The appropriate treatment for elderly gastric cancer patients

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Abstract: Gastric cancer has continued to rise in the elderly as life expectancies increase. The current standard of care practices is often based on clinical trials consisting of much younger patient population and these treatment guidelines need to be assessed for their direct applicability to the elderly population, both in the context of their increased comorbidities as well as differences in their disease pathophysiology and presentation. This article reviews the current state of medical knowledge in the management of gastric cancer and presents evidence from the National Cancer Database (NCDB), with a special focus on the additional considerations that need to be made in the treatment of elderly patients with gastric cancer.

Keywords: Gastric cancer; octogenarian; neoadjuvant therapy; radiation

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Gastric cancer has a peak incidence between 50 and 70 years of age, and has demonstrated a rising incidence in the elderly as life expectancies have increased (1-4). Current treatment guidelines and the standard of care are commonly based on studies and clinical trials of younger patients and need to be assessed for their direct applicability to the elderly population, both in the context of their increased comorbidities as well as potential differences in their disease pathophysiology (1,5,6). This manuscript examines the current state of scientific knowledge in the management of gastric cancer and presents the evidence from the National Cancer Database (NCDB), with a special focus on the important variations and considerations that need to be made for elderly patients.

Incidence and epidemiology

Gastric cancer is the fifth most common cause of cancer and the third leading cause of cancer-related death worldwide (7,8). The incidence and mortality of gastric cancer is disproportionately varied by geographic region, with a higher rate in Eastern Asian countries and a relatively lower rate in Western countries (9,10). In Eastern Asia, gastric cancer of the distal portion of the stomach is more common, while proximal gastric cancer is more often seen in the West (3,11).

Several environmental and lifestyle factors contribute to an increased risk of gastric cancer. Helicobacter pylori (H. pylori) infection is a major cause of gastric carcinogenesis with potential progression to gastric cancer, and is also responsible for the disproportionately high prevalence of gastric cancer in Asian countries (12,13). In Japan and Korea, the substantial decline of H. pylori infection in recent decades has been accompanied by a corresponding decrease in gastric cancer incidence and mortality (14-18). The decline of gastric cancer mortality in these countries can also be attributed to the rigorous screening programs that have been implemented, as more cancers are being diagnosed at an earlier stage (19-22). Dietary and lifestyle factors such as high sodium intake, increased alcohol consumption, and smoking have also been associated with an increased risk of gastric cancer (23-27). Diets high in fruit and vegetable consumption have shown a protective effect against gastric cancer (28-30).

The elderly and gastric cancer

Currently, there is no standard definition of "elderly". Many groups and organizations, including the World Health Organization, have used a chronological age of 65 years and older to define the elderly population; however, as the average life expectancy in many countries are reaching, and at times exceeding, 80 years of age, this definition is rapidly shifting (31,32). As a result, there are also no standard guidelines for the management and treatment of the elderly with gastric cancer.

Several differences have been identified in the presentation and pathologic characteristics of gastric cancer when diagnosed in the elderly compared with younger patients. As expected, elderly patients typically have more medical comorbidities and higher American Society of Anesthesiologists (ASA) classification scores (33-35). Elderly patients also tend to present with symptomatic disease of more advanced clinical stage (33,36,37). The primary tumors tend to be found in the distal third of the stomach (38-41). Histopathologically, elderly patients tend to have tumors that occur in multiples, of larger size, and of well-differentiated and intestinal-type histology (1,33,36,38,42-46). Several studies have also identified potentially different patterns of lymph node metastases in elderly gastric cancer patients compared with younger patients; however, the results are conflicting as some studies have demonstrated a higher propensity of lymph node metastases in the elderly, some have shown a lower propensity, and others have shown no difference (1,33,38,41,42,47-50). The interpretation of these varying findings remains difficult as the elderly often undergo a limited lymphadenectomy compared to the extended D2 lymphadenectomy which is the standard of care among younger patients. We examined 13,836 patients who underwent radical gastrectomy between 2010 and 2014 using NCDB, of which 2,140 patients (15%) were aged ≥80 years. Patients age older than 80 tended to have larger tumors and more lymph node involvement, hence with higher American Joint Committee on Cancer (AJCC) stages compared to younger patients (P<0.0001). These observations are consistent with previous reports.

