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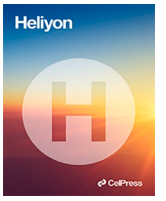

Case report

Case report: Metastatic gastric squamous cell carcinoma with long duration of complete response via three-staged radical concurrent chemoradiotherapy

Rui Zang [1], Linpeng Zheng [1], Lijiao Xie, Liangzhi Zhong, Jianguo Sun [*]

Department of Oncology, Xinqiao Hospital, Army Medical University, Chongqing, 400037, China

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ABSTRACT

Introduction: Primary Gastric Squamous Cell Carcinoma (GSCC), especially in late-stage, is a very rare pathological type with poor prognosis. We report a long duration of Complete Response (CR) of GSCC case with multiple metastases by an elaborate three-staged radical Concurrent Chemoradiotherapy (CCRT).

Case presentation: A 36-year-old male suffered from weakness and melena, and then was diagnosed as primary GSCC with cT3N3M1, Stage IV. According to the characteristics of multiple lymph nodes metastases at supraclavicular, perigastric and pelvic regions, an individualized therapeutic strategy of three-staged radical CCRT was elaborately designed and cautiously performed even after the accidental massive hemorrhage of the upper digestive tract under the guidance of a multidisciplinary team. A long-term CR was achieved, with Progression Free Survival (PFS) and Overall Survival (OS) of 74 months by the last follow-up. The case with multiple metastases was radically treated as local advanced disease with complete success.

Conclusion: Patient with stage IV mGSCC who has achieved CR and unexpected long-term PFS and OS through CCRT due to precise judgement and well-designed individualized therapy. The immunomodulatory effect of radiation therapy on the tumor microenvironment may be a potential mechanism affecting treatment efficacy.

1. Introduction

Gastric Squamous Cell Carcinoma (GSCC) is a very rare pathological type, accounting for approximately 0.04%–0.2 % of Gastric Carcinoma (GC) [1,2]. A Surveillance, Epidemiology, and End Results (SEER) data-based study found that patients with GSCC usually had a poorer prognosis than gastric adenocarcinoma, with a median Overall Survival (OS) of 8.0 months and a 5-year OS rate of 32.7 %, and the 5-year OS rate decreased from 80.0 % to 6.0 % from stage I to stage IV subgroups [2]. More than 90 % of GSCC were diagnosed at a late-stage, which led to the poor survival outcome [3,4]. Currently, no standard treatment was recommended for advanced GSCC. Here, we reported a case of metastatic primary GSCC with long-term Complete Response (CR) and Progression Free Survival (PFS) and OS.

* Corresponding author.
E-mail address: sunjg09@aliyun.com (J. Sun).
[1] Rui Zang and Linpeng Zheng contributed equally.

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2. Case presentation

Written informed consent was obtained from the patient for the publication of all images, clinical data and other data included in the manuscript.

