

## Case report

# Complete response of liver metastatic gastric cancer after FOLFOX-4 chemotherapy regimen followed by salvage gastrectomy: A case report

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A 48-year-old Thai male with metastatic liver gastric adenocarcinoma achieved a complete pathological response after neoadjuvant chemotherapy. The patient underwent an esophagogastroduodenoscopy in October, 2008, which revealed a ten centimeter ulcerated tumor mass at his antrum with complete gastric outlet obstruction. The biopsy of his gastric ulcer showed high grade necrotic adenocarcinoma. Further workups with computed tomography staged his cancer as cT4bN1M1 P0 CYX H1. He received 12 cycles of neoadjuvant chemotherapy consisting of oxaliplatin and fluoropyrimidine. The follow up computerized tomography CT scan, showed a complete regression of liver metastasis. Afterwards, he underwent a subtotal gastrectomy with D2 lymph node dissection showing a complete pathological response (grade 3 according to Japanese Classification of Gastric Carcinoma 3rd English edition). Postoperatively, he received eight cycles of capecitabine. After a 43 month follow up period, there is no recurrent disease.

**Key words:** Gastric cancer, salvage operation, chemotherapy, metastasis, FOLFOX-4, capecitabine.

## INTRODUCTION

Carcinoma of the stomach has one of the worst cancer prognoses. Patients are often diagnosed in an advanced and metastatic stage resulting in great difficulty in obtaining a cure. New regimens of chemotherapy combining a cytotoxic agent and antimetabolite agent such as Folfox-4 have played a role in palliative therapy for advanced gastric cancer (Alberts et al., 2003; Kim et al., 2003). This combination therapy has produced a twenty two percent response rate (Baek et al., 2011). Currently the Folfox-4 regimen is widely used when patients present in advanced stages which include unresectable and metastatic disease (De Vita et al., 2005). Additional studies have shown favorable results of between 38 to 45% (De Vita et al., 2005; Shi et al., 2012; Mohammad et al., 2011; Louvet et al., 2002; Batran et al., 2004). However, a complete response rate is still lower than 8% (De Vita et al., 2005; Shi et al., 2012;

Mohammad et al., 2011; Louvet et al., 2002; Batran et al., 2004). Interleukin-8 gene expression in gastric cancer cells was studied and a higher expression of Interleukin-8 correlated to gastric cancer cell survival, migration and angiogenesis *in vitro* (Wen-Xia et al., 2012). A relationship of the Interleukin-8 protein level with prognosis of gastric cancer in clinical data was also reported (Kido et al., 2001). This study reports a metastatic gastric cancer patient that achieved a curative result after a long follow up period with the additional data of interleukin-8 expression.

## CASE DESCRIPTION

### History and physical examination

A 48 year old male Thai patient presented with dyspepsia and weight loss from 74 to 60 Kg within three months. He was previously treated for peptic ulcer disease with a proton pump inhibitor for six months. No previous

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**Table 1.** Summary of patient data.

Age	52 year
Sex	Male
Nationality	Thai
Weight loss	74 to 60 kg/3months
Staging	stage IV cT4bN1M1 P0 CYX H1
Pathology	High grade adenocarcinoma
1st line chemotherapy	FOLFOX-4
Toxicity	Grade I for anorexia and nausea
Chemo response	Grade 3, no residual carcinoma
Surgery	Subtotal gastrectomy, D2 resection
2nd line chemotherapy	Capecitabine
Disease free survival	3.5 year

endoscopic examination was done. His physical examination found an abdominal mass of 10 cm in diameter at the epigastrium. No ascites, no rectal shelf, and no supraclavicular lymph node were found. Summary of patient data is shown in Table 1.

### Endoscopic finding

An ulcerated tumor mass approximately 10 cm with raised margins, surrounded by a thickened gastric wall without clear margins was found. It was located in the middle to lower portion of stomach type III according to the Japanese Classification of Gastric Carcinoma 3rd English Edition (Japanese Gastric Cancer Association, 2011). The biopsy revealed a high grade necrotic adenocarcinoma.

### Computerized tomography (CT) scan finding

The tumor was located at the body and antrum of the stomach with direct invasion to the pancreas and abdominal wall. A necrotic 10 mm lymph node could be seen in the perigastric region, along the celiac trunk and gastro hepatic ligament. A five centimeter diameter metastasis to segment 3 of the liver was found. The CT scan is shown in Figure 2.

