

Novel use of endoscopically placed fiducial markers for targeted radiation therapy of colonic lymphomas

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Abstract

Non-Hodgkin's lymphomas (NHL) are an important variety of gastrointestinal tumors with increasing incidence and prevalence. Traditional management of NHL with chemotherapy is challenging and expanding evidence points to significant tumor response to radiation therapy (RT). However, there exists a wide range of radiation-related toxicities. Optimization of exact tumor marking coupled with minimization of the radius of radiation delivery is essential to increase patient's tolerance and decrease side effects of the treatment. We report our experience with mantle cell lymphoma of the colon treated with precision RT after endoscopic placement of resolution clips in a "shooting target" fashion in a patient who failed conventional chemotherapy. Fourteen months after completion of RT, the patient remains in complete remission.

Keywords Endoscopy, colonoscopy, mantle cell lymphoma, gastrointestinal cancer, radiation therapy

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Introduction

Current medical literature on the application of radiation therapy (RT) in colon cancer patients has mainly focused on adenocarcinoma but there exists a wide range of non-Hodgkin's lymphomas (NHL) that account for unusual but important variety of colorectal neoplasms. Overall, gastrointestinal lymphomas represent up to 1.2% of all colorectal malignancies with majority of the cases presenting in the cecum or rectum [1]. In the past decade, incidence of extranodal involvement of NHL in the GI tract has nearly doubled. About 17% of cases arise in the colon with diffuse large B-cell lymphoma being the most common, and mantle cell lymphoma (MCL) representing the most rare but aggressive disease [2]. Mainstay of treatment of intestinal NHL remains rituximab-based chemotherapy. Until recently, employment of RT in patients with incomplete response has not been described and its benefits were considered unclear. Potential side effects related to general intolerance, gut mobility, and a significantly large field of

radiation exposure affecting nearby organs limited common use of RT for intestinal lymphomas in clinical practice. Our present case describes a novel use of endoscopically placed clips which aid in tumor marking and facilitate a decrease in radiation volume to achieve complete oncologic response in a patient with recurrent MCL of the colon in whom conventional chemotherapy failed.

Case report

A 72-year-old man was diagnosed with stage IAE extraintestinal MCL in 2008 and was treated with three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) achieving a complete response. He was subsequently placed on rituximab maintenance therapy for two years with intent to augment overall survival. Repeat PET-CT scan in January 2012 showed a single focus of uptake (SUV 5.3) in the descending colon. Colonoscopy confirmed a large protruding erythematous hard mass (Fig. 1A) and biopsy was positive for recurrent MCL (Fig. 2A). The patient was treated with four cycles of bendamustine and rituximab, which he completed in July 2012. A repeat PET-CT in August 2012 showed no evidence of disease. Colonoscopy revealed a substantial decrease in tumor volume (Fig. 1B) with histology positive for persistent MCL confirming only partial tumor response (Fig. 2B). Additional systemic chemotherapy was deferred by the patient and decision was made to proceed with external beam salvage RT. Repeat colonoscopy was performed and the residual tumor area was easily identified by mucosal irregularities and previously placed ink tattoo. Four hemostatic

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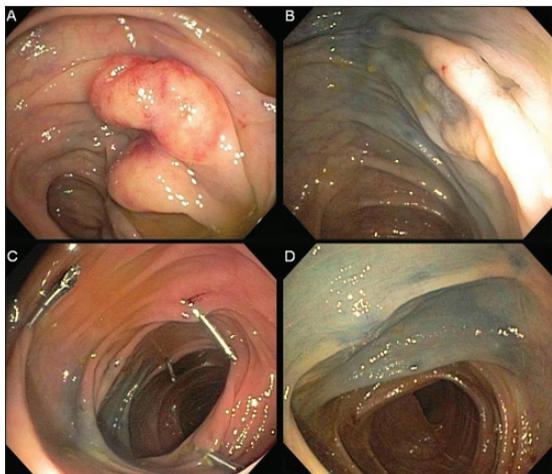


Figure 1 (A) Colonoscopy revealed a large tumor in the descending colon consistent with mantle cell lymphoma (MCL). (B) Colonoscopy showed partial tumor response of MCL in the descending colon after systemic chemotherapy. (C) Four resolution clips were placed in a “target sign” fashion around MCL tumor tissue to facilitate in radiation therapy planning. (D) Repeat colonoscopy after radiation therapy showed resolution of MCL

