

# Long-Term Survival of a Patient with Metastatic Small-Cell Carcinoma of the Stomach Treated with Radiation Therapy

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## Key Words

Stomach · Gastric small-cell carcinoma · Small-cell carcinoma · High-grade neuroendocrine carcinoma · Radiotherapy · Stereotactic body radiation therapy · Oligometastases

## Abstract

Small-cell carcinoma (SCC), or high-grade neuroendocrine carcinoma of the stomach, is a rare subtype of extra-pulmonary SCC which is almost invariably lethal. Gastric SCC often presents with local symptoms indistinguishable from other primary stomach cancers; however, both regional and distant spread are common at the initial presentation. Depending on symptoms and patient performance status, treatment typically consists of chemotherapy or resection followed by adjuvant chemotherapy, as even patients with limited stage gastric SCC likely have micrometastatic disease at the time of diagnosis. In this case report, we describe the long-term survival of a 75-year-old male with recurrent oligometastatic high-grade neuroendocrine carcinoma of the stomach treated with radiation therapy (RT) alone. He presented with abdominal pain and dyspepsia and was found to have a 6 cm locally invasive node-positive gastric SCC initially treated with extensive surgical resection. He was not a candidate for adjuvant chemotherapy, and surveillance imaging subsequently confirmed metachronous liver and local recurrences within 1 year after surgery, which were managed with stereotactic body RT and conventional radiation, respectively. An additional para-aortic nodal recurrence was treated with intensity-modulated radiotherapy 7 years after surgery with good response. He tolerated all RT courses without notable radiation-related toxicity and remains in complete remission 11 years after initial diagnosis.

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## Introduction

Gastric small-cell carcinoma (SCC) is an extremely rare form of extra-pulmonary SCC which is relatively more common in East Asia and affects predominately elderly males. The typical clinical presentation is a large gastric tumor causing local symptoms such as epigastric discomfort, dysphagia, nausea, or melena prompting endoscopic evaluation, and/or systemic symptoms of anorexia and weight loss. Most tumors are staged as either limited or extensive stage (similarly to pulmonary SCC) or, alternatively, according to the AJCC TNM staging system. Given the rarity of the diagnosis, the optimal treatment regimen is not well defined. Management typically includes palliative or radical resection followed by adjuvant chemotherapy in patients with good performance status. Outcomes are extremely poor, even in individuals with limited stage disease who undergo aggressive local and systemic therapy, with few long-term survivors [1]. The role of radiation therapy (RT) is unclear as information on its use in the treatment of gastric SCC is extremely limited, with only two reports in the published literature [2].

In this case report, we describe the long-term survival (>10 years) of a patient with gastric SCC initially managed with surgery and subsequently treated with RT alone to areas of local and oligometastatic recurrence. Our Institutional Research Subject Review Board does not require informed consent from patients for a case report.

## Case Report

In June 2004, a 75-year-old male presented with abdominal pain and dyspepsia, prompting an ultrasound which revealed a left upper quadrant mass. A subsequent CT scan of the abdomen confirmed a large gastric mass measuring approximately 8.1 × 4.6 cm. Upper endoscopy on July 8, 2004 revealed a large ulcerated mass in the gastric cardia which was biopsied revealing small round blue cells staining positive for synaptophysin (fig. 1). Staging chest X-ray on July 15, 2004 revealed no intrathoracic abnormalities.

On July 23, 2004 the patient underwent radical resection including total gastrectomy, splenectomy, partial resection of the diaphragm, distal pancreatectomy, and left adrenalectomy. Surgical pathology noted SCC [high-grade neuroendocrine carcinoma (NEC)] in the greater curvature, 6 × 6 × 5.5 cm grossly, with the tumor infiltrating the full thickness of the stomach wall and the adjacent splenic hilum, pancreas, and diaphragm; however, all surgical margins were negative. Extensive tumor necrosis was present without evidence of lymphovascular space invasion or perineural invasion. Lymph node dissection revealed carcinoma in 2 of 5 sampled lymph nodes. The patient's postoperative course was complicated by a peripancreatic abscess and pneumonia. Following discharge, he was readmitted with NSAID-induced acute kidney injury and was thus not considered a candidate for adjuvant chemotherapy.

The patient made a progressive recovery, and a surveillance CT scan 6 months after surgery demonstrated interval development of a low-attenuation lesion within the right lobe of the liver measuring 3 × 2.7 cm, as well as a focus of soft-tissue attenuation in the surgical bed considered diagnostic of recurrence. He received stereotactic body RT (SBRT) to the liver lesion, delivering 40 Gy in 10 fractions completed in April 2005. A restaging CT scan in November 2005 showed shrinkage of the liver lesion; however, the subhepatic soft-tissue mass continued to increase in size. He remained asymptomatic and continued with close observation alone. A CT scan in February 2006 revealed that the mass had grown to 10 cm and was

causing discomfort which prompted local treatment with palliative RT to the mass, delivering 35 Gy in 14 fractions completed in April 2006.