### Clinical progression

During the process of diagnosis, the patient developed a gastric outlet obstruction. A naso gastric tube was inserted and connected to suction to decompress the stomach. Total parenteral nutrition was utilized for two weeks until his overall condition was improved. The patient underwent an exploratory laparotomy to stage and examine the intra abdominal disease distribution and

to insert a jejunostomy tube for nutritional support. Chemotherapy was initiated ten days postoperatively. Two weeks after chemotherapy was started, the nasogastric tube contents continually decreased from 700 to 1000 ml per day to less than 100 ml per day. The enteric jejunostomy feeding reached 1800 kcal per day. Patient was gradually weaned from the total parenteral nutrition (TPN) and nasogastric tube suction and discharged from the hospital as shown in Figure 1.

### Intraoperative finding - at jejunostomy

Circumferential thickening of the stomach and a tumor mass was found to have invaded the abdominal wall anteriorly, the head and body of the pancreas posteriorly, and the middle colic mesentery inferiorly with enlarged lymph nodes in both the perigastric area and perivascular area. The left lobe of the liver was seeding with tumor so we could not do a palliative resection. These findings classified this patient as metastatic gastric cancer cT4bN1M1 according to the AJCC staging system 7th edition.

There was no peritoneal metastasis (P0) and peritoneal cytology was not performed (CYX) which indicated hepatic metastasis (H1) stage IV cT4bN1M1 P0 CYX H1 according to Japanese classification. A gastrojejunostomy was not performed because of the vagal nerve invasion and primary tumor invasion causing a technical risk of leakage and gastric paresis. If complications occurred, the earlier chemotherapy could not have been administered.

### Neoadjuvant chemotherapy

Chemotherapy was started at on the tenth post operative day with the FOLFOX-4 regimen (oxaliplatin 85 mg/m<sup>2</sup> 5-FU 600 mg bolus dose then continue with 900 mg in 22 h on two consecutive days. The FOLFOX- 4 chemotherapy was continued for 12 cycles.

Complete blood count was done before starting each cycle of chemotherapy. The patient experienced only grade I chemotherapy toxicity with anorexia and nausea according to common toxicity criteria version 3.0 (National Cancer Institute (US), 2003) with no other toxicities noted.

### Follow up computerized tomography (CT) scan result

The follow up CT scan showed a decreased size of the ulcerative mass, decreased thickening of stomach, regression of the hepatic mass at segment 3 and decreased size of lymph nodes in the left gastric, gastrocolic omentum, and celiac region to subcentimeters as shown in Figure 3.

