

Case Report



Long-term Survival after Repeated Local Therapy and Salvage Chemotherapy for Recurrent Metastases from Gastric Cancer: a Case Report and Literature Review

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OPEN ACCESS

Received: Jul 5, 2018

Revised: Aug 9, 2018

Accepted: Aug 14, 2018

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ABSTRACT

We report a rare case of long-term survival in a patient who received local therapy and salvage chemotherapy for recurrent metastases, along with a literature review. A 65-year-old male patient underwent subtotal gastrectomy for advanced gastric adenocarcinoma. Six months after gastrectomy, 2 metastatic intra-abdominal lymph node enlargements were detected, which were treated with radiotherapy. At 55 months after gastrectomy, an abdominal wall mass was detected, which was treated by surgical resection. The patient received 5-fluorouracil/leucovorin/irinotecan chemotherapy for 27 months before and after radiotherapy and docetaxel chemotherapy for 6 months after surgical resection of the abdominal wall metastasis. At the last visit, 7.8 years since the initial resection of the primary gastric cancer and 6.2 years since detection of the first metastases, the patient was disease-free and required no further chemotherapy. This case suggests that repeated local therapy offers potential for long-term survival in a carefully selected subset of patients with recurrent metastases.

Keywords: Chemotherapy; Gastric cancer; Metastasis; Radiotherapy; Surgery

INTRODUCTION

The prognosis for metastatic gastric adenocarcinoma is poor. The duration of survival for most patients is limited, and there are few curative treatment options. Palliative systemic therapy combined with best supportive care is regarded as the standard treatment for metastatic gastric cancer and the reported median survival for patients treated with this approach is approximately 1 year [1,2]. Local therapies, such as surgical resection and/or radiotherapy, are rarely indicated for patients with metastatic gastric cancer because it tends to occur at multiple sites, disseminate to the peritoneum, and show aggressive biological behavior.

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Funding

This research was supported by a Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science and Technology (2017R1A5A2015541).

Author Contributions

Conceptualization: K.J., H.H.S.; Data curation: K.H.K., B.S.W., Y.Y., K.W.D., S.S.M., K.D.H., Y.H.Y., H.H.S.; Supervision: K.H.K., Y.Y., B.S.W., K.J., H.H.S.; Writing - original draft: K.H.K., Y.Y., B.S.W., K.J., H.H.S.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Recently, prolonged patient survival has been associated with the availability of new chemotherapeutic regimens and many reports have shown improved survival following local treatment of metastatic lesions from gastric cancer [3-10], particularly surgical resection for patients with liver metastases [6-10]. However, reports of long-term survival after repeated local therapy for recurrent metastatic lesions from gastric cancer are still extremely rare. Here, we report a rare case of long-term survival in a patient who underwent local therapy and salvage chemotherapy for recurrent metastases detected after resection of the primary gastric cancer and review the relevant literature.

CASE REPORT

A 65-year-old man was diagnosed with advanced gastric adenocarcinoma in May 2010. Written informed consent for publication of this case report and associated images was obtained from the patient. Esophagogastroduodenoscopy revealed a large mass on the prepyloric antrum, and endoscopic biopsy confirmed a histological diagnosis of moderately differentiated tubular adenocarcinoma. A computed tomography (CT) scan of the abdomen revealed lymph node (LN) enlargement in the perigastric area but no evidence of metastasis. The patient underwent a subtotal gastrectomy and D2 LN dissection. Pathologic staging was determined postoperatively as pT4aN2M0, stage IIIB, and treatment with adjuvant tegafur/gimeracil/oteracil (S-1) was initiated.

At 6 months after surgery, routine CT showed well-defined enhancing masses in the peripancreatic area and inferior aspect of the right lobe of the liver (**Fig. 1A**). Positron emission tomography (PET)-CT also revealed 2-deoxy-2-[fluorine-18]fluoro-D-glucose (¹⁸F-FDG) uptake in the peripancreatic area and inferior aspect of the right lobe of the liver (standardized uptake values [SUVs], 6.1 and 3.3, respectively; **Fig. 1B**). A diagnosis of recurrent and metastatic gastric cancer was established, and the patient was treated with capecitabine and oxaliplatin (XELOX) as first-line palliative chemotherapy for 4 months, followed by 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) as second-line palliative chemotherapy. After 4 months of FOLFIRI therapy, tumor assessment showed a partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST), but no further changes were observed over the following 5-month period. In February 2012, 9 months after the start of FOLFIRI chemotherapy, radiotherapy was administered to the LNs at the peripancreatic and inferior aspect of the right lobe of the liver (5,040 cGy in 25 fractions over a 5-week period). This was followed by FOLFIRI chemotherapy for an additional 18 months.

