



Palliative radiotherapy for hepatobiliary obstruction caused by colorectal metastases

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Abstract: Hyperbilirubinemia in the setting of stent-intolerant biliary obstruction is a challenging problem and can prevent cancer patients from pursuing additional treatments such as further systemic therapies. We report a case of a 75-year-old female who underwent treatment with palliative radiotherapy (RT) for relieving persistent biliary obstruction secondary to liver metastases from colorectal disease, despite prior appropriate stent placement. Prior to RT, the patient's total bilirubin was 14.6 mg/dL, and she experienced fatigue, diarrhea, nausea, vomiting, and severe jaundice. After treatment with 37.5 Gy in 15 once daily fractions, total bilirubin decreased to 3.9 mg/dL, with resolution of previous symptoms including jaundice and pruritus. The patient did not experience any significant treatment-related toxicities. This case, along with a succinct literature review, demonstrates that palliative RT can be successful in relieving biliary obstruction unrelieved by biliary stent. Further research is required to evaluate the efficacy of RT in palliating biliary obstruction for liver metastases in a general population.

Keywords: Neoplasm metastasis; colorectal neoplasm; obstructive jaundice; intrahepatic bile ducts

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Introduction

Liver metastases from colorectal cancer can lead to biliary obstruction, and in certain cases, hyperbilirubinemia may persist even after appropriate biliary stenting. While palliative radiotherapy (RT) is a treatment option for these patients, its efficacy in relieving hyperbilirubinemia that is not responsive to biliary stenting is not well-established in the literature. Here, we describe a patient with metastatic colorectal cancer with severe hyperbilirubinemia, unrelieved by biliary stent but successfully relieved with palliative RT.

Case presentation

A 75-year-old woman was referred to the radiation oncology department in November 2018 for progressive colorectal metastases in segment 5 of the liver with persistent biliary obstruction despite appropriate stent placement. The

patient was initially diagnosed in 2011 with Stage III rectal adenocarcinoma. She was treated with resection plus adjuvant pelvic chemoradiation followed by FOLFOX alone. In 2015, surveillance imaging revealed new hepatic lesions, which were subsequently biopsy-confirmed as rectal adenocarcinoma metastases.

The patient was treated with FOLFIRI and bevacizumab and underwent a left hepatectomy, cholecystectomy, and partial hepatectomy of segment 5 of the liver. Subsequent CT imaging revealed no evidence of disease. However, in 2016, the patient's metastatic disease progressed with new hepatic metastases. She underwent multiple rounds of chemotherapy, including FOLFIRI plus bevacizumab, then FOLFOX and bevacizumab, and subsequently cetuximab. In November 2018 her total bilirubin rose to 11.9 mg/dL. An abdominal CT without contrast showed new biliary dilatation, and the patient underwent an endoscopic retrograde cholangiopancreatogram (ERCP) with stent



Figure 1 Stricture was found within the common bile duct with dilatation of the intrahepatic ducts. Balloon dilatation was performed with successful placement of a metallic stent across the stricture.

placement (*Figure 1*). One uncovered, self-expanding, metallic stent was placed into the common hepatic duct, and bile flowed through the stent at the time of placement. Intra-procedural imaging was used to verify stent placement and position, and follow-up CT abdomen showed decompressed central bile ducts. Shortly following the stent placement, total bilirubin continued to rise to 17.8 mg/dL (*Figure 2*). Limitation in the ERCP-directed stenting was attributed to existing portal caval lymphadenopathy. Prior to RT, the patient experienced fatigue, diarrhea, nausea, vomiting, and severe jaundice (*Figure 3*). After a multidisciplinary discussion, the patient commenced palliative RT, in an attempt to relieve her biliary obstructive symptoms clinically. The patient received 37.5 Gy in 15 fractions (once daily) to the tumor surrounding the right hepatic bile duct, with microscopic and setup margins around the gross tumor volume (*Figure 4*). She previously had not received any liver-directed radiotherapy before. At the end of RT, the patient's total bilirubin decreased to 3.9 mg/dL (*Figure 2*). Her symptoms including jaundice and pruritus had resolved (*Figure 3*). She tolerated RT without significant treatment-related toxicities.

