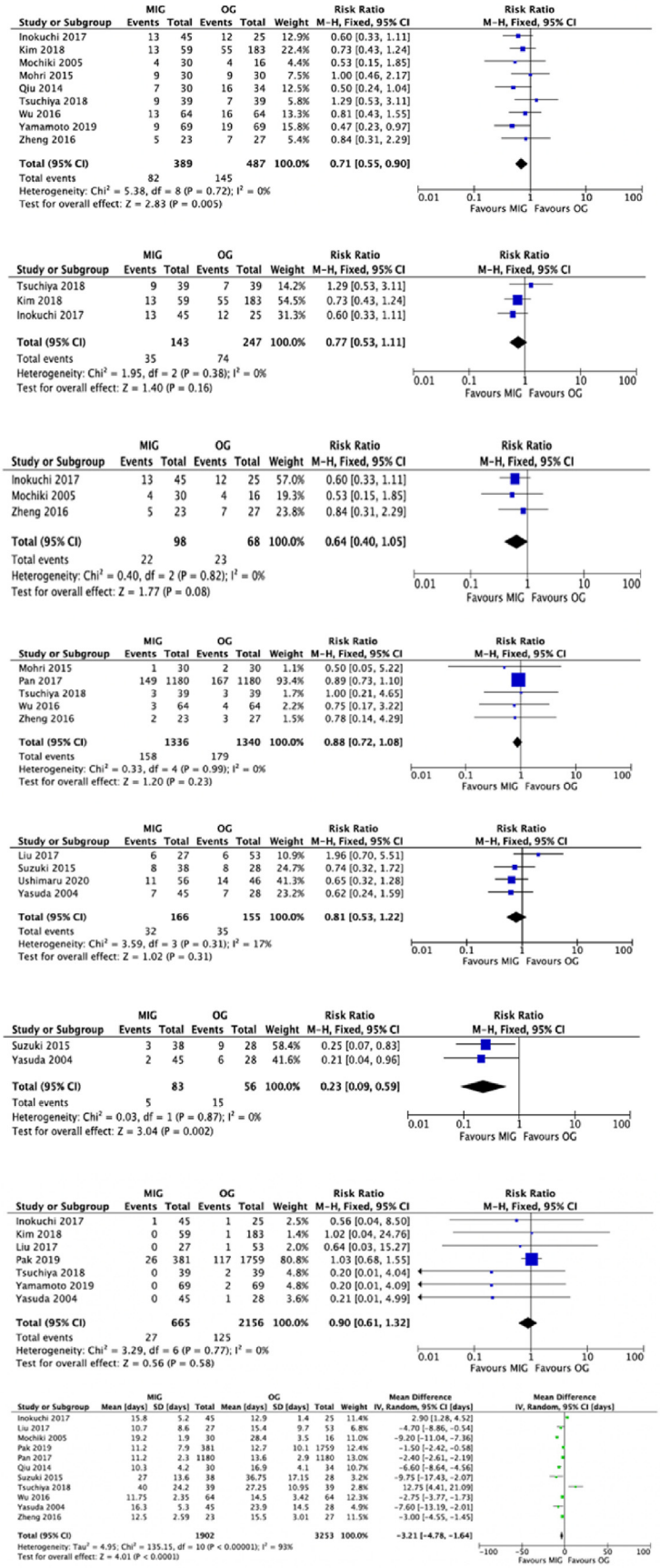

Fig. 2. Pooled analyses regarding postoperative outcomes in patients undergoing minimally invasive versus open gastrectomy.
a. Overall complications in patients ≥70 years, b. Overall complications in patients >80 years, c. Overall complications in patients ≥70 years (distal gastrectomy only), d. Severe complications in patients ≥70 years, e. Surgical complications in patients ≥70 years, f. Medical complications in patients ≥70 years, g. Postoperative mortality in patients ≥70 years, h. Length of stay between in patients ≥70 years.

Table 4
Characteristics and survival outcomes of studies reporting on extended (standard) vs limited lymphadenectomy during gastrectomy for gastric cancer in patients 70 years and older.

