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MINIREVIEWS

# Is surgery the best treatment for elderly gastric cancer patients?

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## Abstract

As the elderly population increases, the number of patients with gastric cancer has also been increasing. Elderly people have various preoperative problems such as malnutrition, high frequency of comorbidities, decreased performance status, and dementia. Furthermore, when surgery is performed, high postoperative complication rates and death from other diseases are also concerns. The goal of surgery in the elderly is that short-term outcomes are comparable to those in nonelderly, and long-term outcomes reach life expectancy. Perioperative problems in the elderly include: (1) Poor perioperative nutritional status; (2) Postoperative pneumonia; and (3) Psychological problems (dementia and postoperative delirium). Malnutrition in the elderly has been reported to be associated with increased postoperative complications and dementia, pointing out the importance of nutritional management. In addition, multidisciplinary team efforts, including perioperative respiratory rehabilitation, preoperative oral care, and early postoperative mobilization programs, are effective in preventing postoperative pneumonia. Furthermore, there are many reports on the usefulness of laparoscopic surgery for the elderly, and we considered that minimally invasive surgery would be the optimal treatment after assessing preoperative risk.

**Key Words:** Elderly; Gastric cancer; Surgery; Laparoscopy; Gastrectomy; Dementia



**Core Tip:** The definition of elderly varies from 75 to 85 years of age and over. Therefore, we classified individuals into ages 75, 80, and 85 years and over. In addition, long-term functional performance in the elderly should consider not only prognosis but also life expectancy. Perioperative problems were discussed separately for preoperative, intraoperative, and postoperative procedures. Regarding surgery,

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based on the latest findings, we discussed surgical indications compared with best supportive care, laparoscopic surgery, total gastrectomy, and the extent of lymph node dissection.

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## INTRODUCTION

Although gastric cancer (GC) has declined over the past decades[1], it is still one of the most common cancers worldwide. It is the fifth leading cancer and the third leading cause of cancer-related death globally[2]. Surgery is the main treatment for GC, and chemotherapy and radiation therapy are adjuvants. Gastric carcinogenesis is a multifactor and multistep process characterized by a complex interplay between the host and environmental factors[3]. Although there are many reports of an association between *Helicobacter pylori* (*H. pylori*) infection and GC, recent reports show that *H. pylori* might be more a commensal and an opportunistic pathogen than a confirmed pathogen[4]. In addition, gut microbiota dysbiosis and chronic inflammation play a greater role in the initiation and progress of GC than in the presence of *H. pylori*[5]. GC due to *H. pylori* infection is recognized as noncardia GC, and a decrease in *H. pylori* infection contributes to a decrease in noncardia GC[6]. On the other hand, cardia GC caused by obesity and gastroesophageal reflux disease has increased[7].

Life expectancy has increased globally. According to the 2020 World Health Statistics released by the World Health Organization, Japan has the highest life expectancy, 84.2 years, followed by Switzerland, with a life expectancy of 83.3 years. Twenty-eight countries have an average life expectancy of over 80 years. Many European countries are ranked high, and Asia, Singapore, and South Korea, in addition to Japan, are also ranked high[8]. As a result, the prevalence of elderly patients with GC increases significantly as the population ages[9].

However, GC treatment in the elderly faces several challenges, such as increased underlying comorbidities[10], low organ function, low immune function, and decreased willingness for treatment. Other problems that arise when surgery is performed are high postoperative complication rates and death from other diseases [11]. In addition, weight loss after gastrectomy significantly worsens quality of life and adversely affects the long-term prognosis of elderly patients with GC[12]. Herein, we consider the problems encountered in GC treatment in the elderly.

## OVERVIEW OF SURGICAL TREATMENTS IN ELDERLY PATIENTS WITH GC

Regarding the evaluation of surgical outcomes, short-term outcomes include postoperative complications and hospital mortality, whereas long-term outcomes include prognosis. The goal of surgical treatment in the elderly is short-term outcomes comparable to the nonelderly and long-term outcomes that reach life expectancy.

Many studies of surgery for elderly patients with GC have been reported. Preoperative characteristics of the elderly include decreased nutritional status, high frequency of comorbidities[13], and high frequency of dementia[14]. In general, the incidence of complications increases with age[10,13]. However, the definition of elderly varies from 75 to 85 years and over.

In studies divided by 75 and 80 years, some reports stated no difference in the postoperative complication rate even though the elderly had many comorbidities and a high American Society of Anesthesiologists (ASA) physical status[15-17]. However, several reports suggest that mortality due to surgical[13,18,19] and severe complications[10] was higher in the elderly (Table 1).

