



Successful laparoscopic conversion surgery for gastric cancer with para-aortic lymph node metastasis after third-line chemotherapy: a case report

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Received: 25 June 2021 / Accepted: 9 October 2021 / Published online: 13 October 2021
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Abstract

We herein reported a case of advanced gastric cancer (GC) with para-aortic lymph node (PALN) metastases who successfully achieved downstaging following systemic chemotherapy and underwent curative laparoscopic conversion surgery. A 74-year-old male patient diagnosed with advanced GC and PALN metastases [cT4N3M1(LYM), stage IVA] was administered chemotherapy and immunotherapy for 28 months. After 27 courses of nivolumab as third-line chemotherapy, PALN enlargement was resolved, for which conversion surgery was planned. Subsequently, laparoscopic distal D2 gastrectomy with sampling para-aortic lymphadenectomy was performed, after which a pathological diagnosis of type V moderately differentiated tubular adenocarcinoma with mucinous adenocarcinoma, stage ypT3 (SS), ly1c, and v0, was established. The pathological proximal and distal tumor margins were negative. One lymph node metastasis was observed (No. 6; 1/25). The sampled lymph nodes were negative (No. 16a1: 0/2). The therapeutic effect was categorized as Grade 1a. The postoperative course was uneventful, with the patient receiving nivolumab to control for potential PALN metastases. Postoperatively, no recurrence was observed over 11 months. Laparoscopic conversion gastrectomy was successfully performed in a patient with advanced GC that was originally unresectable, suggesting that minimally invasive surgery may be a good option for originally unresectable advanced GC that becomes resectable.

Keywords Gastric cancer · Conversion surgery · Laparoscopic surgery · Immune checkpoint inhibitor

Introduction

Gastric cancer (GC) is the second most common cause of cancer death worldwide [1]. As the world confronts the coronavirus disease 2019 (COVID-19) pandemic, reports regarding the deprioritization, delay, and discontinuation of cancer have emerged [2]. Moreover, the diagnosis of new patients with GC has also decreased, indicating that the decrease in the number of gastrointestinal endoscopies has certainly affected the detection and progression of GC [3].

These circumstances would facilitate a future in which more patients present with advanced GC than ever before, subsequently requiring multimodal cancer treatments.

Conversion therapy is defined as a surgical treatment aimed at R0 resection after chemotherapy for tumors that, for technical and/or oncological reasons, were originally unresectable [4]. Despite the availability of standardized criteria for unresectable and metastatic cancers, assessment of resectability after chemotherapy and timing of surgery have yet to be standardized. Studies have clearly shown that R0 surgery after induction chemotherapy with partial or complete response appears to provide better survival outcomes compared to chemotherapy alone [5–7]. The results of the ATTRACTION-2 study showed that nivolumab as third- or later-line chemotherapy prolongs overall survival in patients with advanced GC [8, 9]. However, the clinical indication and prognostic significance of conversion therapy remain unclear in responders to nivolumab.

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Minimally invasive surgery (MIS), such as laparoscopic and robotic gastrectomy, has been widely considered the optimal approach for early GC [10–12]. Recent evidence has suggested that patients with advanced GC can benefit from MIS, which showed postoperative complications and long-term outcomes comparable to those for conventional open surgery [13–15]. MIS may also reduce deaths from other diseases, such as pneumonia [16], and may be indicated for elderly patients with advanced GC.

We herein presented a case of laparoscopic conversion surgery for GC with multiple para-aortic lymph node (PALN) metastases who received nivolumab as third-line chemotherapy.