Surgery in the elderly

The extent of resection is determined by the primary tumor stage and nodal status. The AJCC TNM classification is one of the most commonly used staging criteria (51). T1a tumors, defined by invasion of the lamina propria or muscularis mucosa, are typically amenable to endoscopic resection. For stage IB–III disease with a primary tumor that that invades into and beyond the submucosa but does not violate the visceral peritoneum or adjacent structures, a partial gastrectomy with extended D2 lymphadenectomy is recommended to achieve a curative resection of all microscopic and macroscopic disease (52).

As gastrectomy is a significant abdominal operation, elderly patients must be carefully evaluated preoperatively given their increased risk of morbidity and mortality with surgery. Fujiwara *et al.* compared 115 patients aged ≥80 years with 333 patients aged ≤79 years, who underwent subtotal or total gastrectomy with varying extent of lymphadenectomy, and found that patients aged ≥80 years had more post-operative complications and in-hospital mortality, as well as lower overall survival (OS) and disease-specific survival (DSS) (53). Using a time-dependent receiver operating characteristic curve analysis, the optimum age cut-off identified in this study for gastrectomy to produce a survival benefit at three years was 79.2 years. Hsu *et al.* evaluated the outcomes of 164 patients ≥80 years who underwent subtotal or total gastrectomy with D2 lymphadenectomy in comparison with 2,258 younger patients <80 years and also identified a significantly higher morbidity (18% *vs.* 13%, P=0.035) and in-hospital mortality rate (7% *vs.* 3%, P=0.015) in the elderly group (35). However, unlike the previous study, Hsu *et al.* did not identify any significant differences in long-term disease-specific deaths (44% *vs.* 47%, P=0.407) after a median follow-up of 37.8 months. Applying an even higher age cut-off to define the elderly population, Endo *et al.* compared 56 patients ≥85 years old who underwent distal gastrectomy with 55 patients <85 years old who received best supportive care only using propensity score-matched analysis (54). A survival benefit of gastrectomy over best supportive care in this most elderly group was demonstrated among female patients only (median OS 67 *vs.* 12 months, P<0.0001), but not in male patients (median OS 13 *vs.* 18 months, P=0.037). Post-operative pneumonia, especially among male patients, was a common complication in this study population and was often associated with mortality, which has also been reported in other studies (42,53,55-58). The gender-based survival difference in patients with post-operative pneumonia has also been identified in other elderly and highly comorbid patient populations, and is potentially a result of interactions between various hormonal, immunologic, and microbiologic

factors (59-63). The overall high incidence of post-operative pneumonia in the elderly is likely due to the baseline decreased pulmonary function and reserve, which is then further diminished after a major open abdominal surgery (64-69). Non-pulmonary post-operative complications as well as post-operative death after gastrectomy have also demonstrated increasing incidence with increased patient age (34,45,70-72). These studies indicate the importance of pre-operative risk assessment and patient selection among elderly patients being considered for open gastrectomy.

One technique to reduce the post-operative morbidity and mortality among elderly patients undergoing gastrectomy is to use a minimally-invasive approach. Several studies have demonstrated comparable and, at times even improved, outcomes in elderly patients undergoing laparoscopic or robotic gastrectomy compared to an open approach (73-76). The measured outcomes in these studies included intra-operative blood loss, time to first flatus, time to first oral diet, index length of hospital stay, post-operative complications, and survival. The minimally-invasive approach produces a smaller physiologic insult on the body, with fewer long-term functional impairments (77,78). Unlike prior studies in open gastrectomy where elderly patients consistently had higher rates of post-operative complications than non-elderly patients, several studies have found the complication rates between elderly and non-elderly patients to be similar with the minimally-invasive technique (45,79-83). We have recently conducted our own review of post-operative outcomes in patients aged ≥80 years who had undergone minimally-invasive compared to open subtotal or total gastrectomy using the NCDB. We found that minimally-invasive gastrectomy was associated with decreased length of stay of at least 1 day (P<0.001) compared to open gastrectomy. In addition, there was no difference in the rate of margin-positive resections (P=0.27), adequate lymph node sampling defined as ≥15 lymph nodes (P=0.08), readmissions (P=0.32), or 30- or 90-day mortality (P=0.75, P=0.82) between these two approaches. A minimally-invasive approach to curative resection in the elderly should be highly considered to promote post-operative recovery and improve patient outcomes.