On the other hand, in a report defining the elderly as individuals aged 85 years and over, there was no difference in the complication rate related to surgery. Still, the incidence of pneumonia[20] and delirium[21] was high. However, there are limits to the interpretation of these results, such as the same ASA physical status and performance status in the control group and the elderly[20] and a low rate of total gastrectomy[22] (Table 1).

Several reports[10,13] have shown that the 5-year overall survival as a long-term outcome is lower with older age; however, cancer-related survival was not significantly different. This finding means that elderly individuals often die from other illnesses[23,24]. Some reports revealed that a low preoperative prognostic nutritional index (PNI) or sarcopenia[25] and multiple comorbidities[24] were significant risk factors for death from other diseases. Hashimoto *et al*[11]. revealed that the causes of death from other diseases in the elderly group were other malignancies (22%), pneumonia (18%), cardiovascular disease (10%), cerebrovascular disease (10%), and malnutrition (8%).

Two studies compared life expectancy and long-term outcomes. Life expectancy varies from country to country and should be considered individually for each country.

The first study is from Japan, in which postoperative life expectancy of late-elderly patients (≥ 80 years) was assessed by analyzing patient survival, except for cancer recurrence-related death. As a result, the median estimated life expectancy was equivalent to the life expectancy in the demographic data presented by the Japanese Ministry of Health, Labor, and Welfare[18].

The second study was from South Korea. The postoperative life expectancy of late-elderly patients (≥ 80 years) after eliminating death from recurrence was comparable to the corresponding aged general population after eliminating death from GC[10].

Treatment goals in these studies were achieved because survival from surgery was equivalent to life expectancy.

## CRITICAL PROBLEMS IN THE PERIOPERATIVE CARE FOR ELDERLY PATIENTS

### *Nutritional status during the perioperative period*

Elderly patients with GC are often poorly nourished. Therefore, the nutritional status before surgery in elderly patients is important for surgical risk assessment. Body mass index (BMI), the PNI, controlling nutritional status (CONUT), serum albumin, skeletal muscle mass, and the geriatric nutritional risk index (GNRI) have been reported as nutritional parameters. Among these, GNRI is reported as useful for predicting postoperative complications[26]. The CONUT score is reported as useful for predicting postoperative procedure-unrelated infectious morbidity and prognosis in elderly patients with GC[27].

Furthermore, malnutrition in the elderly is associated with weakness, sarcopenia, and frailty. Preoperative sarcopenia has been reported as a risk factor for severe postoperative complications in elderly patients undergoing gastrectomy[28]. Preoperative exercise and nutritional support programs have recently been actively attempted[29]. Nutritional support[30] and social and financial support are also needed in patients with muscle loss after gastrectomy[31].

### *Postoperative pneumonia*

Postoperative pneumonia is one of the most frequent complications in the elderly and can be fatal[32]. The causes reported are swallowing dysfunction due to age-related anatomical and physiological changes, lower respiratory function, and poor immunocompetence[33].

Age and preoperative albumin levels, hypertension, male gender, D2 dissection[34,35], impaired postoperative respiratory function, diabetes mellitus, and blood transfusion[36] have been reported as risk factors for pneumonia. Postoperative pneumonia is associated with reduced long-term survival[37,38]. Recent multidisciplinary team efforts, including perioperative respiratory rehabilitation, preoperative oral care, and early postoperative mobilization programs, have generally been reported effective in preventing postoperative pneumonia[33,39,40].

### *Psychological problems*

Dementia is increasing due to the aging population. Malnutrition in the elderly has

been reported to be associated with dementia[41]. The degree of dementia varies from mild to severe, and it is necessary to consider the surgical indication. In addition, patients with GC after gastrectomy, especially after total gastrectomy, show an increased risk of Alzheimer's disease[42]. Therefore, those who received continual vitamin B12 supplementation after a total gastrectomy were less likely than controls to develop Alzheimer's.

Likewise, postoperative delirium is common in the elderly[38]. Shim *et al*[43] reported a significant decrease in delirium symptom severity (DSS) over three postoperative days. Age and anesthesia time were positively associated with the initial DSS level, and medication history for memory complaints was related to a slower recovery from delirium symptoms. While propofol as an anesthetic agent was associated with a lower initial DSS, it predicted slower recovery from DSS.

Risk factors for subsyndromal delirium have also been reported in the elderly and poorly educated[44]. Multivariate analysis revealed that male gender, age ≥ 75 years, a history of cerebrovascular disease, and frequent use of sleeping pills were independent predictive factors for postoperative delirium[45]. Therefore, artificial control of the sleep–wake cycle by drug therapy is effective for postoperative delirium[46].