A 36-year-old male patient suffered from weakness for 4 months and melena for 1 month from August 2017. Physical examination revealed anemia and left supraclavicular lymphadenopathy of 2.0 cm × 2.0 cm. Gastroscopy indicated localized thickening of mucosa (2.5 cm × 3.0cm) in the greater curvature of the stomach. No special medical, family or psycho-social history including relevant genetic information was found. There were no relevant past interventions regarding the GSCC. Positron emission tomography-computed tomography (PET-CT) showed a diffuse disease involving the gastric body, supraclavicular lymphadenopathy, the splenic hilum region, abdominal cavity, retroperitoneal abdominal aorta, bilateral iliac vessels and left lateral wall of pelvic (Fig. 1A and B). The hemoglobin level (51g/L) was much lower than normal, and the Cyfra21-1 (5.93 μg/L), a biomarker of squamous carcinoma, was high. An ultrasound-guided biopsy indicated that the left supraclavicular lymphadenopathy and the gastric lesion had the same histopathological morphology. Further Immunohistochemistry (IHC) examination presented with Ki-67 40 %, P63+, P40+, CK+, CK5/6+, EGFR+, CD56^{-}, CD20^{-}, NSE-, CgA-, Syn-, EMA-, LCA-, Vim- and CK7- (Fig. 2A–D). Then, this patient was diagonalized as primary GSCC with cT3N3M1 (Stage IV, UICC, 8th edition). The bone marrow biopsy showed active hyperplasia and decreased iron staining. Fluorescence *In Situ* Hybridization (FISH) revealed that both Her-2 and Epstein Barr virus Encoded small RNA (EBER) were negative. Immunotherapy-related biomarkers presented with abundant CD4^{+}, CD8^{+} T cell infiltration, PD-L1 positive accounted for 10 % of the tumor cells and 20 % of the tumor infiltrating lymphocyte (SP142 staining) (Fig. 2E and F), and mismatch repair proficient (pMMR) (MLH1 +, MSH2 +, MSH6+, PMS2+) (Fig. 2G and H). Next-Generation Sequencing (NGS) demonstrated that NF2, MSH3 mutation, and Tumor Mutational Burden (TMB, 9.03 mt/MB) were low. Due to the multiple lymph node metastases at supraclavicular, perigastric and pelvic regions with subregional distribution, and no organ metastases such as liver, lung, bone, and brain, a three-staged radical Concurrent Chemoradiotherapy (CCRT) following a cycle of induction chemotherapy as a curative strategy was recommended by Multidisciplinary Team (MDT). The patient received a TP regimen (paclitaxel liposomes 240mg, nedaplatin 130mg) every three weeks as induction chemotherapy. From January 13th, 2018 to March 26th, 2018,the first stage CCRT was cautiously conducted as PGTV of stomach 56Gy/30F/6W, PGTV of perigastric lymph nodes 60Gy/30F/6W and PCTV 56Gy/30F/6W (Fig. 3A and B) with same dose TP chemotherapy. After three fractionations of radiotherapy, a massive hemorrhage of the upper digestive tract occurred on January 15th, 2018, and the platelets dropped from 140 × 10^{9}/L to 32 × 10^{9}/L within one week. Due to a challenge of hemorrhage diagnosis and subsequent treatment, an emergency MDT made a judgement of splenic vein blocking, splenic vein cancer embolus, portal hypertension, and hypersplenism caused by lymph nodes enlargement. The patient underwent urgent splenic vein stent implantation and splenic artery embolization under Digital Subtraction Angiography (DSA) on January 23rd, 2018 (Fig. 1C–E). From May 26th to June 21st, 2018,the second-stage CCRT was conducted as PGTV of left supraclavicular lymphadenopathy 66Gy/30F/6W, PCTV 54Gy/30F/6W (Fig. 3C and D) with two cycles of TP chemotherapy. From August 2nd to September 5th,the third-stage CCRT was conducted as PGTV of pelvic lymph nodes 60Gy/25F/5W, PCTV 50Gy/25F/5W (Fig. 3E and F) with 1500 mg capecitabine twice a day. During the CCRT, there were mild nausea, weakness, and leukopenia occurred, and symptomatic relief and supportive treatment were given. No severe gastrointestinal symptoms or myelosuppression was observed. According to the guidelines of Chinese