Follow-up CT scans in July 2006 showed marked interval shrinkage of the subhepatic mass; however, there was interval development of mesenteric and retroperitoneal lymphadenopathy. The patient continued with observation as he was asymptomatic and not a candidate for chemotherapy. On surveillance CT scans over the next several years, some of the nodes grew, some regressed, and occasionally new ones appeared. In April 2011, a CT scan showed 3 enlarging para-aortic lymph nodes prompting treatment with intensity-modulated radiotherapy (IMRT) using TomoTherapy, delivering 35 Gy in 10 fractions completed in May 2011 (fig. 2a). Subsequent CT scans in January 2012 showed resolution of two of the lymph nodes and shrinkage of the third from 3 to 1.3 cm. At his last follow-up visit on April 6, 2015, now 11 years following the initial diagnosis, he remains well with subsequent surveillance CT scans showing no evidence of recurrent or metastatic disease (fig. 2b).

## Discussion

SCC is a form of high-grade NEC, which usually arises in the lung but may develop in a wide range of extra-pulmonary sites including the stomach. Cases of extra-pulmonary SCC account for only 4% of all SCC diagnoses, with gastric SCC comprising only 8.3–14.5% of extra-pulmonary SCC and 0.1–0.4% of all primary gastric malignancies [3]. The etiology is uncertain and no specific risk factors have been identified. However, it is most commonly found in Japan, potentially indicating an environmental association similar to other forms of gastric cancer [4]. Both forms of SCC share common histological and immunohistochemical features such as small round blue cells with scant cytoplasm forming sheets and nests, a high proliferative rate with abundant necrosis, and positive stain for synaptophysin, chromogranin, and CD56. Histology may be either ‘pure’ or ‘mixed’ with adenocarcinoma components commonly admixed in cases of gastrointestinal (GI) SCC [5]. The WHO revised the diagnostic criteria in 2010, now defining neuroendocrine neoplasms as those arising in the stomach with neuroendocrine differentiation, including neuroendocrine tumors (typically low grade) and NECs (high grade) [6]. High-grade NECs may be subclassified into small-cell and large-cell endocrine carcinomas.

There is no specific staging system for GI SCC; however, the Veterans’ Administration Lung Study Group (VALSG) categorizes patients into limited stage (defined as tumor contained within a localized anatomic region with or without regional lymphadenopathy) or extensive stage (cases not meeting the limited stage definition). Chest imaging should invariably be performed to rule out primary pulmonary SCC. The liver and distant lymph nodes are the most frequently involved metastatic sites, although metastases to bones and bone marrow are also common [1]. Prognosis is very poor regardless of stage, with most patients dying within 1 year of diagnosis [7].

A standard treatment for gastric SCC has not been established given its rarity, with the majority of the published literature comprised of case reports and small retrospective series which often include non-gastric GI SCC. Management typically includes palliative or radical resection followed by adjuvant chemotherapy in good performers. Outcomes are extremely poor, even in individuals with limited stage disease who can tolerate radical surgery and adjuvant chemotherapy, with an estimated 5-year overall survival of 20% [1]. Huang et al. [3] recently published a retrospective case series including 19 patients with surgically managed gastric SCC, reporting a median overall survival time of 19.5 months, though only a single patient with distant metastases was included. The administration of postoperative

adjuvant chemotherapy was associated with improved overall survival at 48.5 months compared to 19.0 months ( $p = 0.026$ ). Unfortunately, the applicability of these results, as well as that of other published studies in gastric SCC, is limited due to small patient numbers and significant bias given the retrospective nature of the studies. Hepatic metastases may be managed with systemic chemotherapy and/or liver-directed treatments, with isolated case reports reporting long-term survival in patients treated with intrahepatic chemotherapy [7] or percutaneous microwave coagulating therapy [8]. Others have advocated primary chemotherapy for the SCC variant of high-grade NECs by analogy with pulmonary SCC [9].

The role of RT in treating limited or advanced-stage gastric SCC is unclear. Both primary and metastatic sites appear to be radiosensitive based on published results of case series including patients with SCC arising at other GI sites [10]. Despite this, RT has not routinely been employed in the treatment of gastric SCC, as evidenced by a recent review of the published literature including 205 patients with gastric SCC, which revealed that only 2 patients (1%) received RT as part of their treatment [1]. Our patient had RT alone for the management of a local recurrence as well as metastatic disease involving the liver and abdominal lymph nodes, which is unprecedented in the reported literature. There is a paucity of data on the use of liver-directed RT for metastases from gastric or other GI NECs. A meta-analysis shows Y-90 radioembolization for neuroendocrine neoplasm liver metastases to be quite effective, yielding a 50% complete or partial response and a 86% disease control rate with objective response correlating with improved survival (hazard ratio 0.85,  $p = 0.008$ ), though the overwhelming majority of treated patients had low-grade neuroendocrine tumors rather than high-grade NECs [11]. SBRT has been shown to offer excellent local control and tolerability as a treatment for both liver metastases [12] and intraabdominal lymphadenopathy [13], though their use in treating NECs has not been evaluated.