## TREATMENT-RELATED ASPECTS

### *Laparoscopic surgery*

The use of laparoscopic gastrectomy (LG) has become widespread. It is a surgical option for GC that is minimally invasive. Some multicenter randomized clinical trials have demonstrated that LG can provide similar short- and long-term results to open surgery patients with GC[47,48]. However, the age criteria of these clinical trials were 80 years or younger; therefore, the safety and feasibility of laparoscopic procedures were not fully evaluated in elderly patients.

Several studies of laparoscopic surgery for the elderly over 80 years of age have reported no difference in postoperative complications in the elderly despite a high prevalence of cardiovascular disease, decreased respiratory function[49], and a higher ASA physical score and PS[50,51].

Yoshida *et al*[52] compared the elderly to the nonelderly, and there were significant differences between the two groups in preoperative respiratory and renal function, hemoglobin, and nutritional indicators. However, the only significant differences in postoperative complications were pneumonia and delirium. There were no significant differences in surgery-related complications. On the other hand, some reports have demonstrated the advantages of LG rather than open gastrectomy (OG).

Using propensity score matching analysis, the incidence of postoperative complications grade ≥ 2 in the OG subgroup was significantly higher than in the LG subgroup [53]. Another large-scale propensity score analysis also demonstrated that LG might reduce in-hospital mortality and reduce the incidence of postoperative complications in patients with an ASA ≥ 3[54].

In a nationwide Japanese prospective cohort study, postoperative complications and mortality were significantly higher in OG than in LG. In addition, LG shortened the length of postoperative hospital stay[55].

### *Adjuvant chemotherapy*

The usefulness of adjuvant chemotherapy for Stage II and III GC has been reported in Japan[56-58] and South Korea[59], and it has become a standard treatment. However, since most of the clinical trials in Japan are conducted in patients aged 80 years or younger, the usefulness of adjuvant chemotherapy cannot be directly applied to elderly adults aged 80 years or older. Therefore, in Japan, a phase III study is currently underway to define the prognosis of adjuvant chemotherapy for stage II/III patients aged 80 years or older who have undergone gastrectomy[60]. On the other hand, in South Korea, surgery alone and adjuvant chemotherapy were examined in elderly patients with GC aged 75 years or older. There was no significant difference in the overall 5-year survival rate between the two groups[61].

Elderly adults have reduced physical fitness and organ function, especially renal function; therefore, it is necessary to consider the individual patient's condition before adding adjuvant chemotherapy[62].

**Table 1 Short- and long-term outcomes of surgical treatments in elderly patients with gastric cancer**

| Variables | Gretschel *et al*[13] | Park *et al*[15] | Otowa *et al*[16] | Sakurai *et al*[17] | Takeshita *et al*[18] | Katai *et al*[19] | Yang *et al*[10] | Yamada *et al*[20] | Hikage *et al*[21] | Isobe *et al*[22] |
|---|---|---|---|---|---|---|---|---|---|---|
| Definition of elderly (yr) | > 75 | ≥ 80 | ≥ 80 | ≥ 80 | ≥ 80 | ≥ 80 | ≥ 80 | ≥ 85 | ≥ 85 | ≥ 85 |
| No. of elderly people | 48 | 291 | 39 | 95 | 104 | 112 | 68 | 24 | 55 | 56 |
| BMI | ND | E < N-E | E = N-E | ND | ND | ND | ND | E = N-E | E = N-E | ND |
| Comorbidities | E > N-E[a] | E > N-E[a] | E > N-E | E > N-E[a] | ND | E > N-E[a] | ND | E = N-E | E = N-E | E = N-E |
| PS | ND | ND | ND | ND | ND | ND | ND | E = N-E | E > N-E[a] | ND |
| ASA physical status | E > N-E[a] | E > N-E[a] | E > N-E[a] | E > N-E[a] | ND | ND | E > N-E[a] | E = N-E | E > N-E[a] | ND |
| cStage | ND | E > N-E[a] | ND | ND | E > N-E[a] | E = N-E | E > N-E[a] | E = N-E | E = N-E | E = N-E |
| Rate of TG in surgery | E < N-E[a] | ND | E = N-E | E = N-E | E = N-E | E = N-E | E = N-E | E = N-E | E = N-E | E < N-E[a] |
| Percentage of TG in surgery | 46 | ND | 35.9 | 29.5 | 24 | 32 | 20.6 | 37.5 | 23.6 | 8.9 |
| Complication rate | E = N-E | ND | E = N-E | E = N-E | E = N-E | E = N-E | E > N-E[a] | E = N-E | E = N-E | E < N-E[a] |
| Respiratory complication | E = N-E | ND | E = N-E | E = N-E | E = N-E | E > N-E[a] | E = N-E | E > N-E[a] | E = N-E | E = N-E |
| Delirium rate | ND | ND | ND | ND | ND | ND | ND | ND | E > N-E[a] | E = N-E |
| Mortality rate | E > N-E[a] | ND | ND | E = N-E | E > N-E | E > N-E | E > N-E[a] | ND | E = N-E | E = N-E |
| Adjuvant chemotherapy | ND | ND | E < N-E[a] | E < N-E[a] | ND | ND | E < N-E[a] | ND | E < N-E[a] | ND |
| Overall survival rate | E < N-E[a] | E < N-E[a][1] | E < N-E(stage II)[a] | E < N-E(stage II, III)[a] | E < N-E[a] | E < N-E[a] | E < N-E[a] | ND | E < N-E[a] | E = N-E |
| Disease-specific mortality | E = N-E | E < N-E[a][1] | E < N-E(stage II) | E < N-E(stage II, III)[a] | E = N-E | E = N-E | E = N-E | ND | E = N-E | E = N-E |