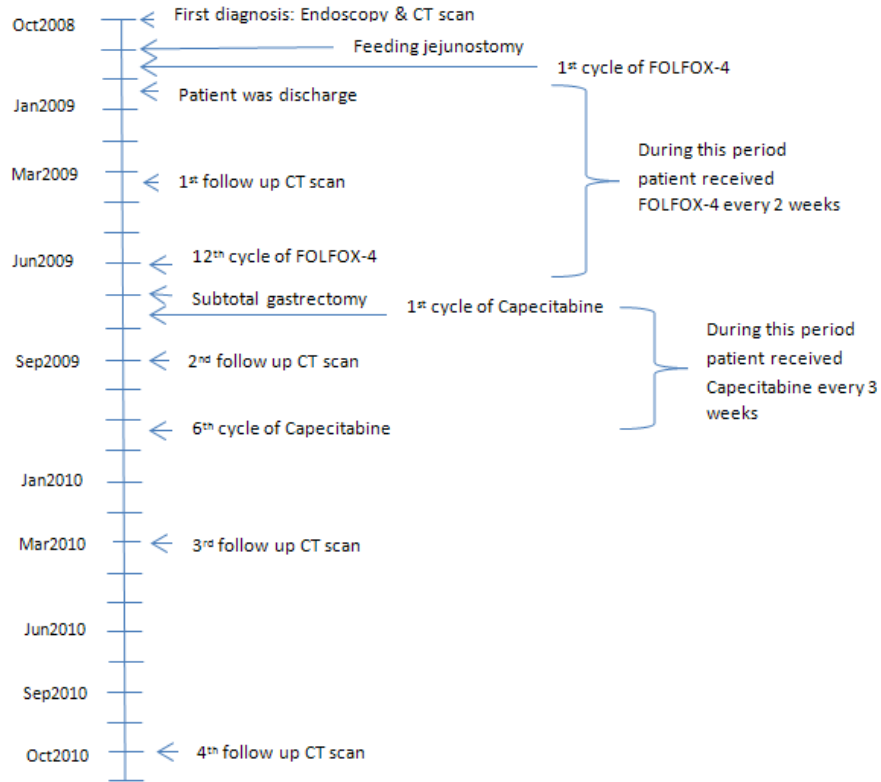


Figure 1. Summary of patient data and scheme of clinical progression.