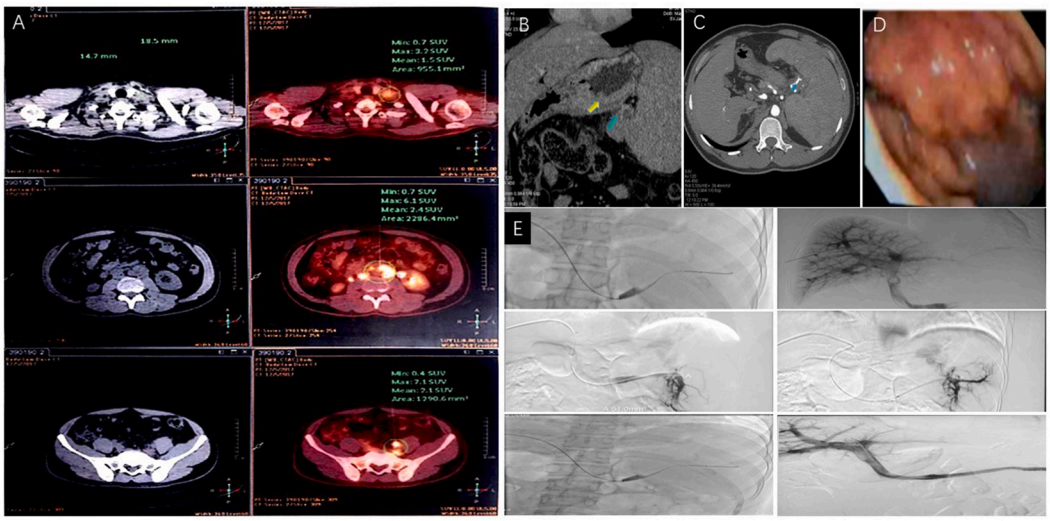

Fig. 1. Radiology diagnosis of advanced gastric cancer and spleen vein stent A. PET-CT shows lesions in the greater curvature of stomach, with multiple enlarged lymph nodes in the supraclavicular fossa, splenic hilum, abdominal cavity, retroperitoneum, bilateral iliac vessels, and left pelvic wall. (Dec. 5th, 2017). B. Left. Primary tumor (yellow arrow) and metastatic lymph node (green arrow) (Jan. 17th, 2018). Middle. Spleen artery invasion (green arrow) (Jan. 17th, 2018). Right. gastric tumor with ulcer at greater curvature (Nov. 28th, 2017). C. Stent for spleen vein under digital subtraction angiography (Jan. 23rd, 2018).

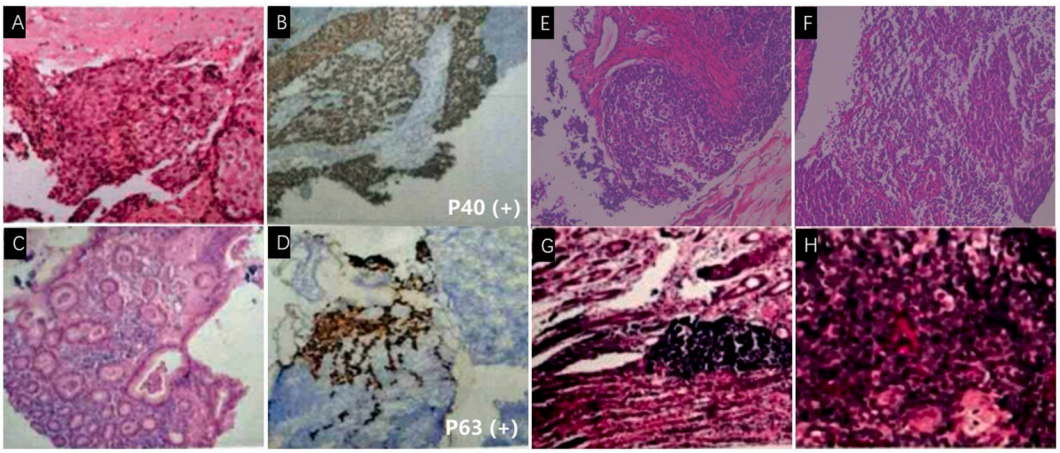

Fig. 2. Pathology diagnosis of advanced gastric cancer at diagnosis A. Squamous cell carcinoma nest in left subclavian lymph node (200x). B. IHC P40+ in lymph node (100x). C. Squamous cell carcinoma in stomach body (200x). D. IHC P63+ in stomach body (100x). E. PD-L1+ accounts for 10 % in tumor cells (200x). F. PD-L1+ accounts for 20 % in tumor infiltrating lymphocytes (200x). G. MLH1 in squamous cell carcinoma (200x). H. MLH2 in squamous cell carcinoma (200x).