[1]Curative treated patient.

[a]$P < 0.05$. BMI: Body mass index; E: Elderly; N-E: Nonelderly; ND: Not described; PS: Performance status; ASA: American Society of Anesthesiologists; TG: Total gastrectomy.

## OPTIMAL SURGICAL TREATMENT FOR ELDERLY GC

Male gender, low BMI, poor PS, low serum albumin levels, and advanced tumor stage were reported as predictors of overall survival[20]. In a report comparing supportive care and surgery in patients aged 85 and older, distal gastrectomy resulted in significantly better long-term survival in women, but not in men[63]. In addition, it has been reported that surgery contributes to a better prognosis than supportive care for patients with early or low-risk GC[64]. In clinical practice, in elderly patients with GC, it is very important to correctly evaluate the patients' organ reserve functions and mental status to select and provide appropriate treatment options to each patient according to these assessments. Also, the indications for surgery of elderly patients over 85 years of age should be carefully considered based on the prognosis.

### *Extent of gastrectomy*

We have reported that total gastrectomy is a risk factor for postoperative pneumonia [37]. However, in this study, the rate of laparotomy was relatively high. Abdominal breathing could be impaired due to incision pain and impairment of the abdominal rectus muscle in laparotomy cases, which might increase pulmonary complications.

On the other hand, in recent years, several studies[53,65,66] of laparoscopic total gastrectomy (LTG) in patients with GC have reported favorable short- and long-term outcomes compared with open surgery. However, LTG is more difficult due to technology than laparoscopic distal gastrectomy, reconstruction is complicated, and it

has been reported that the complication rate is high in the real world[67]. It has been reported that LTG does not increase complications even in the elderly[68]; however, LTG has been reported to have anastomotic leakage[69] and complications[70]. Only well-trained laparoscopic teams should perform LTG. Recent reports have shown that laparoscopic subtotal gastrectomy[71], which leaves a very small residual stomach, has better short-term outcomes and nutritional status than LTG and laparoscopic proximal gastrectomy, suggesting that it may be possible in elderly adults[72].

### *The extent of lymph node dissection*

Standard treatment strategies for Japanese patients with GC, especially the extent of lymph node dissection, have been established in the Japanese Gastric Cancer Treatment Guidelines[73]. However, these guidelines are not standardized for elderly patients with GC, and standard treatments can be highly invasive.

Several studies have reported the extent of reduced dissection in the elderly, and no difference was found between the incidence of complications and prognosis[17] or disease-specific mortality[18] after 80 years of age.

In studies on elderly patients who are over 85 years of age, there was no association between limited lymph node dissection and comorbidities, except for cerebrovascular events. Gastrectomy with radical lymph node dissection appears to be an effective treatment for patients with Stage II GC[74]. On the other hand, D2 dissection has been reported as a risk factor for postoperative pneumonia[34,35]. Studies using the Charson complications score reported a high incidence of postoperative complications and no significant improvement in overall survival[75]. From these studies, the extent of dissection is still controversial.

### *Preoperative prediction of various complications*

Preoperative risk predictions for developing complications have been reported, with male gender, combined resection[76], preoperative albumin, PNI, and Hiroshima POSSUM[77] being risk factors.

Japan has a nationwide database called the National Clinical Database, which can calculate risks, such as postoperative 30-d mortality, surgery-related mortality, suture failure rate, and the pneumonia rate[78,79]. Reliable predictive models must be useful in treatment strategy decision-making in elderly patients with GC.

## CONCLUSION

There are specific problems in the elderly, such as preoperative malnutrition, dementia, postoperative pneumonia, and delirium. However, in recent years, it has been shown that the minimal invasiveness of laparoscopic surgery is as useful or better than open surgery. Pre- and postoperative nutritional support are also important. It is necessary to use these and some risk predictions regarding surgical indications.

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