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Hyperthermia with Chemotherapy for Unresectable Gastric Cancer in a Patient with a Vagus Nerve Stimulator Implant: A Case Report

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Conflict of interest: None declared

Patient: Male, 55-year-old
Final Diagnosis: Gastric cancer
Symptoms: Dermatomal rash • muscle weakness
Medication: —
Clinical Procedure: Chemotherapy • hyperthermia • surgery
Specialty: Gastroenterology and Hepatology
Objective: Unusual setting of medical care

Background: Radiofrequency (RF) hyperthermia is commonly used as an adjunct to established treatment modalities such as chemotherapy and radiotherapy for the management of cancer patients. This case report aims to introduce the use of hyperthermia, in combination with chemotherapy, for the treatment of unresectable gastric cancer in a patient implanted with a vagus nerve stimulator (VNS).

Case Report: A 55-year-old man with dermatomyositis, laryngeal squamous cell carcinoma in situ and double synchronous gastric cancer was found to have unresectable gastric disease during surgery despite neoadjuvant chemotherapy. Postoperatively, he received chemotherapy with RF hyperthermia. The patient had a VNS implant to treat epileptic seizures. VNS failure due to RF hyperthermia was an area of significant concern, and the procedures were completed with a full preparation to manage epileptic seizures in the event of its anticipated occurrence. Twenty-one thermotherapies were performed over 21 weeks. After 3 courses of S-1 chemotherapy (12 weeks) with RF hyperthermia without any adverse events, the regimen was changed to S-1+ CDDP combination chemotherapy (SP) and RF hyperthermia. The patient continued to receive treatment with a decrease in the size of the primary gastric tumors as well as lymph node metastases, without major adverse events, until he died due to disseminated disease.

Conclusions: We report the first case of unresectable gastric cancer with VNS implants in which chemo-hyperthermal therapy was safe and successful. This case report highlights the importance of providing a multidisciplinary treatment with appropriate measures for patients with intractable cancer who have received special treatments for underlying comorbidities.

Keywords: Antineoplastic Combined Chemotherapy Protocols • Dermatomyositis • Hyperthermia, Induced • Radiofrequency Therapy • Stomach Neoplasms • Vagus Nerve Stimulation

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Background

Gastric cancer is commonly diagnosed at an advanced stage, and the prognosis of these patients is extremely poor. For patients with locally advanced and metastatic disease, chemotherapy remains the mainstay of treatment [1-5]. With the advent of immune checkpoint inhibitors and targeted drug therapies, chemotherapy for unresectable advanced gastric cancer has achieved a better response rate [6,7]. However, the overall prognosis continues to remain poor, necessitating progress in multidisciplinary therapeutic strategies and the devising of new alternate treatment methods.

Radiofrequency (RF) hyperthermia kills the tumor cells by RF wave heating, making it a potential new anti-cancer therapeutic option [8-10]. Hyperthermia is commonly used as an adjunct to established therapies (radiation and chemotherapy) to facilitate destruction of tumor cells and cause increased tumor immunogenicity [11,12].

Vagus nerve stimulation therapy is sometimes used as an adjuvant seizure therapy for refractory epilepsy seizures. Because the right vagus nerve innervates the sinoatrial node and its stimulation can cause bradycardia, asystole, and other cardiac adverse effects, the vagus nerve stimulator is usually implanted on the left side [13,14]. There are previous reports stating that RF ablation in patients who have metal electronic device implants, such as a cardiac pacemaker or a vagus nerve stimulator (VNS), can cause failure of the electronic devices or lead to an excessive rise in temperature [15,16]. These reports suggest that RF hyperthermia should be performed with extreme caution in patients with implanted electric devices.

Here, we present the first case of a patient with an VNS implant for intractable seizures, diagnosed with an unresectable gastric cancer and safely treated with hyperthermia combined with chemotherapy, without any major adverse events by thorough preparation. This case report demonstrates the importance of multidisciplinary teamwork to take adequate measures and safely treat patients with intractable cancers having comorbidities requiring special treatments.