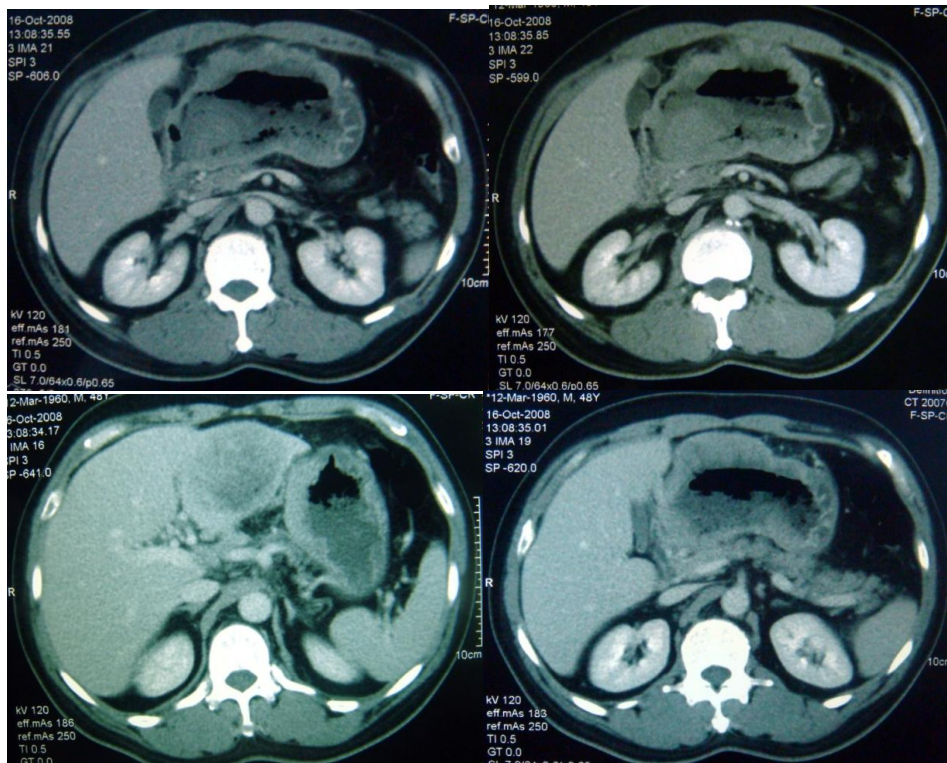
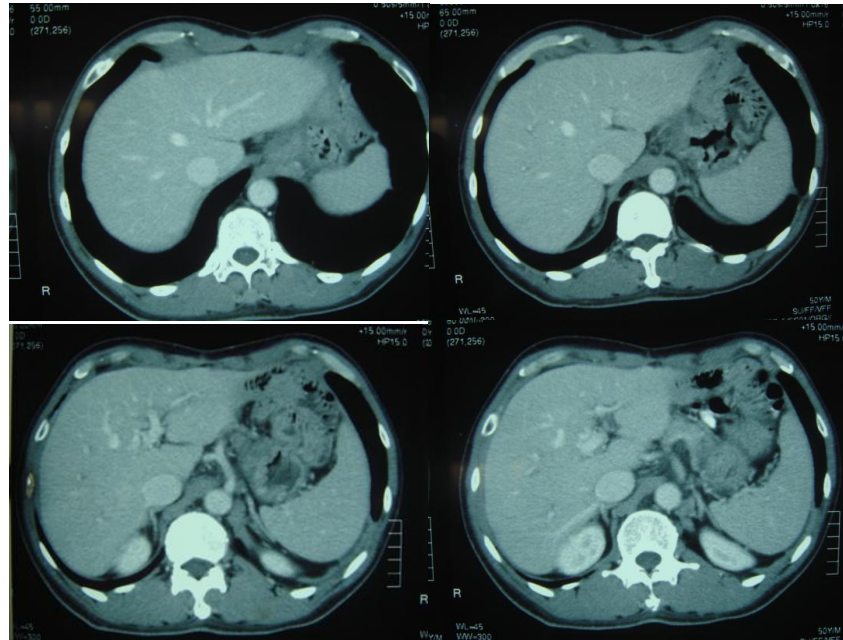
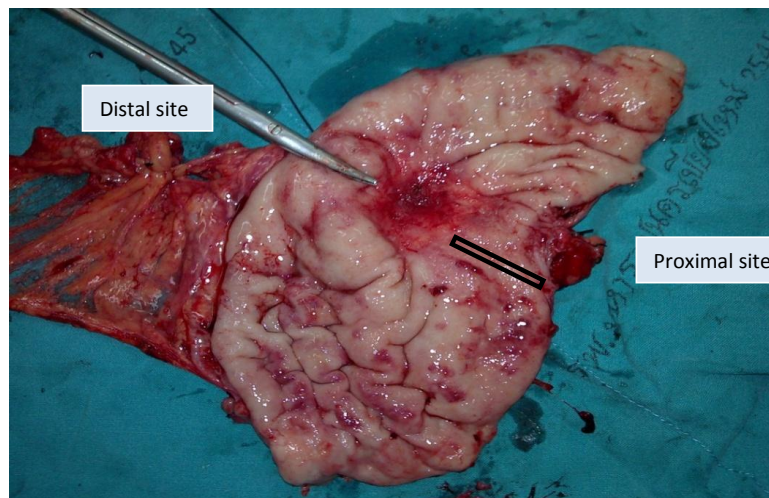