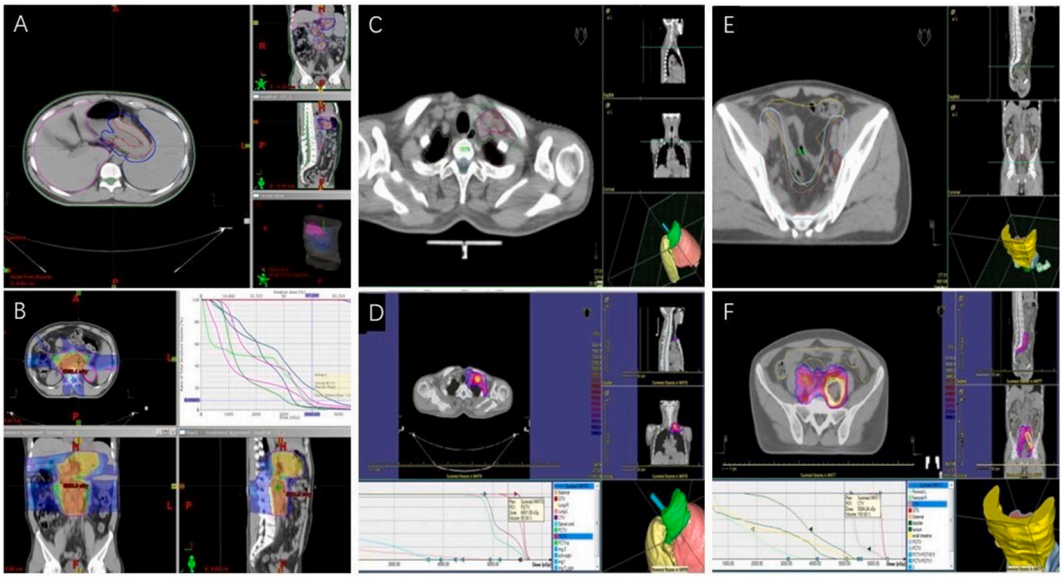

Fig. 3. Three-staged radiotherapy contouring and plan design A-B. First stage radiotherapy of perigastric region from Jan.13th to Mar. 26th, 2018. C-D. Second stage radiotherapy of left subclavian region from May 24th to Jul. 17th, 2018. E-F. Third stage radiotherapy of pelvic region from Aug.2nd to Sep. 5th, 2018.

Society of Clinical Oncology, Gastric cancer (2018. V1), the patient kept taking capecitabine 1500 mg twice a day since then, without any adverse or unanticipated events.

CR was identified and repeatedly confirmed in this patient according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). This patient received regular follow-up by CT scan of neck, thoracic, perigastric and pelvic regions every three months during the first three years, and half a year since the fourth year. Till the last follow-up on March 4th, 2024, no symptom was complained, no tumor image (Fig. 4A), and no ulcer or lesion under gastroscopy (Fig. 4B) was found. Capecitabine was discontinued in February 2022, based on the fact that it had been CR and Circulating Tumor Cell (CTC) was zero. The PFS and OS have reached 74 months by the last follow-up.

3. Discussion

This case report highlighted the long-term clinical benefit of CCRT for metastasized GSCC, which had been regarded as a rare