Case Report

A 55-year-old man was referred to the Department of Neurology of Narita Memorial Hospital from another hospital, reporting he had been experiencing facial rash and muscle weakness for 2 months. A skin biopsy confirmed the diagnosis of dermatomyositis. The patient had a history of refractory epilepsy for which he had received oral treatment and vagus nerve stimulation. The VNS (AspireSR Model 106; LivaNova USA, Inc., USA) was implanted in the left anterior chest. **Figure 1** outlines the clinical course of this patient after visiting our hospital. As dermatomyositis may be associated with malignancy, the patient was investigated further. Both the tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were within the normal range (CEA <5.0 ng/mL, CA19-9 <37 U/mL). The patient also underwent esophagogastroduodenoscopy (EGD), endoscopic ultrasonography (EUS), and a computed tomography (CT) scan. EGD showed ulcerative lesions in the middle of the gastric corpus and the gastric antrum that were biopsied, and histopathological examination revealed a double synchronous gastric cancer (**Figure 2A, 2B**), morphologically diagnosed as poorly differentiated adenocarcinoma. EUS revealed an irregular, low-echoic area on the posterior wall of the gastric antrum that continued from the head to the body of pancreas, and a mass of enlarged lymph nodes and tumor (**Figure 2C, 2D**). Abdominal CT showed a gastric wall thickness and enlarged lymph nodes along the lesser curvature, common hepatic artery, and para-aortic region (**Figure 3A, 3B**). No distant metastases or ascites were identified. However, based on the EUS and CT findings, it was suggested that the tumor in the middle of the gastric corpus may have invaded the pancreatic tail and that the tumor in the gastric antrum might have invaded the pancreatic head (**Figure 3C, 3D**). In addition,

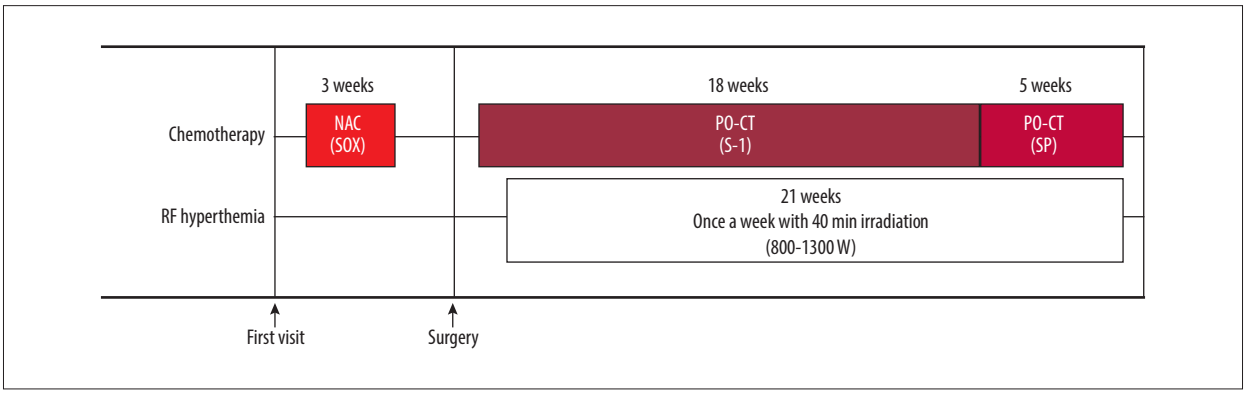

Figure 1. Clinical course of the patient. NAC – neoadjuvant chemotherapy; PO-CT – postoperative chemotherapy; RF – radiofrequency; SOX – S-1+oxaliplatin chemotherapy; SP – S-1+CDDP chemotherapy.