In this report, we describe the long-term survival of a patient who is currently alive without evidence of active disease over 10 years following postsurgical salvage of a local recurrence with conventional RT as well as treatment of metachronous oligometastatic recurrences in the liver and abdominal lymph nodes with SBRT and IMRT, respectively. This is the first case report of its kind published in the medical literature and demonstrates the feasibility and effectiveness of RT as a local treatment of primary and metastatic gastric SCC with long-term local control and minimal toxicity. If this result is generalizable, it would suggest that the SCC variant of high-grade NEC is very sensitive to radiation and that SBRT should be considered in the oligometastatic setting.

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### Statement of Ethics

Our Institutional Research Subject Review Board does not require informed consent from patients for a case report.

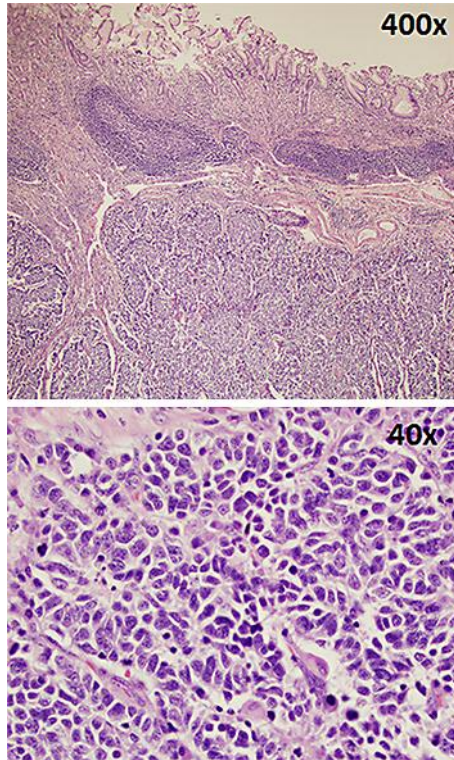
### Disclosure Statement

The authors declare no conflicts of interest.

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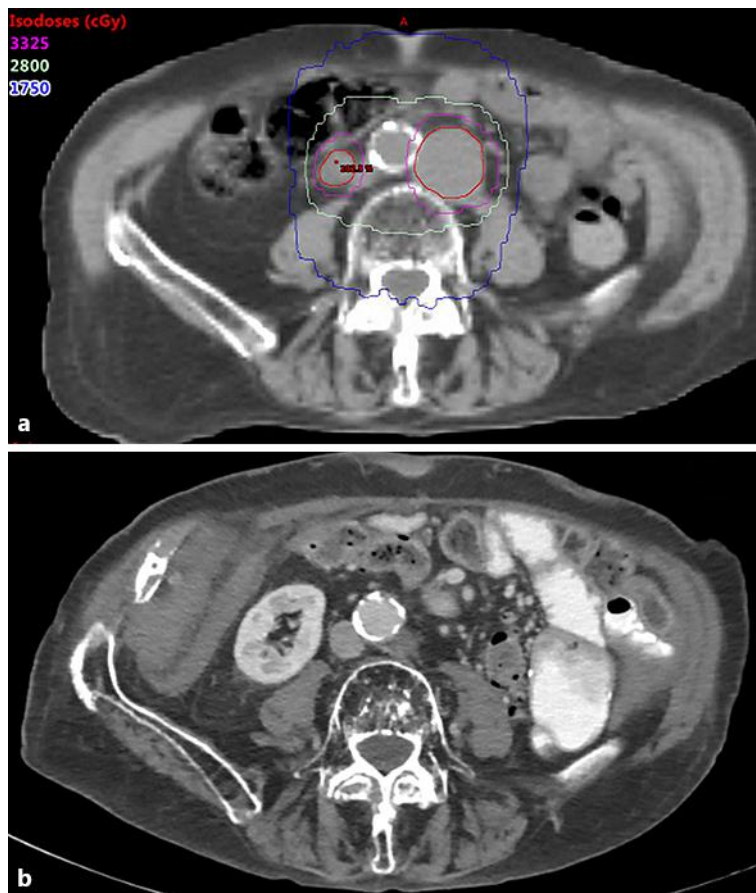
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**Fig. 1.** Upper endoscopy in 2004 revealing a large ulcerated mass in the gastric cardia which was biopsied revealing small round blue cells staining positive for synaptophysin.

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**Fig. 2.** **a** CT scan in 2011 showing 3 enlarging para-aortic lymph nodes prompting treatment with IMRT using TomoTherapy, delivering 35 Gy in 10 fractions. **b** At the patient's last follow-up visit in 2015, now 11 years after the initial diagnosis, no evidence of recurrent or metastatic disease was seen.