Reference	Study design Country Inclusion period	Comparison (N)	Age % males	# lymph nodes	Tumor stage	Total gastrectomy	Multiorgan resection	(Neo)adjuvant therapy	Survival outcomes
Degiuli 2014 [44]	RCT Italy 1998–2005	D2 gastrectomy (35) vs D1 gastrectomy (45)	70–79 70% vs 58%	Mean 37.3 vs 28.2	IA: 19% vs 31% IB-II: 48% vs 33% IIIA-IIIB: 20% vs 27% IV: 11% vs 7%	23% vs 25%	Sx 9% vs 7% Px and Sx 2% vs 2%	None	**Cancer-specific 5-year:** D2: 51% D1: 75%, p = 0.02
Songun 2010 [45]	RCT The Netherlands 1989–1993	D2 gastrectomy (102) vs D1 gastrectomy (128)	70–84 56% vs 57%	Mean 31.5 (range 0–106) vs 18.4 (range 0–73)	IA: 21% vs 20% IB-II: 45% vs 50% IIIA-IIIB: 22% vs 22% IV: 11% vs 7%	38% vs 30%	Sx 37% vs 11% Px 30% vs 3%	None	**Overall 15-year:** D2: mean 5.35 years (95% CI 4.21–6.49) D1: mean 4.97 years (95% CI 4.10–5.82) HR 0.88, 95% CI 0.67–1.16, *ns*
Edwards 2004 [46]	Prospective Wales 1996–2002	D2 gastrectomy (42) vs D1 gastrectomy (24)	>70 70% vs 58%	Median 15 (range 5–32) vs 8 (range 1–24)	I: 20% vs 33% II: 28% vs 25% III: 52% vs 41%	51% vs 31%	Sx 9% vs 8% Px 4% vs 0% Colectomy 13% vs 0%	None	**Overall 5-year (univariable):** D2: 45% D1: 36%, *ns*
Seo 2017 [48]	Retrospective South Korea 2006–2016	D2 gastrectomy (41) vs D1 gastrectomy (62)	>80 49% vs 63%	Mean 43.8 vs 35.1	I: 42% vs 68% II: 24% vs 16% III: 34% vs 16%	15% vs 23%	Multiorgan resection 12% vs 2%	NR	**Overall, mean 33 months (univariable):** D2 vs D1*: HR 2.0 (95% CI 0.59–6.80), *ns* **Cancer-specific (univariable):** D2 vs D1: HR 1.78 (95% CI 0.43–7.28), *ns*
Mikami 2016 [50]	Retrospective Japan 2001–2011	Standard (170) vs limited lymphadenectomy (97)	>70 66% vs 65%	Mean 36.1 vs 27.3	I: 72% vs 23% II: 12% vs 36% III: 15% vs 41%	25% vs 30%	NR	NR	**Overall 5-year (multivariable):** Standard vs limited: HR 1.62 (95% CI 0.087–3.03), *ns* **Cancer-specific (univariable):** Stage I: Standard: 100% vs limited 99%, *ns* Stage II-III: Standard 79% vs limited: 67%, p = 0.04
Brenkman 2018 [47]	Retrospective The Netherlands 2006–2014	High LNY (174) vs intermediate (333) LNY vs low LNY (851)	>75 50% vs 58% vs 62%	>25 vs 15–25 vs < 15	N0: 47% vs 35% vs 56% N1: 10% vs 19% vs 19% N2: 12% vs 14% vs 17% N3: 31% vs 32% vs 8%	33% vs 33% vs 24%	None	Neoadjuvant chemo 18% vs 16% vs 10%	**Overall >1 year (multivariable):** High vs low: HR 0.61 (95% CI 0.47–0.80), p < 0.001 Intermediate vs low: HR 0.75 (95% CI 0.63–0.89), p = 0.001
Passot 2016 [49]	Retrospective France 1997–2010	High LNY (145) vs intermediate (125) LNY vs low LNY (116)	>75 57% vs 50% vs 56%	>25 vs 15–25 vs < 15	N1: 35% vs 37% vs 33% N2: 22% vs 18% vs 13% N3: 7% vs 4% vs 3%	49% vs 47% vs 26%	None	Neoadjuvant chemo 6% vs 6% vs 3% Adjuvant treatment 6% vs 11% vs 3%	**Overall, mean 42 months (univariable):** High LNY: median 27 months Intermediate LNY: median 37 months Low LNY: median 31 months, *ns* **Cancer-specific (univariable):** High LNY: median not reached Intermediate LNY: median

Table 4 (*continued*)

Reference	Study design Country Inclusion period	Comparison (N)	Age % males	# lymph nodes	Tumor stage	Total gastrectomy	Multiorgan resection	(Neo)adjuvant therapy	Survival outcomes
									64 months Low LNY: median 51 months, *ns*

Abbreviations: ASA *American Society of Anesthesiologists;* CI *confidence interval;* LNY *lymph node yield;* HR *hazard ratio;* NR *not reported;* ns *not significant;* RCT *randomized controlled trial;* Px *pancreatectomy;* Sx *splenectomy*.
* Patients with T1N0 tumors were excluded from analysis.

intermediate LNY and low LNY (pooled RR 0.80, 95% CI 0.50–1.26, p = 0.33).