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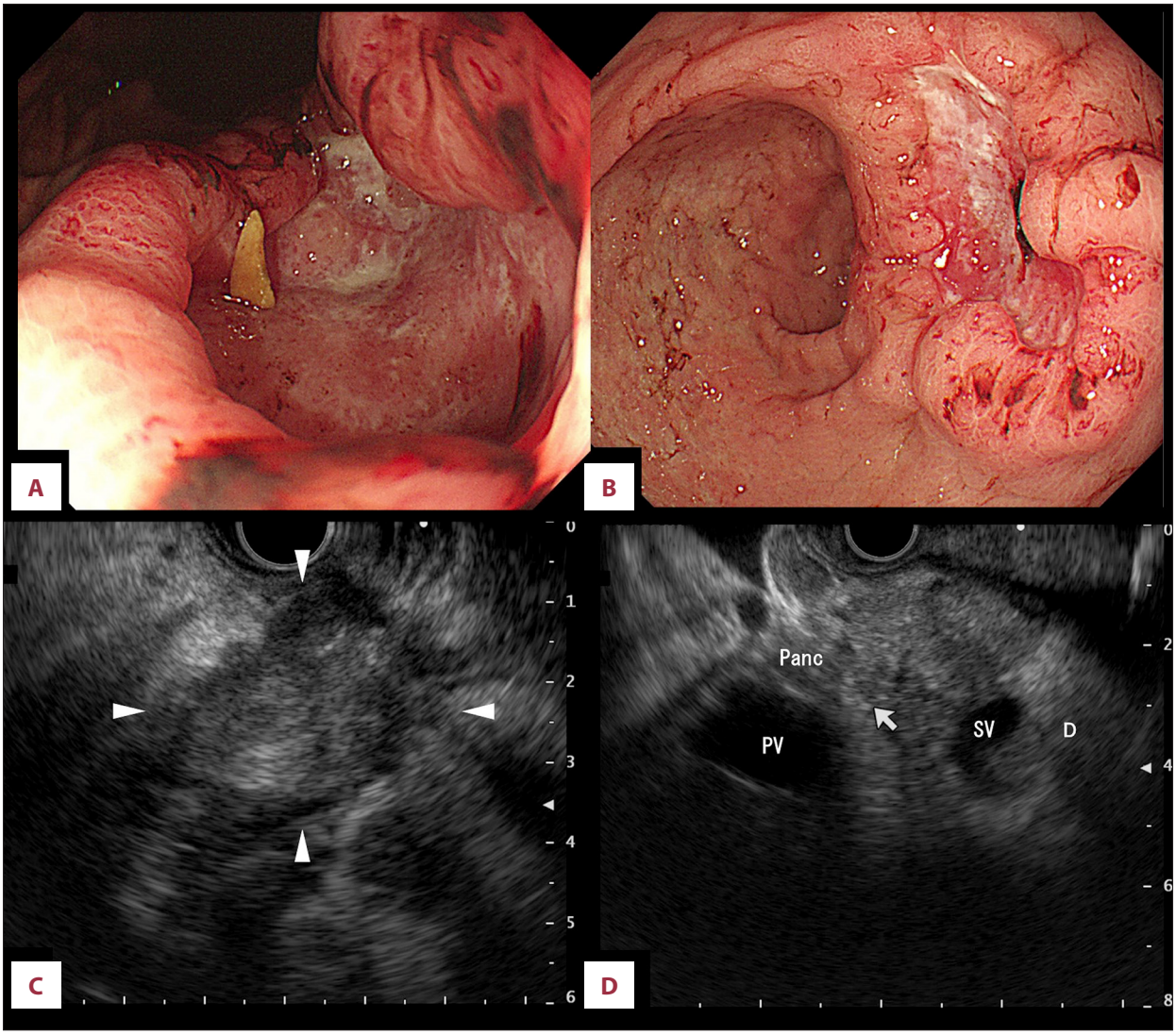

Figure 2. EGD and EUS findings. EGD before chemotherapy showing Borrmann type 3 cancers at the minor curvature of the gastric corpus (**A**) and the posterior wall of the gastric antrum (**B**). EUS showing a tumor mass with regional lymph nodes 27 mm in diameter (white arrowheads) between the posterior wall of the antrum and the head and body of the pancreas (**C**). The tumor in the gastric antrum is seen invading (white arrow) the head and body of the pancreas (**D**). EGD – esophagogastroduodenoscopy; EUS – endoscopic ultrasonography; Panc – pancreatic body; PV – portal vein; SV – splenic vein.

endoscopic examination of the larynx revealed a white plate lesion on the right vocal cord, and a biopsy diagnosed it as squamous cell carcinoma in situ. The patient's primary prognostic factor for survival was determined to be the advanced gastric cancer; thus, he was put on a strict follow-up schedule for the laryngeal in situ cancer.

The gastric carcinoma was clinically staged as cT4bN3aM1 (cStage IVB) according to the 15th edition of the Japanese Classification of Gastric Carcinoma [17]. The fifth edition of the Japanese gastric cancer treatment guidelines suggest surgical resection after neoadjuvant chemotherapy (NAC) in cases of stage IV gastric cancer with limited numbers of para-aortic lymph node metastasis and bulky lymph node metastasis without other non-curative factors [18]. Our patient was informed that he could choose NAC or alternative treatments such as preceding surgery, chemotherapy, and palliative treatment. Then, he chose NAC as the standard treatment, expecting the tumor-reduction effect. Therefore, S-1 (an oral 5-fluorouracil prodrug) and oxaliplatin chemotherapy (SOX) was initiated for the treatment of the unresectable advanced gastric cancer (S-1, 100 mg/body/day for 3 weeks; oxaliplatin, intravenous infusion of 130 mg/m^2 day 1) as NAC for conversion surgery. However, NAC was abandoned at the end of