The extent of lymphadenectomy during gastrectomy and the potential survival benefit of extended D2 lymphadenectomy in elderly patients has also been controversial. While D2 lymphadenectomy, which includes nodes along the left gastric, common hepatic, celiac, and splenic arteries in addition to the perigastric lymph nodes removed in D1 lymphadenectomy, is typically recommended for stage IB–III gastric cancers, the oncologic benefit must be balanced with the potentially increased morbidity and mortality of this more extensive procedure in an elderly population with more medical co-morbidities and less functional reserve. Brenkman *et al.* reviewed 2,387 patients <75 years of age and 1,377 patients ≥75 years who had undergone curative subtotal or total gastrectomy and found that a high lymph node yield improved survival in both age groups, with no increase in postoperative mortality (43). However, the difficulty in interpreting this and similar studies lies in the use of lymph node yield as a measure of the extent of lymphadenectomy. Lymph node yield only records the number of lymph nodes harvested intra-operatively, but may not always accurately convey if nodes were sufficiently taken from all the necessary stations that define a D2 lymphadenectomy. In the Dutch trial of 1,078 patients who were randomized to D1 or D2 lymphadenectomy, patients >70 years consistently had higher morbidity and mortality compared to patients ≤70 years, and these rates were even higher among those >70 years who underwent D2 compared to D1 lymphadenectomy, with limited survival benefit (84). Rausei *et al.* reviewed 1,322 patients who had undergone curative gastrectomy with D2 versus D1 lymphadenectomy and, in addition, to categorizing patients by age (<70 versus >70 years), also stratified patients by their comorbidities using the Charlson comorbidity score (<5 *vs.* >5) (85). Overall, more post-operative complications occurred in patients >70 years (34% *vs.* 28%, P<0.001), and within this elderly population, those with high Charlson scores had an even higher complication rates (38% *vs.* 31%, P=0.007). Patients >70 years with high Charlson scores also trended towards having more complications after D2 lymphadenectomy, but this was not statistically significant (40% *vs.* 35%). Additional studies have also demonstrated the lack of survival benefit conferred by extended D2 lymphadenectomy compared to a more limited D1 lymphadenectomy in elderly patients (46,86-88) (*Table 1*). Our study from the NCDB suggested that elderly patients might not derive the same survival benefit from D2 lymph node dissection as younger patients. Of the 2,140 patients aged ≥80 years who underwent subtotal or total gastrectomy, half had less than 15 lymph nodes examined and half had 15 or more lymph nodes examined. Using this as a proxy for extent of lymph node dissection, there was no difference in OS between the elderly patients who had a limited compared to extensive lymphadenectomy (median

Table 1 Studies evaluating potential survival benefit of extended compared to limited lymphadenectomy in elderly patients

Study	Study design	Study groups	Outcome
Brenkman, 2017 (43)	Retrospective	<75 years =2,387; ≥75 years =1,377	High lymph node yield improves overall survival with no increase in postoperative mortality
Hartgrink, 2004 (84)	Prospective, randomized to D1 or D2 lymphadenectomy, compared by age ≤70 *vs.* >70 years	D1 =380; D2 =331	Higher morbidity and mortality for patients >70 years, especially for D2 compared to D1 lymphadenectomy
Rausei, 2016 (85)	Retrospective, compared by D1 *vs.* D2 lymphadenectomy, age, and Charlson comorbidity score	<70 years =686; >70 years =636	Higher morbidity for patients >70, especially for those with high Charlson scores and those who underwent D2 lymphadenectomy
Passot, 2016 (86)	Retrospective, compared by age and extent of lymphadenectomy	<75 years =962; ≥75 years =386	Patients ≥75 years had greater postoperative morbidity and mortality despite less aggressive medical and surgical treatment, no survival difference with different extents of lymphadenectomy
Eguchi, 2000 (87)	Retrospective, patients >75 years, compared by extent of lymphadenectomy	Limited =161; extended =21	Increased morbidity in mortality in patients with extended lymphadenectomy, no survival benefit
Takeshita, 2013 (88)	Retrospective	<80 years =1,089; ≥80 years =104	Patients ≥80 years who underwent limited lymph node dissection had no difference in disease-specific survival

OS 18.2 *vs.* 19.2 months, P=0.29).