In September 2013, 33 months after the first metastasis from gastric cancer was revealed, abdominal CT revealed a 1-cm enhancing mass in the right abdominal wall (**Fig. 2A**). The peripancreatic LN, which was the first metastatic site, had not changed and the LN at the inferior aspect of the right lobe of the liver had disappeared. A PET-CT scan revealed ¹⁸F-FDG uptake in a mass in the right abdominal wall (SUV, 3.4) but no further ¹⁸F-FDG uptake (including LNs) at the peripancreatic and inferior aspect of the right lobe of the liver (**Fig. 2B**). The patient underwent surgical resection of the abdominal wall mass, histological examination of which resulted in a diagnosis of moderately differentiated tubular adenocarcinoma (**Fig. 3A**). Immunohistochemical staining showed that the tumor cells were positive for CDX2 (1:100; Leica, Newcastle-upon-Tyne, UK), but negative for cytokeratin 7 (1:400; NeoMarkers, Fremont, CA, USA) and cytokeratin 20 (1:100; Leica; **Fig. 3B-D**), which

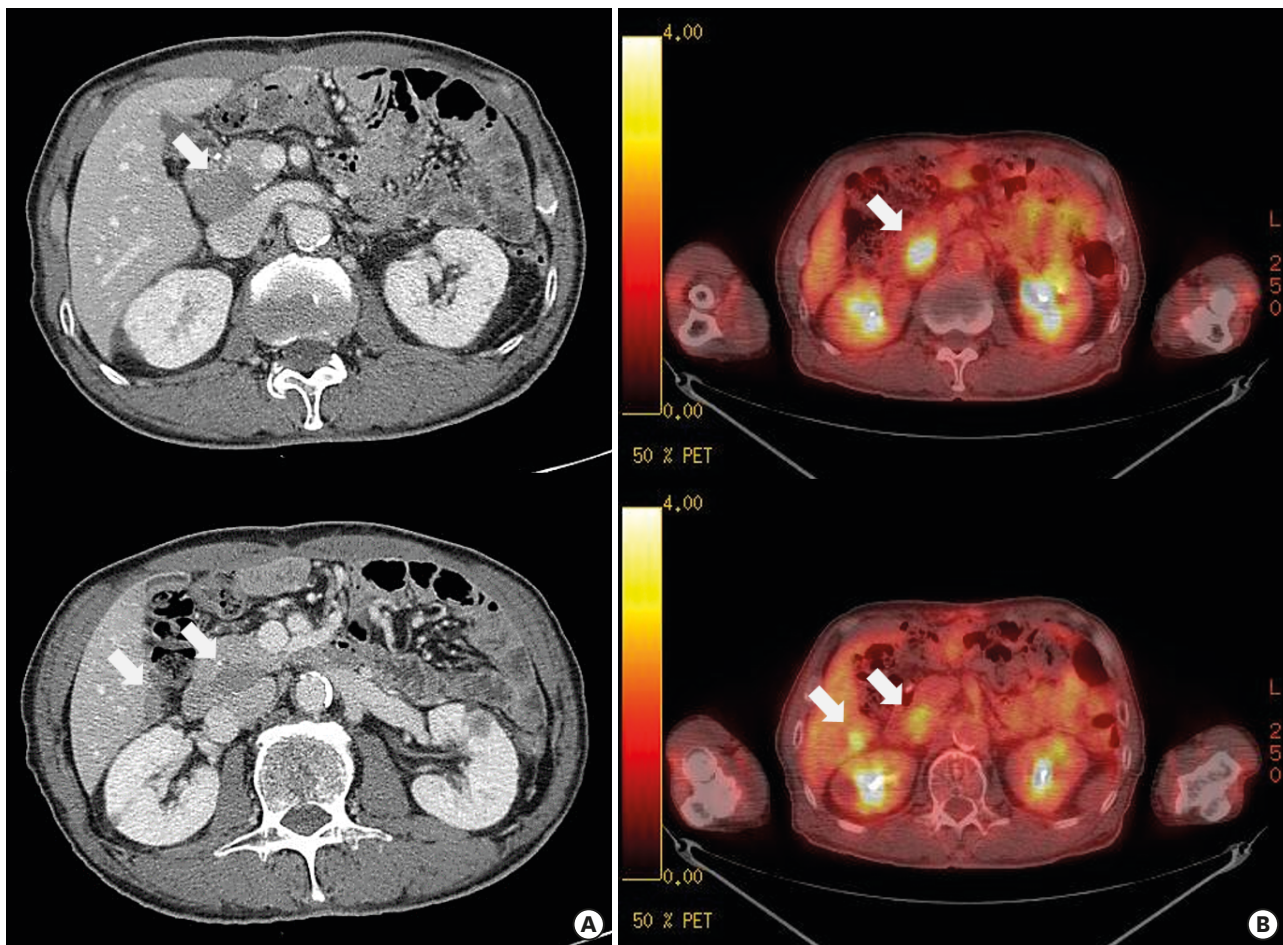


Fig. 1. CT and PET scans at first recurrence to the intra-abdominal LNs. (A) CT of the abdomen revealed well-defined enhancing masses in the peripancreatic area and inferior aspect of the right lobe of the liver. (B) PET revealed ^{18}F -FDG uptake in the peripancreatic area and inferior aspect of the right lobe of the liver (standardized uptake values, 6.1 and 3.3, respectively).

CT = computed tomography; PET = positron emission tomography; LN = lymph node; ^{18}F -FDG = 2-deoxy-2-[fluorine-18]fluoro-D-glucose.

was consistent with results previously obtained from the primary gastric tumor (**Fig. 3E-H**). He was additionally treated with third-line docetaxel chemotherapy for 6 months.

At the last outpatient visit (7.8 years since the initial resection of the primary gastric cancer and 6.2 years since receiving local therapy for the first metastasis), the patient was disease-free and required no further chemotherapy.

DISCUSSION

Although substantial evidence exists to support surgical resection as the optimal treatment for liver or lung metastasis from colorectal cancer [11], data evaluating the role of local therapy for metastatic gastric cancer are limited and controversial. Some reports of patients with gastric cancer and synchronous metastasis demonstrate long-term survival following complete surgical resection of the metastatic lesions and appropriate systemic chemotherapy [3-10]. In addition, local therapy (such as surgical resection, radiofrequency ablation, or hepatic arterial infusion chemotherapy) for the treatment of liver metastasis from primary