One month following RT, the patient's total bilirubin further improved to 2.5 mg/dL. Two months following RT, she was hospitalized at an outside institution for sepsis. At the onset of sepsis, total bilirubin remained at 2.5 mg/dL and was not clinically considered to be related to the septic event.

At last clinical follow-up being three months following RT, total bilirubin was 2.8 mg/dL, and the patient pursued hospice care and died from her underlying extrahepatic disease shortly thereafter. At the time of her death, she remained symptom-free from hepatobiliary obstruction.

Discussion

The liver is the most frequent site for distant metastases from lung, breast, and colorectal cancers. Liver metastases occur in more than 50% of colorectal cancer patients and result in death in about two thirds of this population (1,2). Hepatic tumor burden may lead to severe hyperbilirubinemia and intrahepatic bile duct obstruction. Biliary decompression can be difficult in many cases. For patients with persistent jaundice who do not obtain adequate symptomatic relief even with appropriate stent placement in the context of liver metastases, palliative RT may be effective for reducing symptoms as an additional treatment.

In metastatic colorectal cancer, the onset of jaundice is associated with very poor median survival of 1.5 months (3). Physiologically, severe jaundice is incompatible with life, and often precludes further treatment such as meaningful systemic therapy administration. Successful biliary drainage has been shown to be a significant prognostic factor in malignant obstructive jaundice (4,5). Unfortunately, attempts at relieving jaundice in the setting of metastatic colorectal cancer are often ineffective, with less than one fifth of patients being able to receive further chemotherapy (3).

Various palliative treatments are available to relieve malignant biliary obstruction including stent placement during an ERCP. However, biliary obstruction may persist due to various factors, such as biliary sludge formation, tumor ingrowth/overgrowth, or stent migration/obstruction. Another palliative treatment is percutaneous transhepatic biliary drainage (PTBD) with self-expandable stents, but many patients experience recurrent jaundice and cholangitis. Surgery is another palliative approach that can result in long-term patency but has high rates of morbidity and postoperative mortality (6). Additionally, most of these patients are near end of life and do not have the physiologic reserve to be surgical candidates; furthermore, they may not desire aggressive interventions. In cases with inoperable biliary obstruction or debilitated patients who cannot withstand further systemic therapies due to severe hyperbilirubinemia, RT is an alternative and often suitable treatment option which is currently underutilized in

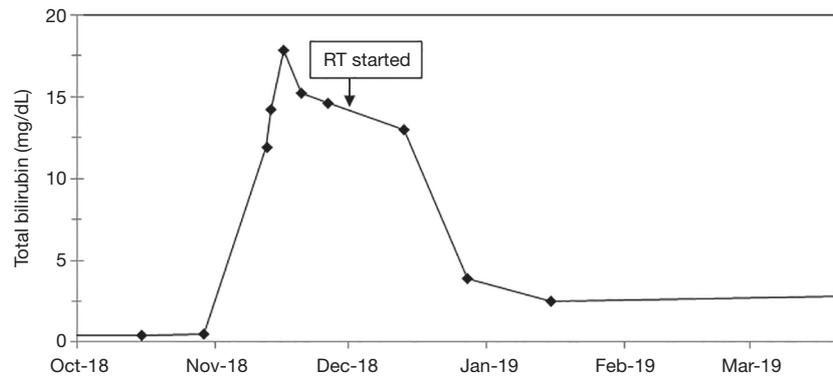


Figure 2 Changes in total bilirubin levels during the treatment.