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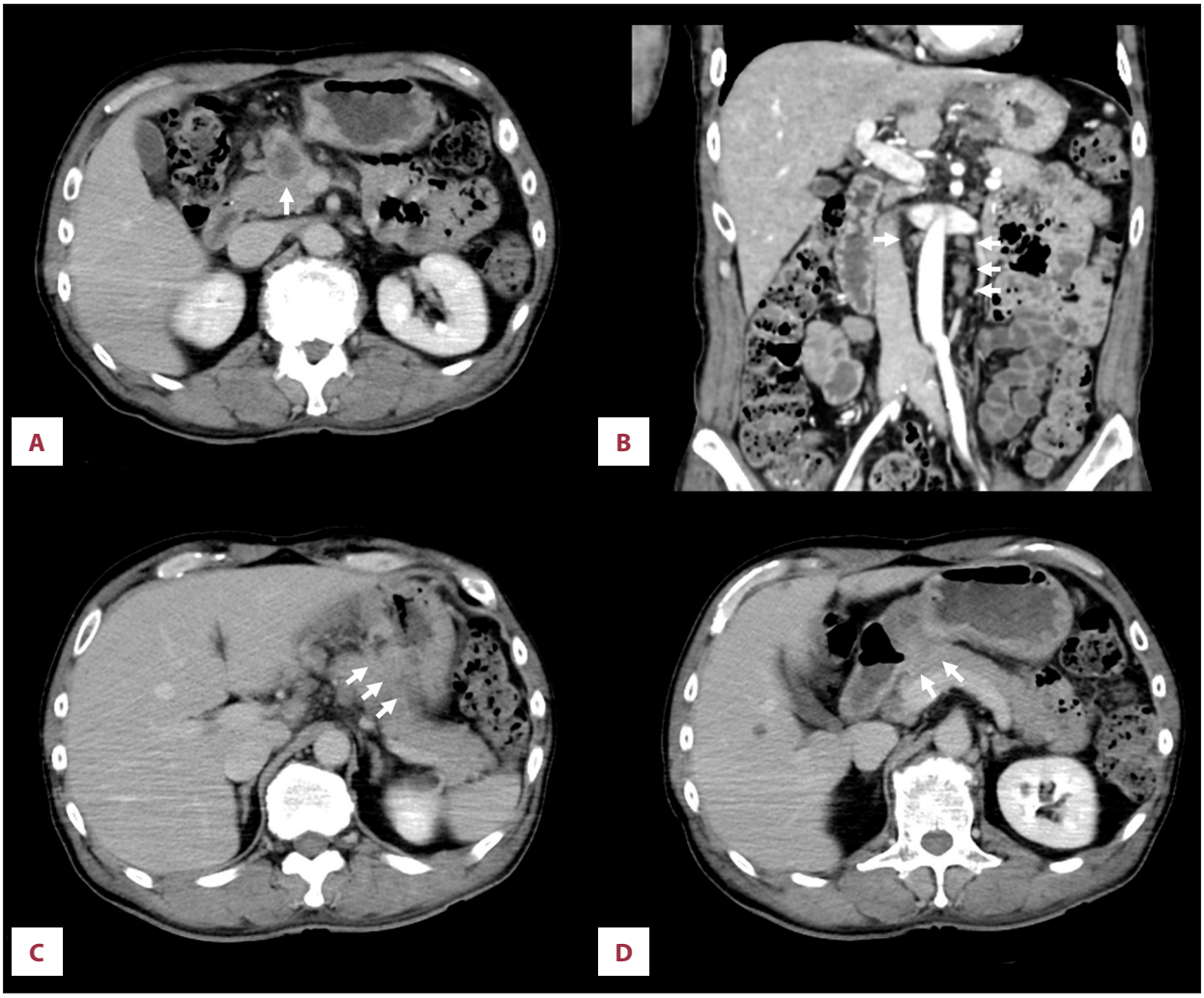

Figure 3. Enhanced CT images before chemotherapy. Abdominal CT before chemotherapy showing swollen regional lymph nodes (white arrow) and para-aortic lymph nodes (white arrow) on enhanced imaging (**A, B**). CT scans demonstrating the tumor in the middle of the gastric corpus invading (white arrows) the tail of the pancreas (**C**), and that the tumor in the gastric antrum invading (white arrows) the head and body of the pancreas (**D**). CT, computed tomography.

1 course due to the adverse events of appetite loss, further weight loss, and progression of anemia. A follow-up CT scan after the single course of SOX therapy revealed smaller regional lymph nodes (**Figure 4**); thus, the patient was considered for total gastrectomy.