3.3.3.3. Overall survival. Six studies reported on OS [45–50] (Table 4). No meta-analysis was performed due to differences in populations and interventions between the studies. In a subgroup analysis in patients >70 years in the Dutch RCT [45], D2 gastrectomy seemed to be associated with slightly improved OS, although the results were not significant (D2 vs D1: mean OS 5.35 vs 4.97 years, 15-year OS: 13% (95% CI 6–20) vs 3% (95% CI 0–6)). In a subgroup analysis of patients ≥70 years in a prospective cohort study from Wales [46], 5-year OS rates between D2 and D1 gastrectomy were not significantly different (45% vs 36%, no p-value reported). In a South Korean study [48], D2 gastrectomy was not associated with a survival advantage in a subgroup of patients with >T1N0 tumors (HR 2.0, 95% CI 0.59–6.80). In a Japanese cohort [50], compared to limited lymphadenectomy, standard lymphadenectomy was associated with improved 5-year OS in a subgroup of patients with stage II-III tumors (72% vs 41%, p = 0.001) but not with stage I tumors (91% vs 86%, p = 0.53). In multivariable analysis adjusted for tumor stage, type of resection, comorbidities and other risk factors, no survival benefit was observed for standard lymphadenectomy (HR 1.62, p = 0.13).

Finally, two studies compared OS between groups with high, intermediate and low LNY [47,49]. A Dutch population-based study [47] showed that, compared to patients with low LNY, high LNY and intermediate LNY were associated with improved OS when adjusted for confounder variables such as total gastrectomy, surgical approach and tumor stage (high LNY vs low LNY: adjusted HR 0.61, 95% CI 0.47–0.80, p = 0.001; intermediate LNY vs low LNY: adjusted HR 0.75, 95% CI 0.63–0.89, p = 0.001). In an Italian cohort study [49], no difference was found in OS between the groups in univariable analyses. No multivariable analyses were performed despite the presence of several potential confounders such as differences in total gastrectomy rates, and percentage of patients treated in high volume centers or receiving adjuvant chemotherapy.

3.3.3.4. Cancer-specific survival. In the Italian RCT [44], better 5-year CSS was observed for older patients who underwent D1 vs D2 gastrectomy (75% vs 51%, p = 0.02). However, more patients in the D1 group had early gastric cancer, and no multivariable analysis was performed in the subgroup of older patients. In a South Korean cohort [48], no difference was found in CSS between patients who underwent D2 or D1 gastrectomy (HR 1.78, 95% CI 0.43–7.28). In a Japanese cohort [50], standard lymphadenectomy was associated with improved 5-year CSS in patients with stage II-III disease (standard vs limited: 79% vs 67%, p = 0.04), but not in patients with stage I disease. In multivariable analysis, standard lymphadenectomy was not associated with improved CSS (HR 2.2, 95% CI 0.77–6.10).

In an Italian cohort study [49], no difference was found in CSS between patients with high, intermediate or low LNY in univariable analyses.

4. Discussion

In this review, we found low-quality evidence that older patients (>75 years) may gain a survival benefit from undergoing gastrectomy compared to conservative treatment. The results of our meta-analyses support MIG as the preferred treatment option compared to the more traditional OG in older patients. The effect of extended lymphadenectomy on survival outcomes in older patients remains unclear and studies addressing QoL are absent. Baseline frailty assessment of older patients were lacking in all studies.

To our knowledge, this is the first review that has compared survival outcomes between gastrectomy and conservative treatment in older patients with potentially resectable gastric cancer. In general, the quality of evidence was poor due to retrospective data collection, limited group sizes and confounding by indication. In most studies, there were significant between-group differences in preoperative PS or comorbidity burden. In addition, unmeasured differences in frailty parameters that are prevalent in older patients with cancer (malnutrition, mobility problems, low muscle mass or poor cardiopulmonary capacity) presumably contributed to the decision on whether to proceed with surgery. Patients with higher frailty levels and thus lower life expectancy were possibly not considered candidates for surgery which probably led to an overestimation of the survival benefits that could be assigned to gastrectomy.