Case report

A 74-year-old male with abdominal distension was admitted to our department with advanced GC. Preoperative esophagogastroduodenoscopy revealed a circumferential type 3 tumor extending from the middle to lower portions of the gastric body (Fig. 1a). Biopsy revealed moderately to poorly differentiated adenocarcinoma (Fig. 1b, c) with positive human epidermal growth factor receptor type 2 (HER2) upon immunohistochemical staining. Subsequent

preoperative computed tomography (CT) revealed gastric wall thickening at the primary tumor site without surrounding organs invasion (Fig. 2a) and enlarged regional and PALNs (No. 16b1) (Fig. 2b); the clinical stage was cT4aN2M1(LYM) [17]. The patient received capecitabine, cisplatin, and trastuzumab (XPH) as first-line chemotherapy (XPH at 8 mg/kg on day 1 for the first cycle and then 6 mg/kg for subsequent cycles, oral capecitabine at 3000 mg/m²/day on days 1–14, and cisplatin at 80 mg/m² on day 1, every 3 weeks). After three cycles, CT revealed regression of the primary tumor and regional and PALNs. After ten cycles of XPH, the primary tumor and another PALNs (No. 16a1) had increased in size. After five cycles of paclitaxel plus ramucirumab (paclitaxel at 80 mg/m² and ramucirumab at 8 mg/kg) as second-line chemotherapy, the primary tumor still remained (Fig. 2d), whereas PALNs (No. 16a1) had increased in size (Fig. 2e, f). Therefore, third-line chemotherapy with nivolumab at 240 mg/body was initiated. After six cycles of nivolumab, a notable reduction in the size of PALNs (No. 16b1) was observed with mild reduction of the primary tumor site.

Given the absence of immune-related adverse effects, nivolumab was continued for 27 courses, with subsequent endoscopy and follow-up CT revealing no changes in the primary tumor (Fig. 1d, 2g). Biopsy revealed moderately to

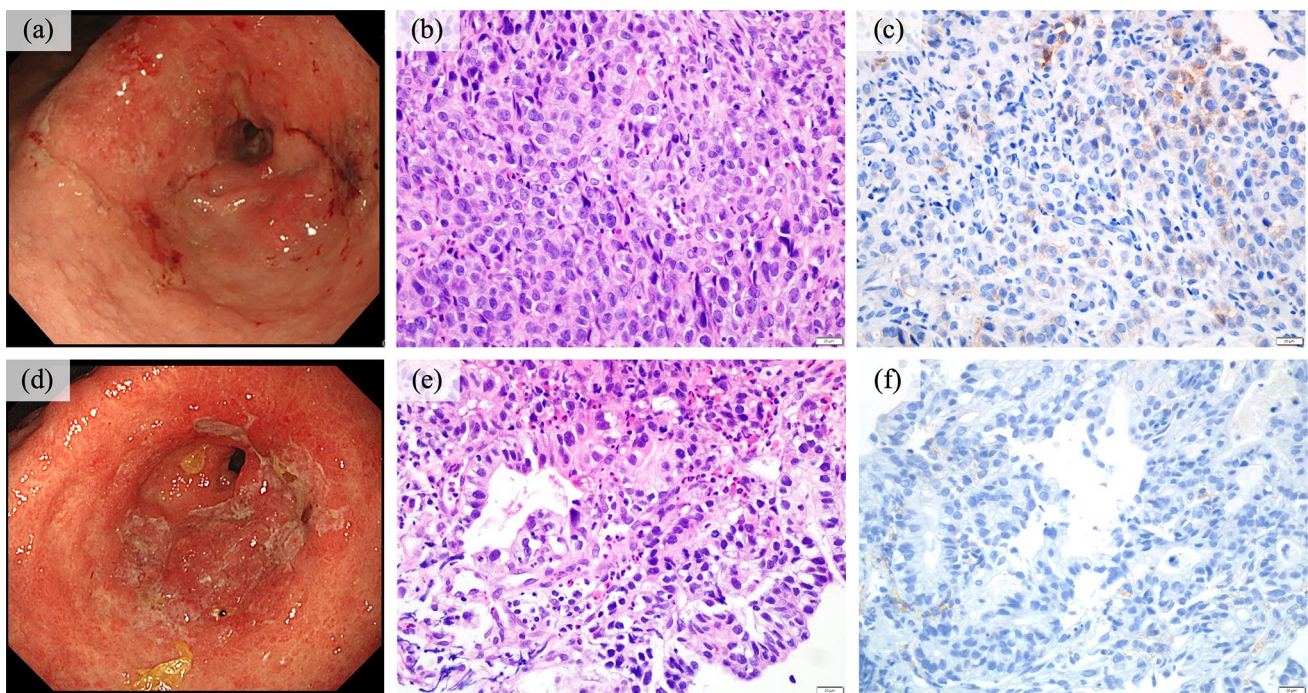


Fig. 1 Endoscopic and pathological findings. Upper panel: upon initial visit. Type 3 advanced gastric cancer was identified occupying the entire circumference of the lower third region of the stomach (a). Pathological examination revealed a moderately to poorly differentiated tubular adenocarcinoma (b) and PD-L1(22C3) positivity