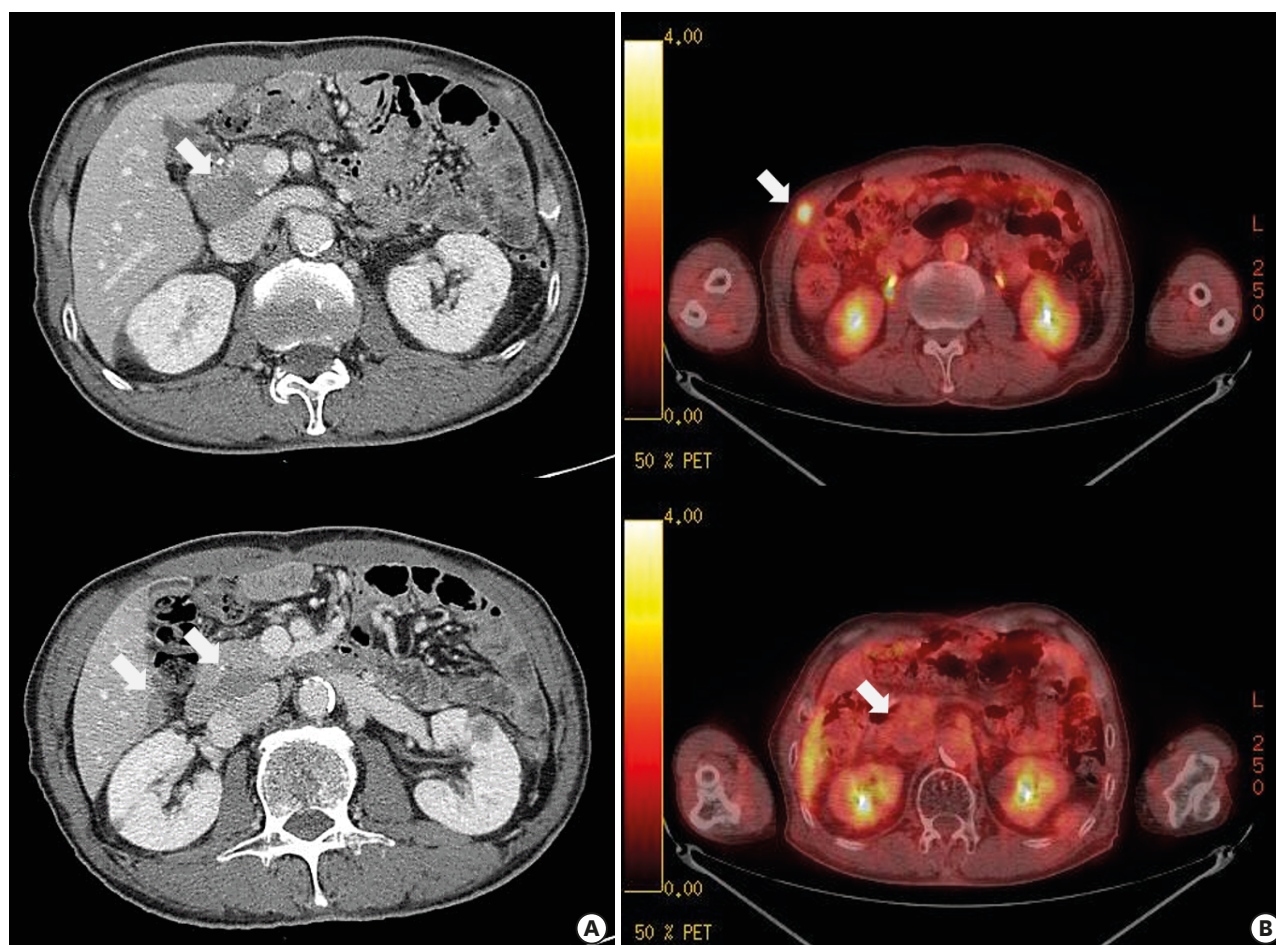


Fig. 2. CT and PET scan at second recurrence to the abdominal wall. (A) CT of the abdomen revealed a 1-cm enhancing mass at the right abdominal wall. The peripancreatic LN, which was the first metastatic site, did not change with the partial response, and the LN at the inferior aspect of the right lobe of the liver had disappeared. (B) PET revealed ¹⁸F-FDG uptake in the mass at the right abdominal wall (standardized uptake value, 3.4) and no further ¹⁸F-FDG uptake including in the LNs at the peripancreatic and inferior aspect of the right lobe of the liver. CT = computed tomography; PET = positron emission tomography; LN = lymph node; ¹⁸F-FDG = 2-deoxy-2-[fluorine-18]fluoro-D-glucose.

gastric cancer has been shown to be potentially curative in carefully selected patients [6-10]. However, metastatic disease is essentially a systemic condition that manifests as hematogenous spread from the primary tumor, and recurrence is frequently observed after local therapy of the initial metastatic lesion.

Several studies of recurrent liver or lung metastasis from colorectal cancer report that repeated metastasectomy is effective, and current international guidelines also discuss the potential benefit of this approach [11-13]. By contrast, reports of repeated local therapy for recurrent metastatic lesions from gastric cancer are still extremely rare, and a review of PubMed yielded only three English reports, which are summarized alongside the current case in **Table 1** [14-16]. In previous case reports on surgical resections of recurrent metastases from gastric cancer, the majority of the cases were lung or adrenal metastasis. Nakahashi et al. [14] reported a case of 7-year survival achieved by repeated resection of pulmonary and adrenal metastases in a patient with α -fetoprotein-producing gastric cancer. Mokuno et al. [15] reported a case of 9-year survival achieved by repeated adrenalectomy of bilateral adrenal metastases from mucinous adenocarcinoma of the stomach. Kojima et al. [16] documented