Neoadjuvant therapy for the elderly

For patients with ≥T1b tumors, neoadjuvant chemotherapy with a platinum/fluoropyrimidine combination is recommended (52). The MAGIC trial demonstrated a significant improvement in both overall (5-year 36% *vs.* 23%) and progression-free survival (PFS) (HR 0.66; 95% CI: 0.53–0.81) for patients with resectable gastric cancer treated with three cycles of pre-operative and three cycles of post-operative epirubicin, cisplatin, and fluorouracil compared to those who underwent surgery alone (89). Additional trials have supported the survival benefit of this neoadjuvant chemotherapy combination in patients with resectable gastric cancer (90,91). However, many the patients in these trials were young or middle-aged, with a limited number of elderly patients, especially those ≥80 years. Trials focusing specifically on elderly patients have demonstrated an oncologic benefit with neoadjuvant chemotherapy but at the expense of increased toxicities and decreased quality of life (92,93).

The role of neoadjuvant chemoradiation remains unclear and remains an active area of investigation (94-97). Additional studies will be needed to determine if the potential benefits are also applicable to the elderly population. Our investigation of the NCDB showed that among all the elderly patients who underwent radical gastrectomy, only 7.5% received neoadjuvant chemo/radiation therapy, whereas the proportion is much higher in other age groups (44.5% for patients <65 years and 33.6% for patients aged 65–79 years, P<0.001).

Adjuvant therapy for the elderly

For patients who did not receive neoadjuvant chemotherapy prior to undergoing resection, adjuvant chemotherapy or chemoradiation is recommended for patients with high risk of disease recurrence (98). The survival benefit of adjuvant chemotherapy for resected patients compared to surgery alone has been well documented in two randomized phase III trials from Asia. The CLASSIC trial reported an improved 3-year disease-free survival (DFS) of 74% in patients who underwent D2 gastrectomy followed by chemotherapy compared to 59% in patients who received surgery alone (99). In a subgroup analysis by age, patients ≥65 years receiving adjuvant chemotherapy also had improved 3-year DFS. In the ACTS GC trial, the 5-year DFS in patients who received adjuvant chemotherapy was 65% compared to 53% in the surgery-only group; 5-year

OS was 72% and 61% in the adjuvant chemotherapy and surgery-only groups, respectively (100). However, in subgroup analysis by age, there was no difference in DFS for patients ≥60 years and no difference in OS for patients ≥70 years. To date, no randomized trials have been conducted to evaluate the benefit of adjuvant chemotherapy specifically in elderly patients who have undergone gastrectomy. Retrospective studies focusing on elderly patients have reported conflicting results and, without randomization, are difficult to interpret due to the potential effect of selection bias in which elderly patients received the addition of adjuvant chemotherapy (101-105).

Intergroup 0116 was the first randomized phase III trial conducted in Western patients to demonstrate the benefit of adjuvant chemoradiation after surgery compared to surgery alone (106). The initial study findings published in 2001 reported an improved median OS of 36 months in patients who received adjuvant chemoradiation compared to 27 months for those who had surgery only (106). The final update from this study cohort was published after more than ten years of follow-up and demonstrated a persistent benefit in both OS and DFS for patients who had received adjuvant chemoradiation (107). Yeh *et al.* used the Surveillance, Epidemiology, and End Results-Medicare database to review 1,519 patients ≥65 years of age who had undergone gastrectomy, of whom 42% received adjuvant chemoradiation (108). In this retrospective, population-based study, adjuvant chemoradiation demonstrated a survival benefit (HR 0.59, 95% CI: 0.50–0.67) over surgery alone, particularly for patients with stages II and III disease.

The benefit of adjuvant therapy continues to be supported in subsequent trials and reviews; however, the added benefit of adjuvant chemoradiation compared to adjuvant chemotherapy alone remains under debate (109-112). Future prospective clinical trials need to be conducted to study the potential benefit of adjuvant therapy in elderly patients and to determine the optimal treatment regimens to maximize disease control as well as maintain their quality of life.