Considering the nature of the research question, randomizing patients in a treatment and control group is not feasible, but prospective detailed and well-powered data collection would be able to address some of the bias. In addition, future studies would benefit from collecting information on patient-reported outcome measures such as QoL and physical functioning. These outcomes were not addressed in the studies in this review, although most older patients with life-limiting illness value QoL and the ability to remain functionally independent over the possible survival benefits [53]. Furthermore, we included studies that defined the conservative treatment group as patients who were deemed operable but did not undergo surgery. It is possible that older patients who would have to undergo a total gastrectomy (high-risk surgery) were deemed inoperable and were thus not included in the present studies. It would be interesting to explore which tumor- and patient-related factors affect the decision on which treatment is pursued in older patients.

The results of our meta-analysis indicate that MIG is the preferred treatment option for gastric cancer compared to OG in older patients. A previous meta-analysis showed that MIG was associated with less postoperative complications and shorter LOS without compromising oncological outcomes in patients >65 years

[11]. In this review, we employed stricter inclusion criteria regarding participant age (≥70 years). Our results regarding postoperative outcomes were comparable to the earlier meta-analysis: MIG was associated with fewer overall complications and shorter LOS. Severe complication rates and mortality rates were comparable between the groups. Although only one study was conducted in a Western population [40], the results were comparable to the Asian studies with regard to shorter LOS in the MIG group and similar postoperative mortality rates between the groups. In a recent Dutch population-based study in patients with a mean age of 66–70 years, MIG was also associated with less complications and shorter LOS after distal gastrectomy [54]. Previous RCTs from Asian countries have shown comparable morbidity and mortality between MIG and OG [55] and better QoL after MIG [56]. Two Western RCTs have compared MIG and OG in gastric cancer patients. The STOMACH trial included patients with a mean age of 60 years undergoing total gastrectomy in six European countries. Non-inferiority analyses revealed no difference in morbidity and mortality rates between MIG and OG [13]. The LOGICA trial was a multicenter RCT in the Netherlands comparing OG and MIG in patients (mean age 67 years) with resectable gastric cancer. No differences in postoperative complications, LOS, 1-year survival or QoL were found [12]. Therefore, although no RCTs have been conducted exclusively in older patients, the results of this meta-analysis together with evidence from previous RCTs support MIG as a safe alternative option to OG also in older patients.

In this review, we analyzed the available evidence on the optimal level of lymphadenectomy in older patients. Regarding short-term outcomes, there were no significant between-group differences in the postoperative morbidity and mortality rates in the studies, implying that more extensive resections can be safely performed in older patients. Regarding long-term survival outcomes, only two studies found that extended lymphadenectomy was associated with better OS [47] or CSS [50]. Both studies had a retrospective design and although several relevant confounders including tumor characteristics and operation type were adjusted for in the Dutch population-based study [47], no information was available on preoperative frailty parameters. Current treatment guidelines are increasingly opting for D2 dissections, but based on the results of this review there is limited evidence for a survival benefit after extended lymphadenectomy in the older patient population. Apart from survival outcomes, there are few studies that have explored QoL or functional outcomes after limited or extended lymphadenectomy. A retrospective Spanish study found no difference in QoL after D1 and D2 lymphadenectomy [57] whereas an Italian study showed that D2 dissection was associated with more gastrointestinal symptoms [58]. Studies addressing QoL or functional outcomes in older patients are still lacking. Therefore, at the moment, it is not possible to make a recommendation on whether a D1 or a D2 lymphadenectomy is preferred for older patients.

The strengths of this review include the strict inclusion criteria regarding age as well as the inclusion of both RCTs and cohort studies to gain a comprehensive view on the current evidence regarding gastric cancer surgery outcomes in older patients. We also attempted to collect data on baseline frailty and QoL outcomes which are especially relevant parameters to consider during preoperative shared decision-making, and showed that studies addressing these parameters are scarce. Despite the wide scope of the review, we did not include a comparison between total or distal gastrectomy although the extent of gastrectomy can have consequences regarding postoperative complications and QoL. Previous reviews have shown that distal gastrectomy is the preferred treatment option for distal gastric cancer compared to total gastrectomy [59,60]. It would be useful to confirm these findings also in the older patient population. We also did not address the impact of (neo)adjuvant therapies on survival or QoL outcomes. Several RCTs have demonstrated increased survival after perioperative chemotherapy regimens [3,61,62], or after adjuvant chemo (radio) therapy [63–65]. However, chemotherapy or radiotherapy may be less well tolerated in older patients, and future studies weighing survival and QoL outcomes after multimodal treatment in this population are warranted.