(c). Lower panel: During the follow-up examination after third-line chemotherapy. The primary lesion was mildly reduced but stenotic (d). Pathological examination indicated adenocarcinoma (e), although negative for PD-L1(22C3) (f)

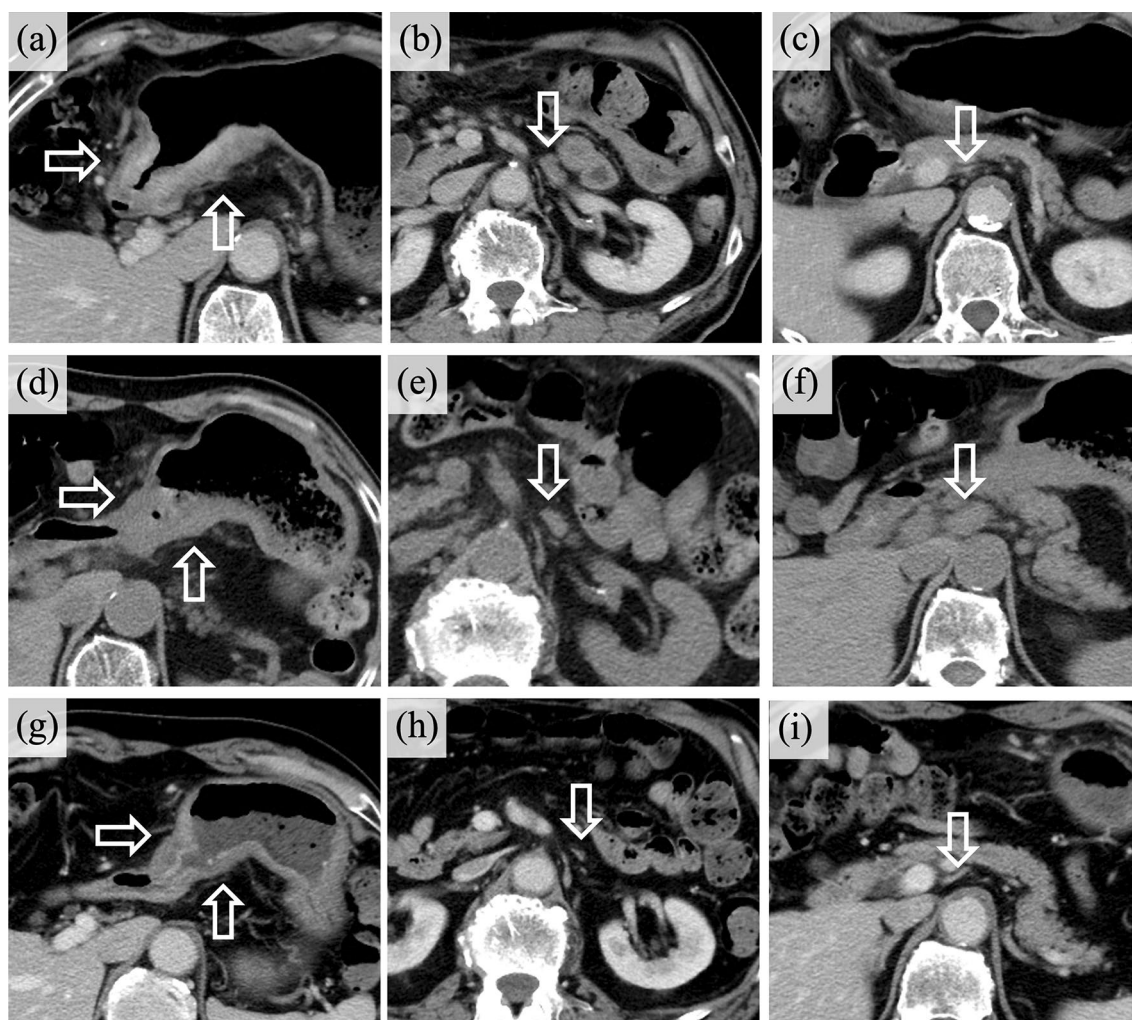


Fig. 2 Computed tomography findings. Upper panel: first computed tomography (CT) image showing gastric wall thickening at the tumor site (white arrows) (a). Para-aortic lymph nodes (PALN) were enlarged (16b1, white arrow) (b). Initially, no enlarged PALNs were observed in 16a1 (white arrow) (c). Middle panel: CT images before nivolumab therapy showing decreased gastric wall thickness in

the primary tumor site (white arrows) (d). Although a PALN (16b1) had decreased in size (white arrow) (e), another PALN (16a1) was enlarged (white arrow) (f). Lower panel: CT images after nivolumab therapy showing no changes in gastric wall thickness at the primary lesion (white arrows) (g). The CT image showed complete response by PALN (white arrow) (h, i)

poorly differentiated adenocarcinoma (Fig. 1e, f). Follow-up CT revealed a decrease in the size of the regional and PALNs (Fig. 2h, i), whereas fluorodeoxyglucose positron emission tomography showed a negative response in PALNs; the clinical stage was ycT3N2M0. Considering the aforementioned findings, we decided to perform laparoscopic gastrectomy given the prospect of radical resection and the onset of stenosis symptoms caused by the