Table 2 presents a review of chemotherapy, radiation, and chemoradiation trials and studies comprising gastric cancer patients of all ages. *Table 3* summarizes trials and studies that focused specifically on the treatment of elderly patients.

Treatment of metastatic disease for the elderly

In the setting of metastatic disease, combination therapy with platinum and fluoropyrimidines is recommended. In a multi-center phase III trial of 50 patients ≥70 years with metastatic cancer, double therapy with oxaliplatin and capecitabine improved both PFS and OS compared to monotherapy with capecitabine (PFS 7.1 *vs.* 2.6 months, OS 11.1 *vs.* 6.3 months) (113). This is comparable to the median OS times reported in phase III trials comprised of patients of all ages with metastatic gastric cancer (114-116). Sasaki *et al.* reported in a phase II trial that combination cisplatin and S-1, an oral fluoropyrimidine, was also safe and effective for elderly patients ≥76 years, with median PFS and OS of 7.8 and 12.3 months, respectively (117). In a sub-group analysis of patients ≥70 years who were enrolled in the Japanese randomized phase III G-SOX comparing S-1 and oxaliplatin with S-1 and cisplatin therapy, there were no differences in PFS or OS between the two combination regimens but elderly patients receiving S-1 and oxaliplatin experienced fewer toxicities (118). A retrospective review of 129 patients ≥65 years with metastatic or recurrent gastric cancer also showed that combination S-1 and oxaliplatin was well-tolerated in this older age group (119) (*Table 4*).

Summary statement

(I) Patient and tumor characteristics of elderly patients:

Elderly patients tend to have more comorbidities and present with more advanced stage of disease. Histologically, elderly patients tend to have larger, multiple tumors of well-differentiated and intestinal-type histology.

(II) Surgery in elderly patients:

Gastric cancer surgery, including total gastrectomy, is safe for physically-fit elderly patients. We recommend a minimally-invasive approach with less extensive lymph node dissection to minimize post-operative morbidity and mortality.

(III) Neoadjuvant therapy for the elderly:

Based on clinical trials conducted among participants of all ages, patients with ≥T1b tumors are recommended to receive neoadjuvant chemotherapy with a platinum/fluoropyrimidine combination regimen. Among elderly patients, the oncologic benefit of neoadjuvant therapy must be balanced with the potentially increased toxicities and decreased quality of life.

(IV) Adjuvant therapy for the elderly:

Based on clinical trials conducted among

Table 2 Review of adjuvant therapy trials and reviews in the treatment of gastric cancer patients of all ages

Study	Study design	Study groups	Outcome
Adjuvant chemotherapy vs. surgery alone			
Bang, 2012 (CLASSIC trial) (99)	Phase III randomized controlled trial of adjuvant capecitabine/oxaliplatin *vs.* surgery alone	Adjuvant chemotherapy =520; surgery alone =515	Improved 3-year DFS (74% *vs.* 59%) in adjuvant chemotherapy arm
Sasako, 2011 (ACTS GC trial) (100)	Phase III randomized controlled trial of adjuvant S-1 *vs.* surgery alone	Adjuvant chemotherapy =529; surgery alone = 530	Improved 5-year DFS (65% *vs.* 53%) and 5-year OS (72% *vs.* 61%) in adjuvant chemotherapy arm
Adjuvant chemoradiation vs. surgery alone			
Macdonald, 2001 & Smalley, 2012 (Intergroup 0116) (106,107)	Phase III randomized controlled trial of adjuvant chemoradiation *vs.* surgery alone	Adjuvant chemoradiation =282; surgery alone =277	Improved RFS (HR 1.51, 95% CI: 1.25–1.83) and OS (HR 1.32, 95% CI: 1.1–1.6) in adjuvant chemoradiation arm
Dikken, 2010 (111)	Retrospective review	Adjuvant chemoradiation =91; surgery alone =694	improved local control with adjuvant chemoradiation in patient who underwent D1 lymphadenectomy, no difference in patients who underwent D2 lymphadenectomy
Adjuvant chemotherapy vs. adjuvant chemoradiation			
Park, 2015 & Lee, 2012 (ARTIST trial) (109,112)	Phase III randomized controlled trial of adjuvant chemotherapy (capecitabine/ cisplatin) *vs.* adjuvant chemoradiation	Adjuvant chemotherapy =228; adjuvant chemoradiation =230	Improved DFS for patients with node-positive disease and those with intestinal-type GC
Zhou, 2016 (110)	Meta-analysis of randomized controlled trials of adjuvant chemotherapy *vs.* adjuvant chemoradiation	4 trials, 960 patients	Improved loco-regional control and DFS with adjuvant chemoradiation, no difference in distant metastasis rate or OS

DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival.