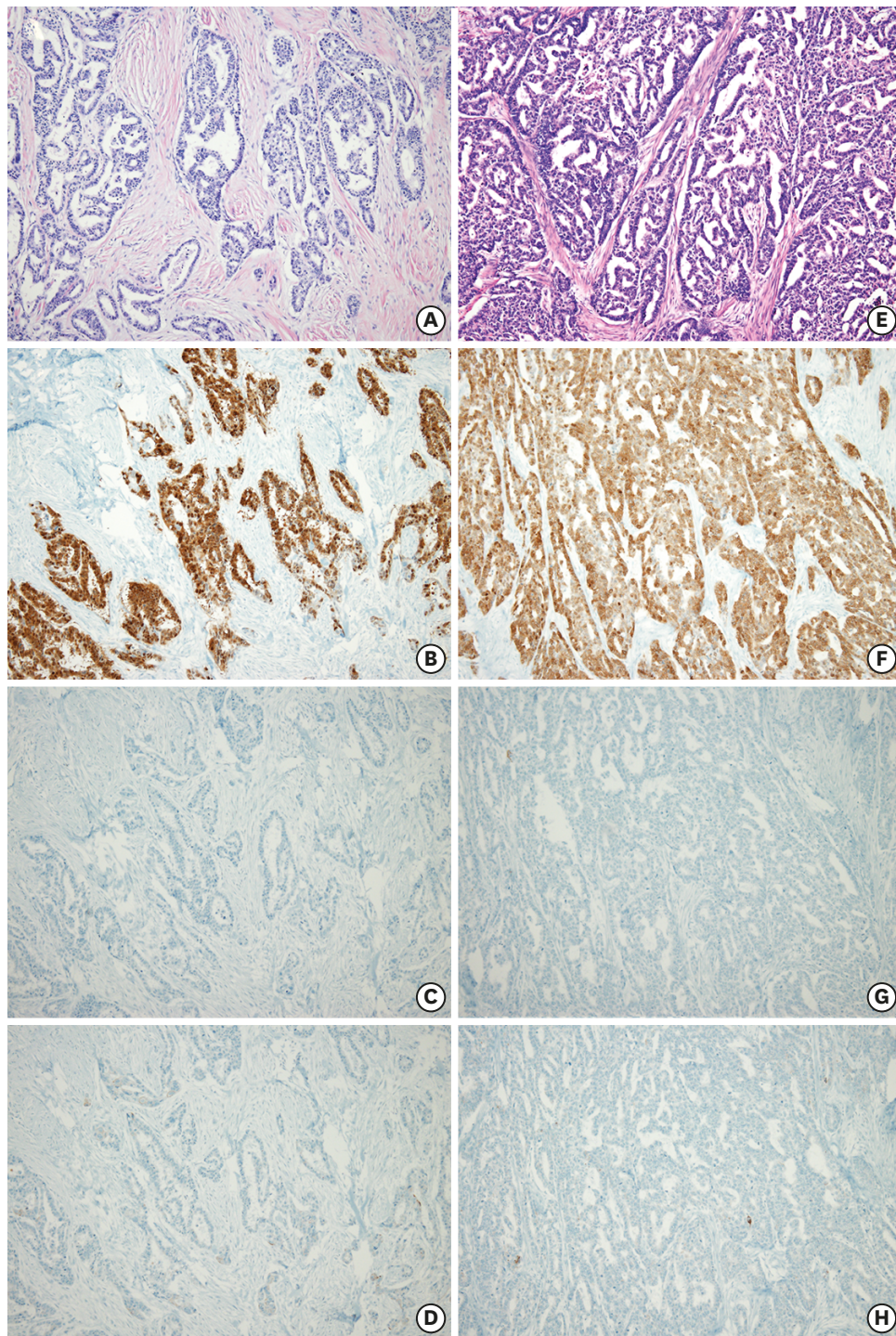


Fig. 3. Pathologic features of the abdominal wall mass (A-D) and the gastric tumor (E-H) obtained by surgical resection. The histologic examination of the resected abdominal wall mass and previously resected gastric tumor revealed moderately differentiated adenocarcinoma (A and E: hematoxylin and eosin, $\times 100$). Immunohistochemistry shows tumor cells in the resected abdominal wall mass positive for CDX-2 ($\times 400$), but negative for cytokeratin 7 ($\times 400$) and cytokeratin 20 ($\times 400$) (B-D) consistent with that obtained previously for the gastric tumor (F-H).

a case of 10-year survival achieved by repeated pulmonary resection for multiple lung metastases from gastric cancer. We report a case of 8-year survival achieved by radiotherapy of the metastatic abdominal LNs and local resection of the abdominal wall metastases

Table 1. Case reports of long-term survival in patients without recurrence after repeated local therapies for recurrent metastases from gastric cancer