On laparotomy examination, there was no remarkable peritoneal dissemination, and peritoneal lavage cytology showed no cancer cells in the abdominal cavity. However, the status of pancreatic invasion, as diagnosed before the operation, remained unchanged (**Figure 5**). Considering the patient's general condition and comorbidities, radical resection was abandoned and a palliative gastrojejunal bypass was performed. The postoperative course was uneventful, and he was discharged on the 9th postoperative day. While awaiting recovery of the patient's general condition, postoperative oral S-1, twice daily, at a dose of 100 mg/body/day, was administered for 28 consecutive days followed by a 14-day rest period. When chemotherapy was started, the patient expressed a strong desire to receive RF hyperthermia in combination with the chemotherapy. Because he had an implanted VNS for the management of epileptic seizures, we were concerned about device failure due to RF hyperthermia. Therefore, we provided the patient with sufficient information about expected complications and adverse events of RF hyperthermia and obtained an informed consent for the same. The VNS was suspended during the hyperthermia treatment, which was performed with full preparation to manage epileptic seizures in the event of its anticipated occurrence. RF hyperthermia was performed once a week, over 21 weeks, with a 40-min irradiation with an 8-MHz RF capacitive heating device (Thermotron RF-8; Yamamoto Vinita Co., Ltd., Japan). As there were no adverse events such as pain

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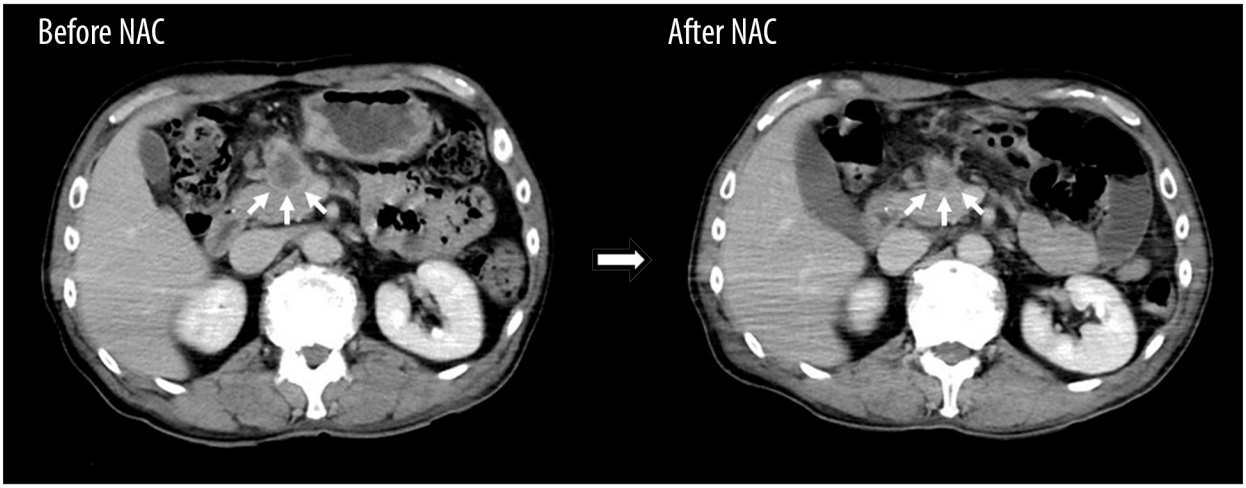

Figure 4. Change in lymph node size before and after NAC on CT images. After NAC, the mass consisting of tumor and regional lymph nodes between the posterior wall of the gastric antrum and the head and body of the pancreas is smaller than it was prior to chemotherapy (white arrows). CT – computed tomography; NAC – neoadjuvant chemotherapy.