Table 3 Review of adjuvant therapy trials and studies in elderly gastric cancer patients

Study	Study design	Outcome
Adjuvant chemotherapy vs. surgery alone		
Bang, 2012 (CLASSIC trial) (99)	Subgroup analysis of phase III trial of adjuvant chemotherapy *vs.* surgery alone of patients ≥65 years (n=269)	Improved 3-year DFS in adjuvant chemotherapy group (HR 0.48, 95% CI: 0.30–0.78) compared to surgery-alone group
Sasako, 2011 (ACTS GC trial) (100)	Subgroup analysis of phase III trial of adjuvant chemotherapy *vs.* surgery alone of patients ≥60 years, ≥70 years	No difference in DFS for patients ≥60 years, no difference in OS for patients ≥70 years
Jeong, 2016 (101)	Retrospective review of 130 patients ≥75 years (48% received adjuvant chemotherapy)	No difference in 5-year OS
Jo, 2015 (102)	Retrospective review of 94 patients ≥70 years (59% received adjuvant chemotherapy)	Longer RFS in adjuvant chemotherapy group, no difference in OS
Jin, 2013 (103)	Retrospective review of 360 patients ≥65 years (35% received adjuvant chemotherapy)	Improved OS only for stage III patients who received adjuvant chemotherapy
Hanazaki, 2000 (104)	Retrospective review of 53 patients ≥75 years (26% received adjuvant chemotherapy)	No difference in 1-, 3-, 5-year survival
Maehara, 1994 (105)	Retrospective review of 268 patients ≥70 years (60% received adjuvant chemotherapy)	Improved survival only for stage III patients who received adjuvant chemotherapy
Adjuvant chemoradiation vs. surgery alone		
Yeh, 2017 (108)	Retrospective review of 1,519 patients ≥65 years (42% received adjuvant chemoradiation)	Survival benefit for patients who received adjuvant chemoradiation (HR 0.58, 95% CI: 0.50–0.67), especially for Stage II/III disease

DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival.

Table 4 Review of chemotherapy trials and studies in elderly patients with metastatic gastric cancer

Study	Study design	Study groups	Outcome
Hwang, 2017 (113)	Phase III randomized controlled trial of patients ≥70 years	Capecitabine/oxaliplatin =24; capecitabine only =26	Improved PFS (7.1 *vs.* 2.6 months) and OS (11.1 *vs.* 6.3 months) with dual-therapy
Sasaki, 2017 (117)	Phase II trial of cisplatin and S1 in patients ≥76 years	40 patients	Well-tolerated and effective in elderly patients
Bando, 2016 (G-SOX trial) (118)	Subgroup analysis of patients ≥70 years from phase III randomized controlled trial	S-1/oxaliplatin =116; S-1/cisplatin =104	No significant difference in PFS or OS, fewer toxicities in S-1/oxaliplatin group
Zhong, 2015 (119)	Retrospective review of patients ≥65 years treated with S-1/oxaliplatin	129 patients	Well-tolerated and effective in elderly patients

PFS, progression-free survival; OS, overall survival.

participants of all ages, patients who did not receive neoadjuvant chemotherapy should receive adjuvant chemotherapy or chemoradiation. There is no strong evidence to support the additional benefit of adjuvant radiation therapy for patients who received adjuvant chemotherapy. To date, no randomized trials have been conducted to evaluate the benefit of adjuvant therapy specifically in elderly patients who have undergone gastrectomy.

(V) Treatment of metastatic disease for the elderly:

Combination therapy with platinum and fluoropyrimidines is recommended in the setting of metastatic disease. This regimen has been shown to be safe and well-tolerated in elderly patients.

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Footnote

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