primary lesion. Throughout the surgery, we found no intraperitoneal nodules indicating metastasis, whereas cytology results came back negative. Moreover, given that the frozen sections were negative for PALN, laparoscopic D2 distal gastrectomy was performed. The total operative time was 5 h and 18 min, with a total blood loss of 80 mL, forgoing the need for transfusions. Postoperative delirium was observed the day after

the surgery, with the patient needing a few days to wean. Finally, he was allowed to leave the hospital on the 12th day after the surgery.

The pathological findings of the postoperative excised specimens were as follows. Macroscopically, the tumor measured 90 × 65 mm and was classified as type 5, with a scar-like appearance at the center of the tumor. Histological findings suggested moderately to poorly differentiated tubular adenocarcinoma with focally mucinous adenocarcinoma component, stage ypT3 (SS), Ly1c, and V0 (Fig. 3). The therapeutic effect was categorized as Grade 1a. HER2 immunohistochemical staining, which was positive before chemotherapy, returned negative. The pathological proximal and distal margins were free from carcinoma cells. Although seven metastatic lymph nodes were observed,

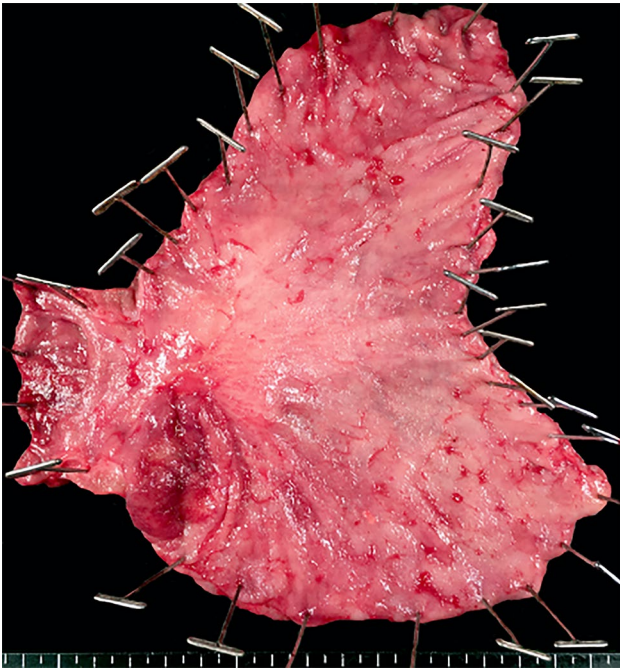


Fig. 3 Macroscopic findings of the resected stomach. Mucosal side of the stomach. The tumor classified as type 5 and occupied the entire circumference of the lower third region of the stomach