5. Conclusion

In this review, we addressed outcomes of different surgical treatment strategies of gastric cancer in older patients. Unfortunately, we are not able to draw substantial practice-changing conclusions from the available literature due to paucity of data and lack of high-quality studies. There is low-quality evidence demonstrating that undergoing gastrectomy is associated with a survival benefit in patients >75 years of age. Results of our meta-analyses support MIG as the preferred treatment option compared to OG in older patients. The evidence on extended lymphadenectomy in older patients is limited and survival benefits remain unclear. Future studies on surgical treatment of gastric cancer in older patients need to include baseline frailty measures. Finally, in addition to complications and survival, QoL and physical functioning should be addressed in future studies as they are equally relevant outcome measures in the older population.

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CRediT authorship contribution statement

T.E. Argillander: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **S. Festen:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **H.J. van der Zaag-Loonen:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **P. de Graeff:** Methodology, Writing – original draft, Writing – review & editing. **E.S. van der Zaag:** Writing – original draft, Writing – review & editing. **B.L. van Leeuwen:** Writing – original draft, Writing – review & editing. **W.B. Nagengast:** Writing – original draft, Writing – review & editing. **R.J.J. Verhage:** Writing – original draft, Writing – review & editing. **J.P. Ruurda:** Writing – original draft, Writing – review & editing. **B.C. van Munster:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **P. van Duijvendijk:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.05.003.

Appendix A. Search strategy for MEDLINE

Search 1

"Aged" [Mesh] OR "Aged, 80 and over" [Mesh] OR "Frail Elderly" [Mesh] OR Geriatrics [Mesh] OR "elder*" [tiab] OR old age*[tiab] OR oldest old [tiab] OR oldest-old [tiab] OR senior*[tiab] OR senium [tiab] OR very old [tiab] OR septuagenarian*[tiab] OR octogenarian* [tiab] OR nonagenarian*[tiab] OR centenarian*[tiab] OR super-centenarian*[tiab] OR older people [tiab] OR older subject*[tiab] OR older patient*[tiab] OR older age*[tiab] OR older adult*[tiab] OR older man [tiab] OR older men [tiab] OR older male*[tiab] OR older woman [tiab] OR older women [tiab] OR older female*[tiab] OR older population*[tiab] OR geriatri*[tiab] OR eldest [tiab].

Search 2

"Stomach Neoplasms" [Mesh] OR stomach tumor*[tiab] OR stomach tumor*[tiab] OR stomach cancer*[tiab] OR stomach neoplasm*[tiab] OR stomach carcinoma*[tiab] OR stomach adenocarcinoma*[tiab] OR gastric tumor*[tiab] OR gastric tumor*[tiab] OR gastric cancer*[tiab] OR gastric neoplasm*[tiab] OR gastric adenocarcinoma*[tiab].

Search 3

"Gastrectomy" [Mesh] OR "Surgical Procedures, Operative" [Mesh] OR gastrectomy [tiab] OR gastrectomies [tiab] OR resect* [tiab] OR surgery [tiab] OR surgeries [tiab] OR surgical [tiab] OR operative [tiab] OR "non-surgical" [tiab] OR operation*[tiab] OR supportive care [tiab] OR lymphadenectomy [tiab] OR lymphadenectomies [tiab] OR lymph node dissection [tiab] OR nodal dissection [tiab].

Search 4

"Patient Outcome Assessment" [Mesh] OR "Survivors" [Mesh] OR "Physical Fitness" [Mesh] OR "Quality of Life" [Mesh] OR "Mortality" [Mesh] OR "Activities of Daily Living" [Mesh] OR complication*[tiab] OR prom [tiab] OR health status [tiab] OR health profile*[tiab] OR outcome*[tiab] OR health index*[tiab] OR health indices [tiab] OR disability [tiab] OR wellbeing [tiab] OR well-being [tiab] OR activities of daily living [tiab] OR daily living activity [tiab] OR ADL [tiab] OR quality of life [tiab] OR HRQL [tiab] OR HRQoL [tiab] OR QoL [tiab] OR surviv*[tiab] OR case fatality rate*[tiab] OR death rate*[tiab] OR recovery [tiab] OR physical fitness [tiab] OR length of hospital stay [tiab] OR length of stay [tiab] OR LOS [tiab] OR discharge [tiab] OR loss of function*[tiab] OR functional loss [tiab] OR delirium [tiab].

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