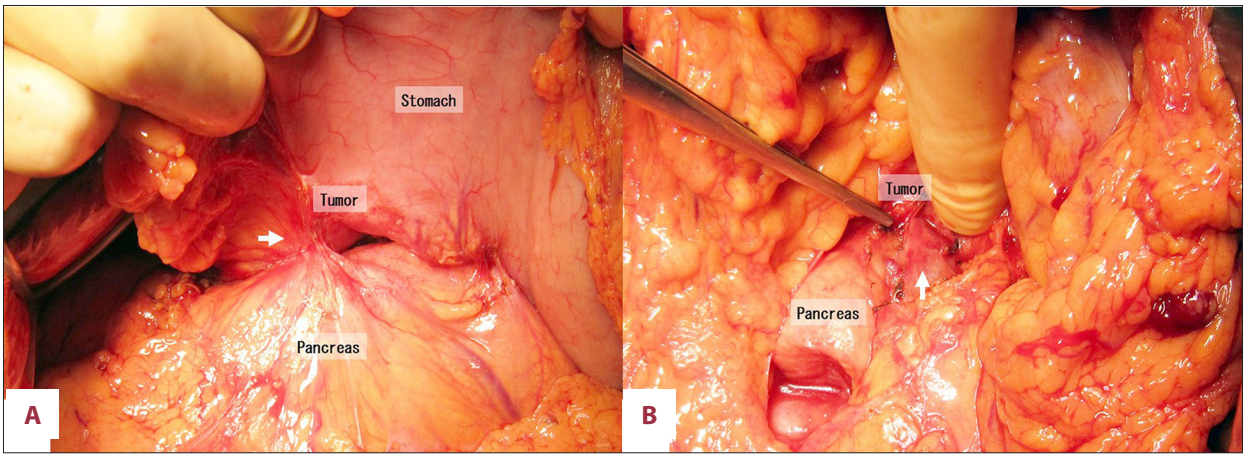

Figure 5. Intraoperative findings. The tumor in the gastric antrum invaded (white arrow) the capsule of pancreatic head (**A**). When the pancreatic capsule was peeled off, invasion of gastric cancer into the pancreatic parenchyma (white arrow) was observed (**B**).

and heat due to RF hyperthermia, the patient continued to receive hyperthermia at RF output at 1400-1500 W each time. After 3 courses of S-1 chemotherapy combined with RF hyperthermia without any adverse events, the treatment regimen was changed to S-1+ CDDP combination chemotherapy (SP; S-1, 100 mg/body/day for 21 consecutive days followed by a 14-day rest; CDDP, intravenous infusion of 60 mg/m^2 day 8) for stronger antitumor efficacy. Five months after treatment, the follow-up EGD showed reduction in size of the double gastric cancers, and CT confirmed the reduction in the size of the lymph node metastases (**Figure 6A-6D**). However, after receiving 1 course of SP chemotherapy, the patients' general condition rapidly deteriorated. CT images revealed ascites and an increase in the size of the primary tumor. The patient was diagnosed with peritoneal dissemination (**Figure 7A, 7B**) and he unfortunately died due to his illness 8 months after beginning treatment at our hospital.

Written consent was obtained from the patient for publication of this study according to guidelines of the Ethics Committee of Narita Memorial Hospital (approval number, R1-22-01).

Discussion

Hyperthermia is a treatment that raises the temperature either locally or systemically [19]. In cancer patients it can weaken or kill tumor cells without affecting normal cells. Cancerous cells have difficulty in dissipating heat due to disorganized vascular structures. Even if the cancerous cells do not die completely, hyperthermia can cause cancerous cells to become more sensitive to radiotherapy or chemotherapy, allowing dose reduction. Recently, several reports have documented the usefulness of hyperthermia; especially comparison of anti-cancer therapeutic effects with chemotherapy and radiotherapy,

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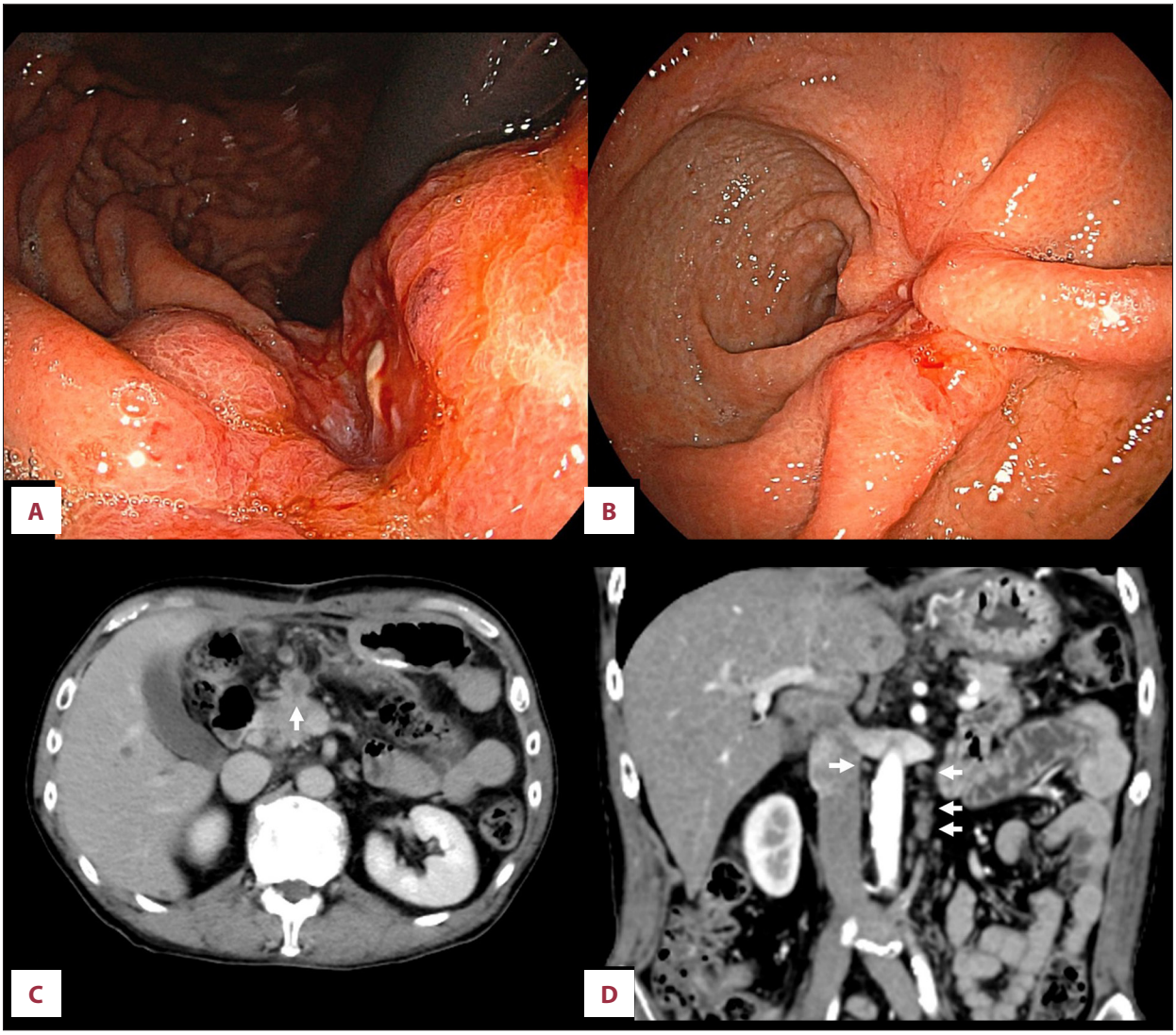