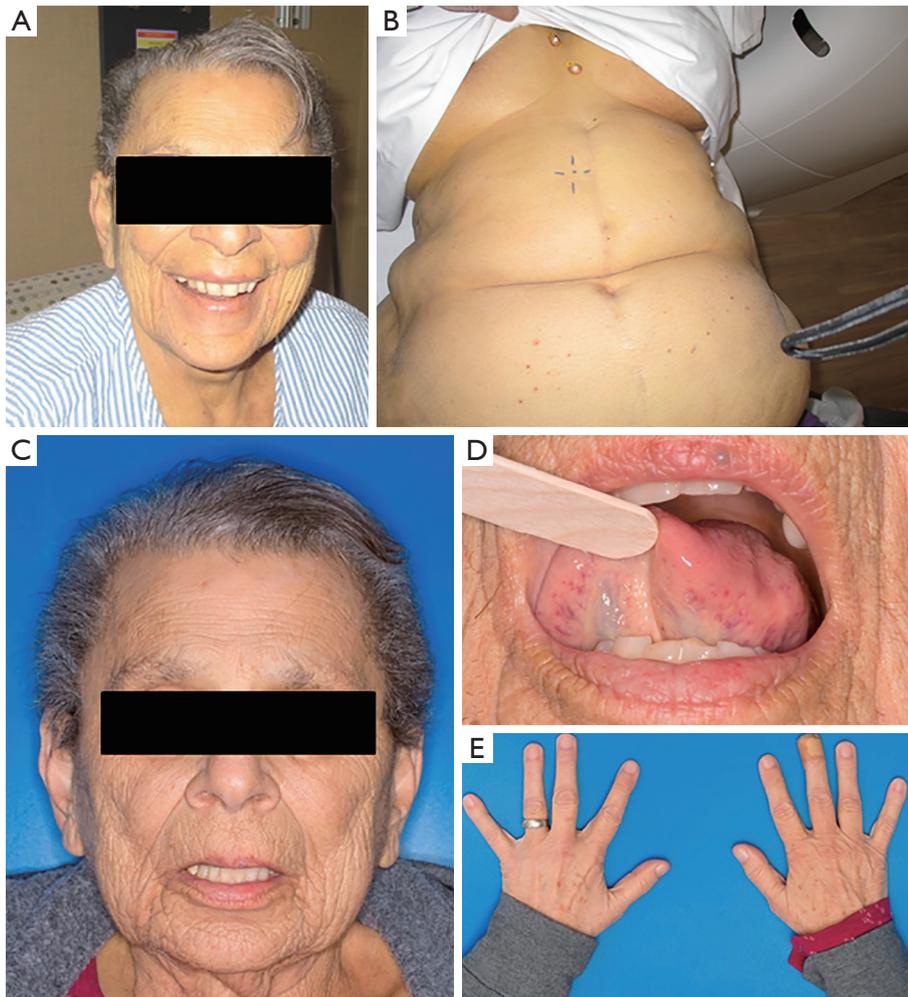


Figure 3 Patient presentation before (A,B) and after (C,D,E) radiotherapy.

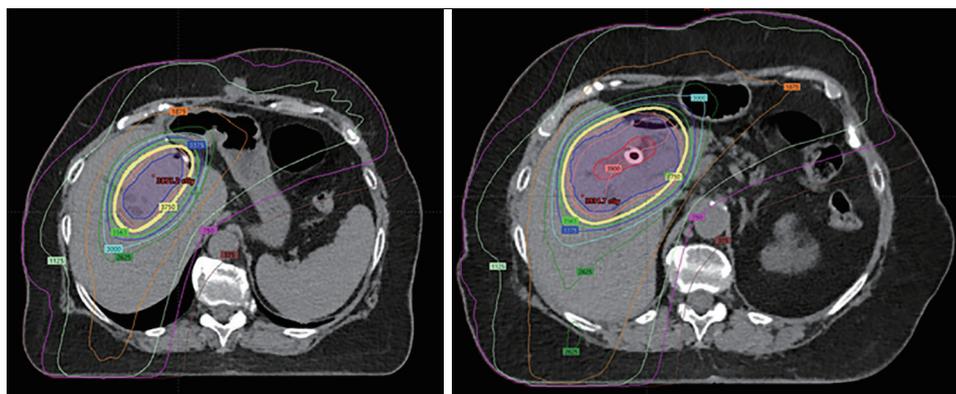


Figure 4 Axial images of intensity-modulated radiation therapy plan; yellow corresponds to the 100% isodose line. Stent visible in image on the right.