viable cells were found in only one metastatic lymph node (No. 6: 1/25). Moreover, one of the two sampled lymph

nodes showed metastasis but no viable cells (No. 16a1: 0/2). Immunohistochemical staining for CD4, CD8, CD68, and CD163 was then performed at three sites of the resected specimen: primary GC lesion (Fig. 4a, lymph node No. 6 with viable tumor cells (Fig. 4b), and lymph node No. 16a1 without viable tumor cells (Fig. 4c). In the primary lesion and metastatic residual lymph node, the panel showed negative staining and low macrophage density. On the other hand, the panel showed positive staining for CD8-dominant lymphocyte profile and high CD163/CD68 positive macrophage density in the lymph nodes that seemed to have become negative.

Currently, the patient is receiving nivolumab to control potential PALN metastases and has survived for 41 months after first-line chemotherapy, with no signs of disease recurrence 14 months after surgery.

Discussion

Generally, GC with non-curative factors carries a poor prognosis, with a median overall survival of approximately 13–16 months, even with standard chemotherapy [18–20]. The REGATTA trials showed that additional gastrectomy over chemotherapy alone provided no survival benefits in patients with non-curable advanced GC [21]. On the other hand, studies on unresectable advanced GC have shown that R0 resection after induction chemotherapy with partial or

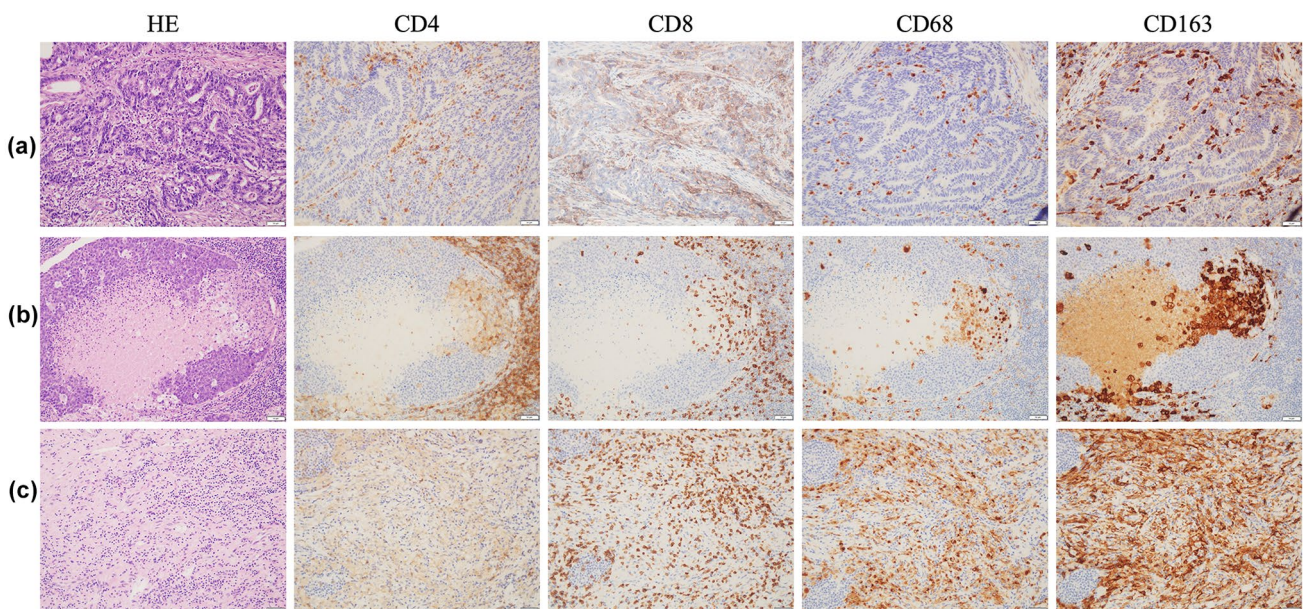


Fig. 4 Immunohistochemistry results. Upper panel: (a) Primary gastric cancer lesion. No lymphocyte infiltration was noted. Middle panel: (b) Lymph node with viable tumor cells (No. 6). The center of the lymph node was necrotic, and CD8-positive lymphocytes infil-