Case	Baseline characteristics			First metastasis			Second metastasis				Survival after initial gastrectomy/ after local therapy for first metastasis (yr)	
	Author (yr)	Age/ sex	Primary tumor, location/ histology/ stage	Interval between initial gastrectomy and first metastasis (mon)	Site of metastasis (number)	Local treatment	Systemic chemotherapy (timing/ regimen)	Interval between first and second metastasis (mon)	Site of metastasis (number)	Local treatment		Systemic chemotherapy (timing/ regimen)
1	Nakahashi et al. (2004) [14]	59/ M	U/MD/ pT4aN3	24	Lung (1)	Lobectomy	No	6	Adrenal (1)	Adrenalectomy	No	7.0/5.0
2	Mokuno et al. (2006) [15]	68/ M	L/PD/ pT4bN1	4	Adrenal, Rt, PAN (2)	Adrenalectomy, PAN dissection	Yes (postoperative/ 5FU+MTX)	41	Adrenal, Lt (1)	Adrenalectomy	Yes (preoperative/ 5FU+MTX)	9.2/3.3
3	Kojima et al. (2018) [16]	67/ M	L/MD/ pT1bNO	26	Lung (2)	Wedge resections	Yes (postoperative/ S-1)	26	Lung (1)	Lobectomy	Yes (postoperative/ S-1+cisplatin)	10.2/8.0
4	Kwon et al. (2018) (present study)	65/ M	L/MD/ pT4aN3	6	Distant LNs (2)	Radiotherapy	Yes (preoperative/ XELOX, FOLFIRI)	33	Abdominal wall (1)	Local excision	Yes (postoperative/ docetaxel)	7.8/6.2

U = upper third; L = lower third; MD = moderately differentiated adenocarcinoma; PD = poorly differentiated adenocarcinoma; PAN = para-aortic lymph node; 5FU = 5-fluorouracil; MTX = methotrexate; S-1 = tegafur/gimeracil/oteracil; LN = lymph node; XELOX = capecitabine/oxaliplatin; FOLFIRI = 5-fluorouracil/ leucovorin/irinotecan.

from tubular adenocarcinoma of the stomach. Our case, therefore, differs from the three previously reported cases in terms of metastatic site and the application of radiotherapy as local treatment.

The selection of appropriate patients and treatment modality is key to the success of local therapy for gastric cancer metastasis. Although the application of local therapy for gastric cancer metastasis is increasing, the exact indication has not yet been defined. Recently, several reports have identified favorable prognostic factors, including limited number and size of metastases, long disease-free intervals, absence of peritoneal disease, early pathologic stage or highly differentiated grade of the primary gastric cancer, and excellent tumor regression or a longer duration of response following systemic chemotherapy [6-9]. Based on these reports, repeated local therapy for the treatment of recurrent metastases from gastric cancer should be considered only in carefully selected patients with good prognostic indicators. Regarding the four case reports of long-term survival summarized in **Table 1**, although most of the primary tumors were at an advanced stage, all reported limited metastatic sites, long-disease-free intervals, and the absence of peritoneal disease. In addition to careful patient selection, the choice of local treatment modality is also important. Various factors such as timing of metastasis, metastatic features, possibility of R0 resection, technical limitations of a procedure, and the patient's performance status should be considered when selecting a surgical or nonsurgical approach. In our case, cancer at the first metastatic site (peripancreatic LN) had invaded the pancreatic head and major vessels; as R0 resection was not possible, radiotherapy was performed as the first local therapy.

Furthermore, systemic chemotherapy should be considered before or after local therapy since metastatic disease is essentially a systemic disease with micrometastasis. Of the four cases presented in **Table 1**, chemotherapy was initiated before or after local therapy in three. When considering systemic chemotherapy, we suggest that treatment should be initiated before rather than after local therapy to achieve better disease control and to identify aggressive disease that progresses rapidly and does not respond to chemotherapy in order to avoid futile

local therapy. In our case, gastric cancer with recurrent abdominal LN metastasis showed a good response to second-line FOLFIRI chemotherapy and radiotherapy of the metastatic site could be performed. Subsequently, no recurrence was seen after third-line docetaxel chemotherapy. Recently, the response rate to new chemotherapeutic regimens has improved markedly and the indications for local therapy in patients with gastric cancer metastasis may be expanded in light of these new therapeutic options.

In conclusion, this report describes a case of long-term survival after repeated local therapy and salvage chemotherapy for recurrent metastases from gastric cancer. Our case suggests that even in cases with recurrent metastases from gastric cancer, repeated local therapy offers excellent potential for long-term survival in a carefully selected subset of patients.

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