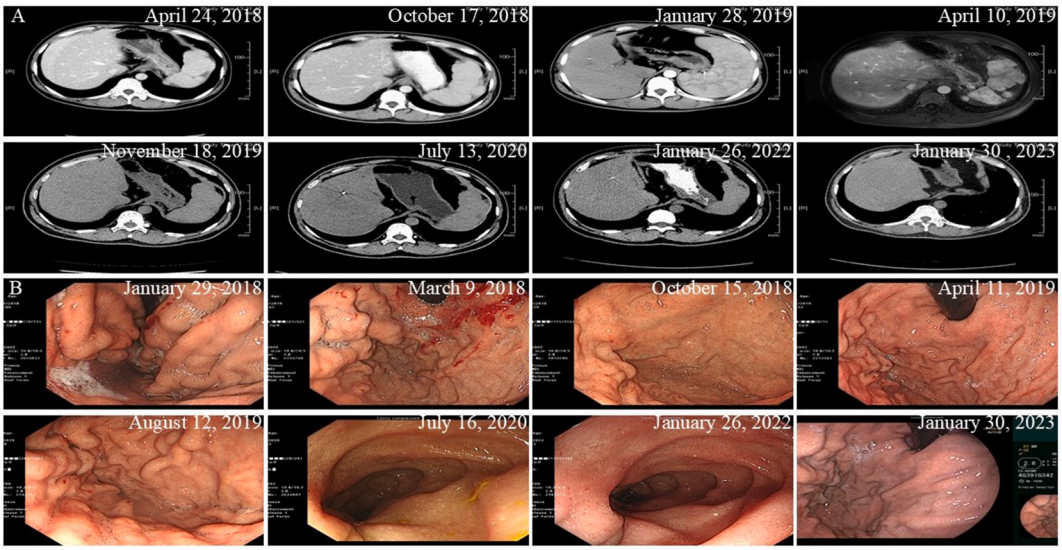

Fig. 4. Radiological examination and gastricscopy after treatment from 2018 to 2023 A. No lesion under CT or MRI scan of neck, upper abdomen and pelvic. B. No lesion under gastricscopy.

subtype of GC with poor prognosis.

It should be emphasized that the diagnosis of primary GSCC should exclude the squamous cell carcinoma (SCC) secondary to other sites, such as esophagus. In this case, we confirmed the diagnosis of primary GSCC by performing multiple IHC, and consultations of pathology confirmation in various hospitals from China, and excluded the origin of other organs.

There were no treatment recommendations from guidelines for primary GSCC. Surgical resection is a preferred treatment approach for localized GSCC [2,5], but not suitable for this patient with multiple metastases. The MDT elaborately designed an individualized strategy of three-staged radical CCRT and cautiously performed even after the accidental massive hemorrhage of the upper digestive tract. Finally, the patient achieved long-term CR, PFS and OS.

In addition, the strategy of splenic vein stent and splenic artery embolization is very crucial. After the operation, the splenic vein, portal vein, and superior mesenteric veins patency restored, and thrombocytopenia recovered. Thus, the planned three-staged radical CCRT could be continued and accomplished. The patient is fortunate to benefit from the well-designed individualized therapy. Patient and participation in the treatment program are also important so that all the treatment plans can be done. He returns to work and exercises as usual, always willing to share his story. A very long survival is expecting in future.

The underlying rationale of the long-term CR for the patient is not clear. The most potential rationale could be the abundant immune infiltration cells in the tumor, which could enhance the efficacy of radiotherapy, and even induce the abscopal effect. Although the patient didn't receive immune-checkpoint inhibitors (ICIs) after CCRT, ICIs therapy could be a potential regime according to CheckMate 649 [6]. The main limitation of this case was that there was no detection of PET-CT and molecular residual disease when capecitabine was discontinued.

4. Conclusion

This case of primary mGSCC achieved unexpected long-term clinical benefit after a three-staged radical CCRT due to the precise judgement and well-designed individualized therapy. The interaction between radiotherapy and immune response may be the underlying mechanism which affect the therapeutic effect.

CRediT authorship contribution statement

Rui Zang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Formal analysis, Data curation. **Linpeng Zheng:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Lijiao Xie:** Writing – original draft, Validation, Software, Resources, Formal analysis, Data curation. **Liangzhi Zhong:** Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis. **Jianguo Sun:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

The research related to human use has complied with all the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration, and has been approved by the Ethics Committee of Army Medical University (Chongqing, China).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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