Figure 2. Pre chemotherapy CT scan showed liver metastasis and locally advanced tumor.



**Figure 3.** Showed markedly decreased gastric wall thickening.



**Figure 4.** shrinkage and deformity in the opened gross specimen in the lesser curve and body of stomach.

### Follow up endoscopic result

The follow up endoscopic exam revealed a marked regression of the gastric outlet obstruction previously caused by the tumor.

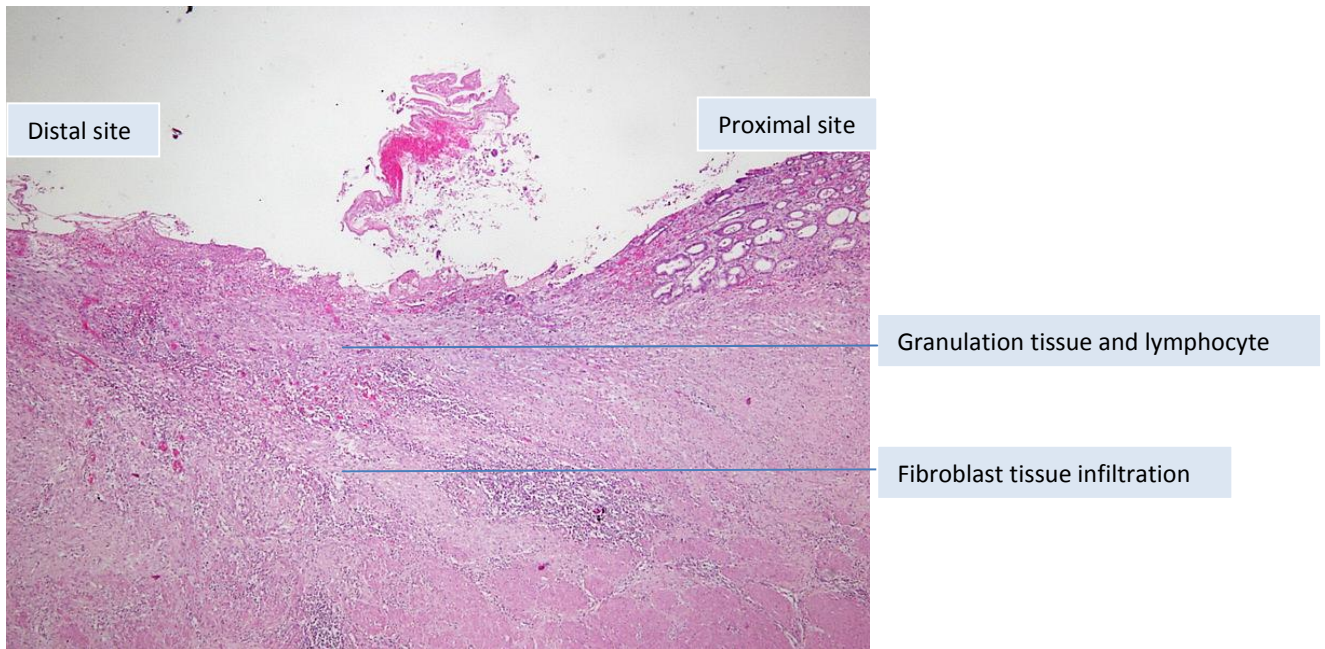
### 2nd operative finding

The intraoperative ultrasound revealed thickening of the body and the antrum of the stomach. In addition no gross

lymph node enlargement, no visible peritoneal seeding and no liver mass were identified. A subtotal gastrectomy with D2 lymph node dissection was performed. There was shrinkage and deformity in the opened gross specimen in the lesser curve and body of stomach (Figure 4). Section in Figure 5 was cut according to illustration.

### Pathologic report

Pathologic result showed a chronic hypertrophic ulcer



**Figure 5.** histological finding at base of ulcer without tumor cell residual.

and chronic atrophic gastritis with intestinal metaplasia. No residual carcinoma was found. Total number of lymphnode was eight, which was all negative for cancer. Histological evaluation showed grade 3 response (complete response) after neoadjuvant chemotherapy therapy according to Japanese Classification of Gastric carcinoma 3rd English Edition (Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2011).

#### **Interleukin-8 gene expression from real time polymerase chain reaction (PCR)**

This patient was also enrolled in another study which focused on biologic markers of gastric tissue. A tissue biopsy was performed during endoscopic examination followed by a total ribonucleic acid (RNA) extraction. The RNA extraction was converted to cDNA and tested for Interleukin-8 expression with Human TaqMan probe primer (No 4331182 Hs 99999034-m1 Applied biosystem) by using glyceraldehyde-3-phosphate dehydrogenase (GAPDH No 4331182 Hs 9999905-m1 Applied biosystem) as an internal control and comparing with cDNA of advanced gastric cancer cell line culture extraction at cell counting of  $2-4 \times 10^6$  as a baseline level. There was interesting result that Interleukin-8 gene expression was surprisingly dropped from Raw RQ (relative quantitation) = 822.7,  $\log_{10} = 2.92$  to Raw RQ = 74.427,  $\log_{10} = 1.87173$  as compared to result from Pre-chemotherapy period.

#### **Adjuvant chemotherapy**

Capecitabine  $2000 \text{ mg/m}^2$  was administered postoperatively for 14 consecutive days per cycle. Each cycle took 3 weeks. Total 6 cycles were administered to this patient. There were no major side effects of chemotherapy during both courses of chemotherapy

#### **Follow up**

Lastly liver metastasis was identified in CT scan. This patient was reevaluated with CT scan and endoscopy every six months. After three years and six months of follow up, no evidence of recurrence was found. During last visit in May 2012, the patient had no sign or symptom of cancer and his CT scan also showed no evidence of recurrence.

#### **DISCUSSION**

Currently, palliative gastric cancer resection is done in for the following tumor cell groups of patients including locoregional advanced (level 3 or 4 lymph node highly suspicious or confirmed by biopsy, invasion or encasement of major vascular structure) and distance metastasis or peritoneal seeding (including positive peritoneal cytology). Publications that propose palliative resection for improving patient survival continue to be released (Dittmar et al., 2009). In this case, despite

metastasis to the liver, gastric outlet obstruction in this patient was an indication which dictated the first operation for bypass or enteric feeding access. Unfortunately, due to the advanced primary lesion the surgeon was not able to do a palliative resection or gastro jejunostomy bypass surgery secondary to the thickening of the gastric wall which included the body of stomach and tumor that adhered to the abdominal wall.

After the failed palliative resection to correct the obstructive complication, we might conclude that the aim of this patient's treatment was the best supportive care. Much of the literature indicated that an unresectable lesion especially with complications has a much worse prognosis. Most of patients in this group have a very short life expectancy within two to four months. However, jejunostomy feeding was done with enteric nutrition providing a positive effect to his nutritional status and overall condition to permit chemotherapy administration.