Figure 6. Follow-up EGD findings and CT images. EGD reveals reduction in size of the tumor at the minor curvature of the gastric corpus (**A**) and the posterior wall of the gastric antrum (**B**). CT scan shows reduction in size of the tumor mass and regional lymph nodes (white arrows) between the posterior wall of the gastric antrum and the head and body of the pancreas (**C**). The size of para-aortic lymph node metastases (white arrows) is reduced (**D**). CT – computed tomography; EGD – esophagogastroduodenoscopy.

and the effects of their combination treatments have been reported [20-22].

Hyperthermia is more commonly used as an adjunct to chemotherapy, radiotherapy, or chemoradiotherapy, and more recently to gene therapy and immunotherapy, rather than being used as a stand-alone primary cancer treatment modality. In the field of oncology, many studies on hyperthermia have been published [23-25]. Recently, Shoji et al demonstrated that standardized RF hyperthermia could be established as a potential new treatment for rectal cancer in combination with chemoradiotherapy [8]. We have also reported the efficacy of hyperthermia combined with chemotherapy for recurrent breast cancer [26]. Our patient was also treated with 8-MHz RF hyperthermia in combination with chemotherapy, and he did not report any major adverse events.

However, RF hyperthermia in patients with metal electronic device implants, such as a cardiac pacemaker and VNS, may cause failure of the electronic devices or an excessive rise in temperature. Therefore, the procedure must be planned in consultation with the patient's physician in order to turn off the active mode of the electric devices during the procedure. After the RF hyperthermia procedure, these devices must be re-programmed as necessary. We consulted the relevant epilepsy specialists, clinical radiologists, clinical engineers, VNS

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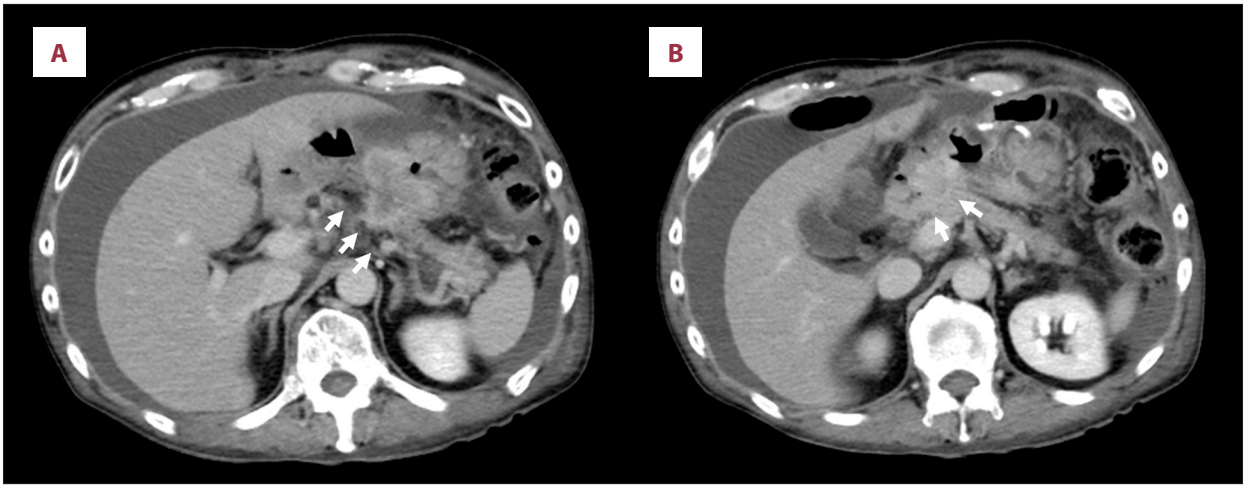