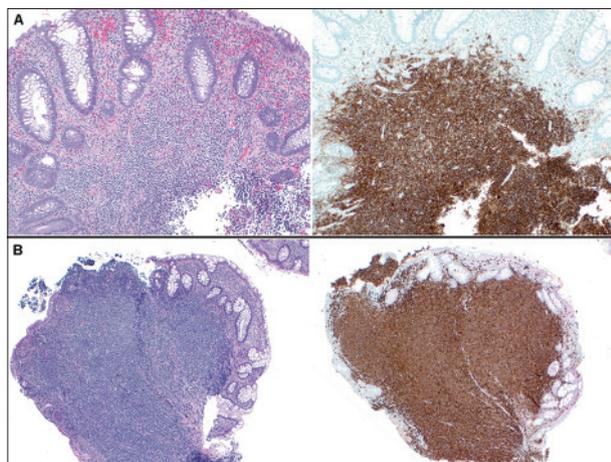


Figure 2 (A) Histological evaluation (H&E) of the tissue tumor in the descending colon showed lymphoid tissue proliferation in the lamina propria with positive CD20 immunostain consistent with diagnosis of mantle cell lymphoma. (B) Post-chemotherapy, histological evaluation (H&E) of the tissue tumor in the descending colon with positive CD5 immunostain confirmed only partial tumor response

resolution clips (Boston Scientific, Massachusetts, USA) were endoscopically placed to mark the superior, inferior, lateral and medial extent of the tumor, in a “shooting target” fashion to facilitate in planned directed external beam RT (Fig. 1C) and to minimize the radius of toxic radiation exposure to the adjacent normal tissue (Fig. 3, arrow). Patient underwent uneventful RT with twenty targeted fractions and total radiation dose of 36 Gy without side effects or adverse events. Follow up colonoscopy with biopsy 6 months after RT showed no endoscopic or



Figure 3 Radiation therapy planning; arrow shows endoscopically placed resolution clips as metallic densities on computed tomography scan

histologic evidence of residual disease or toxicity (Fig. 1D). Fourteen months after completion of RT, the patient remains in complete remission.

Discussion

MCL is a rare subtype of B-cell NHL that accounts for approximately 4-9% of adult NHL and typically presents with clinically more aggressive form with overall shorter median survival [3]. Gastrointestinal involvement of MCL was noted in 25% of the cases in earlier literature [4], largely an underestimate due to generally asymptomatic presentation in the majority of patients. However, recent prospective analysis of 60 consecutive patients showed that colonic dissemination may be histologically detectable in up to 88%. GI disease in absence of apparent bone marrow involvement is seen in approximately 8% of the patients [5].

The mainstay of established therapy of the MCL remains rituximab-based multi-agent chemotherapy but the disease is considered incurable with conventional therapy with average survival of less than 5 years. Second-line agents, including bendamustine in combination with rituximab, may achieve complete response in approximately half of the patients, lacking effective long-term strategy for disease control [6,7]. Rosenbluth and Yahalom have reported high degree of radiation sensitivity in MCL patients, with estimated 100% of local response rate and 64% of complete response rate in patients who failed prescribed systemic chemotherapy [8].

Our case is a novel description of endoscopic utilization of fiducial markers in the colon for treatment of MCL using RT. While anecdotal use of metal clips as a guide in RT planning for patients suffering from lung and esophageal cancers has been described, this “targeted” approach has not yet been applied for intestinal tumors [9-11]. Given high

predilection of MCL to the gut, colonoscopy may be essential in post-treatment assessment and additional guidance, including radiation planning. Given the close proximity of the colon to other intra-abdominal structures and its regional mobility, RT planning is challenging. Use of endoscopically placed markers (metallic clips) may offer advantage in calculating exact field and volume prior to application of toxic radiation. Retrospective tumor volume and radiation dose analysis in our patient showed “clip-free” standard approach would have overestimated planning and gross tumor volume (GTV) for a total of 717 mL. With the endoscopically placed clips as markers, GTV was calculated at 268 mL - effectively reducing the volume by 63% and thus allowing for more targeted radiation delivery. This approach avoided excess toxicity to the surrounding organs and tremendously reduced risk of radiation-related morbidity. In fact, our patient tolerated RT well, without side effects and a post-treatment colonoscopy confirmed resolution of lymphoma and absence of significant radiation injury to the adjacent tissue.

Applications in GI endoscopy have revolutionized the oncological field, providing for effective multidisciplinary approach to diagnosis, staging, and treatment of GI tumors. Here we report successful treatment of a patient with MCL of the colon with endoscopically targeted salvage RT following partial tumor response with chemotherapy. We suggest that repeat colonoscopy should be performed on patients with intestinal MCL after chemotherapy to assess for complete response. We propose use of fiducial markers for RT of intestinal tumors to help provide exact coordinates of neoplasm with the goal of achieving complete oncologic response and prolonging the patient's survival while minimizing potential side effects from RT.

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