trated from the failed area. Lower panel: (c) Lymph node showing a complete response (No. 16a1). Mainly CD8-positive lymphocytes infiltrated the stroma site, with some CD68-positive lymphocytes also being present

complete response appears to provide better survival outcomes compared to chemotherapy alone [5–7]. Therefore, conversion gastrectomy has become an attractive option for stage IV GC with controlled distant metastasis. In the current case, the PALN metastasis showed a complete response to chemotherapy. Considering the findings of a previous study, which showed that prophylactic D2 dissection with extended lymphadenectomy did not improve the prognosis of curable GC [22], we opted to perform laparoscopic D2 distal gastrectomy with sampling para-aortic lymphadenectomy. Nonetheless, para-aortic lymphadenectomy during conversion surgery has remained controversial [23, 24] and requires additional investigations.

Laparoscopic gastrectomy, which is considered more effective than conventional open surgery, has been more commonly used for early GC given the recent technical and instrumental advancements [10–12]. Notably, a randomized phase II study (JLSSG0901) found that laparoscopic distal gastrectomy was technically safe for locally advanced GC [13], while another large phase III trial (KLASS-02-RCT) showed fewer complications, less pain, and faster recovery with laparoscopic distal gastrectomy [14]. Furthermore, a large phase III randomized clinical trial (CLASS-01) showed similar long-term outcomes [15]. Recent evidence has shown that MIS can be safely performed as conversion surgery following chemotherapy for stage IV GC [25], indicating the safety of MIS for conversion surgery, especially when no additional resection is planned.

In our case, the therapeutic effect had been categorized as Grade 1a in the primary lesion. However, the clinical course showed downstaging, that is, a reduction in the primary tumor volume and a complete response by the PALNs. Moreover, the Programmed Death Ligand 1 Immunohistochemistry Assay, which evaluates the effect of nivolumab, revealed a discrepancy between residual metastatic lymph nodes and negative lymph nodes—a result that seems to be exciting. The reasons for this are discussed below. Accordingly, pathological examination revealed that CD68-positive macrophages and CD8 positive lymphocytes and macrophages infiltrated the lymph nodes that showed a complete response (Fig. 4C). On the other hand, the same phenomenon did not occur at the residual tumor area (Fig. 4A,B). The CD68-positive macrophages were also positive for CD163 (M2-like macrophage), a marker for immunosuppressive tumor-associated macrophages (TAMs). Considering the availability of similar reports in the past [26], the excellent therapeutic effects observed in our case can be attributed to the following scenarios: (1) TAMs suppressed CD8-positive lymphocytes, (2) nivolumab inhibited the negative interaction of M2 macrophages, and (3) CD8-positive lymphocytes were released and attacked the tumor. However, given that this is a case report, future case series are needed to validate such mechanisms.

There are still little data on postoperative adjuvant chemotherapy for stage IV GC that has reached conversion surgery. Despite a generally worse clinical status in stage IV GC, some previous study indicated that postoperative chemotherapy does have a survival benefit for GC patients with surgical resection that leaved no macroscopically visible disease [27, 28]. The magnitude of the additive effect of postoperative adjuvant chemotherapy on prognosis is unknown, but the improvement in cure rate is evident. In this case, we performed a pick-up dissection of PALN in addition to the standard lymph nodes dissection. Also, there was a possibility that cancer was left in the remaining PALN. Therefore, we aimed to achieve complete cancer control by adding postoperative adjuvant chemotherapy. In the choice of drug, we chose nivolumab because of its high efficacy before surgery.

In conclusion, we herein reported a case of successful laparoscopic conversion surgery for GC with PALN metastases after third-line chemotherapy with nivolumab. Our results suggest that conversion surgery might be clinically beneficial for preventing tumor progression among responders to immune checkpoint inhibitors, particularly nivolumab therapy.

Acknowledgements There is no further acknowledgement that need to be made either to persons or institutions.

Funding The authors have not been funded for this work.

Declarations

Conflict of interest The authors have no competing interests to declare.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication The patient provided written informed consent for the publication of this manuscript and images.

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