Table 1 Studies that have demonstrated efficacy of radiotherapy in the relief of jaundice in patients with malignant biliary obstruction

RT characteristics	Ohnishi <i>et al.</i> (7) [1995]	Kuvshinoff <i>et al.</i> (8) [1995]	Mayer <i>et al.</i> (9) [2003]	Park <i>et al.</i> (10) [2011]
Number of patients	14	12	14	1
Pathology/disease	Hilar cholangiocarcinoma	Hilar cholangiocarcinoma	Biliary cancer	HCC
Intent of therapy	definitive	definitive	palliative	definitive
Types of radiation	EBRT	ILRT + EBRT	ILRT +/- EBRT	EBRT
Radiation dose/number of fractions	50–60 Gy/1.8–2.0 Gy fractions	ILRT: 20 Gy/48 hrs; EBRT: 50.4 Gy/1.8 Gy fractions	ILRT: 10 Gy/48 hrs; EBRT: 45–50.4 Gy/1.8 Gy fractions	37 Gy/3 fractions
Other therapies	PTBD	Tumor resection or hepaticojejunostomy (internal biliary drainage)	PTBD	PTBD + TACL
Number of patients with relief from jaundice	10/11 pts	10/12 pts	14/14 pts	1/1 pts
Overall survival	3–25 mo	14.5 mo	ILRT: 4.5 mo; ILRT + EBRT: 6.5 mo	N/A

RT, radiotherapy; EBRT, external beam radiation therapy; ILRT, intraluminal radiation therapy; PTBD, percutaneous transhepatic biliary drainage; TACL, transarterial chemolipiodolization.

radiation oncology clinics.

RT has demonstrated efficacy in relieving jaundice from biliary cancers. Ohnishi *et al.* (7) demonstrated that 50–60 Gy of conventionally fractionated external beam RT and PTBD improved serum total bilirubin levels to normal in 10 (91%) of 11 patients with obstructive jaundice secondary to hilar cholangiocarcinoma (*Table 1*). Kuvshinoff *et al.* (8) showed that jaundice was relieved in 10 (83%) of 12 patients with unresectable hilar cholangiocarcinoma treated with internal biliary drainage in conjunction with RT (*Table 1*). In highly selected patients, RT may have a role in prolonging

survivals; patients with unresectable bile duct tumors who received intraluminal therapy with external beam RT had a median survival of 6.5 months, while patients who received intraluminal therapy alone had a median survival of 4.5 months (*Table 1*) (9). In a more recent study (11), patients with hilar cholangiocarcinoma who received external beam RT and intraluminal therapy had an overall survival of 22.1 months, compared with patients who received best supportive care alone (5.7 months). Finally, RT has also been shown to increase stent patency in patients with inoperable biliary cancers, when compared to patients

receiving best supportive care only (12).

Hepatobiliary obstruction caused by liver metastases is challenging from a surgical perspective. Moreover, drainage by interventional radiology-guided procedures may be difficult (13). In addition, such treatments may become ineffective for patients with multiple sites of biliary obstruction or diffusely metastatic diseases within the liver. In this case study, we demonstrated that palliative RT can be a successful treatment option for stent-intolerant biliary obstruction, and our patient obtained significant and complete symptomatic relief which happened shortly during and after her completion of RT. Clinically, patency and force of the self-expanding stent as applied radially may have also contributed to further decrease of the patient's bilirubin level one month following RT. Further studies are needed to evaluate the efficacy of RT for palliating biliary obstruction for liver metastases, an often challenging scenario that deserves our attention clinically.

Acknowledgments

None.

Footnote

Conflicts of Interest: Terence T. Sio provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc., which is not in any way associated with the content or disease site as presented in this manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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