Figure 7. CT images 8 months after the start of treatment. CT scan showing increased primary tumors in the middle of the gastric corpus invading (white arrows) the tail of the pancreas (**A**), and the tumor in the gastric antrum invading (white arrows) the head and body of the pancreas (**B**). CT – computed tomography.

distributors, and hyperthermia equipment manufacturers on the indication of RF hyperthermia for this patient, and the patient was provided detailed information on the risks of treatment prior to obtaining his consent for the treatment. The patient received RF hyperthermia, owing to his request for the same, with sufficient precautionary measures against complications. With adequate preparation, such as immediate availability of antiepileptic drugs in the event of an epileptic seizure or a temporary suspension of the VNS by a clinical engineer, the patient received hyperthermia without any adverse events. To the best of our knowledge, there are no previously published reports in PubMed on the use of hyperthermia in combination with chemotherapy for cancer patients with VNS implants. We herein report the first case of unresectable gastric cancer in a patient with an VNS implant who was successfully treated with chemo-hyperthermal therapy without major adverse events.

Autoimmunity has been reported as an alternative etiology of gastric inflammation, the initiating event in the gastric carcinogenic cascade, and may be associated with gastric carcinogenesis through different potential pathways [27,28]. Dermatomyositis has been reported to increase the risk of malignancy. About 9-30% of patients with dermatomyositis have malignancies, which is 2.4-5 times higher than that seen in the normal population [29,30]. The fact that our patient had synchronous gastric primaries along with in situ squamous cell carcinoma of the larynx also suggests that dermatomyositis is associated with a higher risk of malignancy. Regarding dermatomyositis in association with gastric cancer, it has been previously reported that dermatomyositis improved after tumor resection. In our case, tumor reduction surgery was initially considered but later abandoned due to advanced tumor invasion into the head and tail of the pancreas. It was feared that a total gastrectomy along with total pancreatectomy as a tumor debulking procedure in this case would cause significant difficulties in introducing postoperative chemotherapy due to serious surgical damage and rapid progression of cancerous peritonitis due to exposure of the tumor. Hence, the patient did not undergo resection and was given chemotherapy in combination with hyperthermia for unresectable gastric cancer.

Although the advanced gastric cancer in this case was not cured, EGD showed reduction in the size of the gastric tumors and CT revealed reduction in the size of lymph node metastases in a follow-up examination during treatment. Unfortunately, the patient died of peritoneal dissemination 8 months after treatment was started at our hospital. He, however, remained calm throughout his course of treatment and was able to receive RF hyperthermia with chemotherapy on an outpatient basis until the peritoneal dissemination was confirmed. It has been reported that the median overall survival (OS) is about 6-14 months and the median progression-free survival (PFS) is about 4-6 months in patients with unresectable gastric cancer receiving chemotherapy with a good performance status (an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2) [1-5]. In this case, hyperthermia combined with chemotherapy was unable to prolong OS, but it did prolong PFS of this patient and maintain his quality of life, despite a poor ECOG PS of 3.

This is the first reported case of a patient with VNS implant for intractable seizures, diagnosed with an unresectable gastric cancer and treated with hyperthermia in combination with chemotherapy, without any major adverse events. Of course, the effectiveness of this treatment may be limited to specific cases; therefore, more cases need to be accumulated to examine the usefulness of this treatment in detail.

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Conclusions

This case report indicates the importance of providing a multidisciplinary treatment with appropriate measures for intractable cancer patients who have received special treatments for underlying comorbidities. Of course, further clinical trials are certainly needed to establish further multidisciplinary treatment. Adequate and safe palliative therapies go a long way in maintaining the quality of life even though treatment with curative intent is not possible in these patients.

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Department and Institution Where Work Was Done

The Department of Surgery, Narita Memorial Hospital, the Department of Medical Technique, Narita Memorial Hospital, and the Department of Proton, Narita Memorial Proton Center, Toyohashi, Aichi, Japan.

Conflicts of Interest

None declared.

Declaration of Figure Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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