According to many published data and reviews, patients who tolerate a palliative chemotherapy have a much better overall survival. In this case, after the overall condition of the patient was improved chemotherapy was administered. Although there are many regimens of chemotherapy available, all reviews of data suggest a combination of chemotherapy over a single chemotherapy regimen. Two of the most popular combination regimens are ECF (Epirubicin, Cisplatin, and Fluorouracil) regimen and FOLFOX-4 regimen (Baek et al., 2011). Not much difference was found between these two regimens in terms of response and complications. The response rate of both regimens are 38 to 45% (Baek et al., 2011; De Vita et al., 2005; Shi et al., 2012; Mohammad et al., 2011; Louvet et al., 2002; Batran et al., 2004; D' Ugo et al., Kim et al., 2011; Li et al., 2012; Cavanna et al., 2006; Zhao et al., 2009). The FOLFOX-4 regimen was chosen because we had more experience with this regimen and most of our patients have had a greater toleration for this treatment. There are also reports of FOLFOX-4 being well tolerated in elderly patients with gastric cancer (Zhao et al., 2009). One case report from Korea also showed a similar patient who had gastric outlet obstruction and responded well to the FOLFOX-4 regimen (Park and Chi, 2010).

There are still no consensus about further surgical treatment in advance gastric cancer patients who have achieved a complete response to chemotherapy. There are publications which support a salvage surgery. They suggest that salvage surgery was found to be only independent prognosis factor despite other significant prognosis factors were reported which included histology type, T4 staging and clinical response. However, most data are retrospective analysis and case report (Yano et al., 2002; Sasaki et al., 2007). We decided to perform a resection in primary tumor to prevent recurrence and complication with standard D2 resection.

Although, some researcher posses that salvage surgery may be the most important factor of survival in

advance gastric cancer patient (Yano et al., 2002; Sasaki et al., 2007). There is also a case report about curative result in a metastatic gastric cancer patient despite previous surgery could not get rid of all tumor. In this report, curative outcome was achieved by a complete response of tumor via multiple drug regimens (Fukasawa et al., 2006).

Therefore, it is difficult to claim that salvage surgery is an independent prognosis factor because degree of chemotherapy response is the factor that determines a possibility of a salvage surgery.

There is almost no data to support further chemotherapy after a salvage resection. In publication from japan, patient usually received additional S1 chemotherapy which is composed of Tegafur, Gimeracil, and Oteracil potassium (Sasaki et al., 2007; Sakuramoto et al., 2007). However, this chemotherapy is not available in our country. Therefore, we decided to use another regimen of chemotherapy; capecitabine which was widely used in Thailand for advance stage gastrointestinal tract cancer.

According to Interleukin-8 expression level which was measured by reverse transcription polymerase chain reaction (RT-PCR) method, lessened after chemotherapy treatment. It suggests that inflammatory cytokine response may have a role in chemotherapy. An action of Interleukin-8 can be explained in different way though many gene expression; HIF-1, NF- $\kappa$ B, AP1, AR, STAT3 and  $\beta$ -Catenin. These gene expressions effect in survival, invasion, proliferation and angiogenesis of tumor cell (Vaugh and Wilson, 2008). Moreover, *in vitro* study show that Interleukin-8 expression correlates with adhesion, migration, invasion and chemoresistance of gastric cancer cell.

Higher expression of Interleukin-8 means that tumor is more aggressive (Wen-Xia et al., 2012). However, in our study initial level of interleukin expression was quite high, Raw RQ (relative quantitation) = 822.7, log 10 = 2.92 which might suggest poorer prognosis according to previous report but eventually curative treatment result could be achieved. Decreasing of interleukin-8 expression level might correlate with chemotherapy response of gastric cancer which may be a useful biologic marker in nearby future.

## Conclusion

In unresectable gastric cancer, we suggest treatment with FOLFOX-4 regimen chemotherapy followed by salvage resection. Then other regimen of oral base fluoropyrimidine should be added after salvage resection. We propose that response to chemotherapy is the most important factor that determine the outcome of advance gastric cancer patients. Nutritional management will maintain the patient's fitness in order to tolerate the chemotherapy and surgery.

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