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## Case report

## Resurrection of whole liver radiotherapy—A case report

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## ABSTRACT

**Introduction:** This is a case report of a patient of lymphoma with liver metastasis who had persistent pain and jaundice despite multiple lines of chemotherapy. She underwent palliative liver irradiation. This is an uncommon modality due to fear of radiation induced hepatitis. We reviewed literature available on the use of liver irradiation for palliation and concluded that it can be safely used with good results. A 33-year-old female with Non-Hodgkin's Lymphoma (NHL) presented with obstructive jaundice. She underwent stenting followed by chemotherapy. She was lost to follow up to later present with a progressively increasing right hypochondrial mass, pain and icterus. Ultrasound abdomen revealed massive hepatomegaly with hypodense lesions in both liver lobes and centring the porta with dilatation of biliary radicals. Despite multiple lines of chemotherapy and use of opioids, there was no symptomatic relief in pain, size of mass or any decrease in biochemical parameters. Then she was offered palliative radiation in the form of partial liver irradiation to a dose of 21 Gy/7 fractions. She had >50% pain relief after 2 fractions and was off opioids by last fraction. Liver span reduced from 6 cm to 1 cm below costal margin in mid clavicular line. Radiologically 60% reduction in size of liver lesions was observed. Also, a decreasing trend in biochemical parameters was observed. Use of whole or partial liver irradiation is rare in clinical practice due to fear of radiation induced hepatitis by conventional techniques. Newer techniques of delivering radiation can highly improvise accuracy and permit further dose escalation.

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## Case report

A 33-year-old female belonging to low socioeconomic status group from Delhi presented to Rajiv Gandhi Cancer Institute and Research Centre with obstructive jaundice. A CT scan of the abdomen was done, which revealed abdominal and retroperitoneal lymph nodes and dilated IHBR. Biopsy from the axillary lymph node was suggestive of Diffuse Large B Cell Lymphoma (DLBCL) (CD 20, CD 10 & bcl2 was positive). She underwent Endoscopic Retrograde Cholangio Pancreatogram (ERCP) and a plastic stent was placed for relieving jaundice. She received 6 cycles of Rituximab, Cyclophosphamide, Adriamycin, Oncovin and Prednisolone (RCHOP) for the next six months.

Positron Emission Tomogram (PET) scan evaluation after a month revealed progressive disease. Hence second line chemotherapy Ifosfamide, Carboplatin and Etoposide (ICE) was started. ERCP was done again and previously placed stents were removed and selective cannulation of Common Bile Duct (CBD) was done and

two plastic stents were placed in the CBD to drain bile into the duodenum. Unfortunately, the patient was lost to follow up to later present after 4 months with complaints of fever, weight loss, enlarged tender right hypochondrial mass, axillary and cervical lymphadenopathy. She received 2 cycles of GVD (Gemcitabine, Vinorelbine, Dexamthasone) regimen with no relief in symptoms and progressive disease was seen on PET scan.

As a result, the chemotherapy schedule was changed to Bendamustine and Bortezomib. In view of the persistent pain and icterus, an interim Ultrasonogram (USG) abdomen was done which showed hepatomegaly with multiple varying sized hypodense lesions involving both lobes with mild dilatation of CBD and IHBR (Intra Hepatic Biliary Radicals) along with multiple abdominal and retropancreatic lymph nodes. Biochemical parameters showed increasing trend in total and direct bilirubin. She was put on findrid patch for pain relief and the dose was increased from 25 to 50 µg over a span of 2 days. Yet, she had no relief in pain. Then she was referred to our radiation oncology team for palliative radiation in view of the persistent pain.

She was assessed clinically before starting radiation. The patient had icterus, abdominal distension. The liver mass was palpable 4 fingers (6 cm) below the right costal margin in mid clavicular line.

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Blood examination showed raised total and direct bilirubin. CT scan revealed hepatomegaly with large hypodense lesions involving both lobes of liver and centred around the porta. IHBRs were mildly dilated. Biliary stent was seen in situ. She was started on palliative radiation to liver in the form of partial liver irradiation to a dose of 21 Gy/7 fractions at 3 Gy per fraction over a span of 9 days by conventional 2D simulation technique. The radiation was delivered by Anteroposterior/Posteroanterior (AP/PA portals). The upper limit was upper border of D8 vertebra, lower limit was lower border of L1 vertebra. Medial limit was 1.5 cm from vertebral body left lateral border. Lateral limit was flash of skin. The patient had more than 50% pain relief after 2 fractions of radiation. Liver span reduced from 4 fingers (6 cm) to 2 fingers (3 cm) below costal margin in midclavicular line. By the end of 7 fractions, patient was free of pain and was off the fentanyl patch and liver span reduced to 1 finger below costal margin in mid clavicular line. There was also a decreasing trend seen in the biochemical parameters associated with liver damage in the form of decreasing total and direct bilirubin. Icterus was no more visible. Radiologically the liver lesion showed to have a 60% reduction in size.

The patient succumbed to disease after 4 months of radiation. He had significant pain relief during the time he survived indicated by no use of opioids during those months. Also there was no further rise in the biochemical liver parameters assessed biweekly. No radiological imaging was done during these months.

## Discussion

Liver is a common site of metastasis in various malignancies like breast, Gastrointestinal, lung, rectum etc. Involvement of liver in disseminated Non-Hodgkin's Lymphoma (NHL) is common but it is rarely a presenting organ. Systemic therapy is the usual approach for diffuse liver metastasis. For selected patients, surgical resection is done with the aim of improving time to disease progression and overall survival. Radiation appears to be underused in this situation in contrast to the frequency and effective use of RT for palliation of metastasis in other conditions like bone/brain metastasis.

Palliation is defined as the treatment aimed at alleviating symptomatic effects of a disease rather than at curing the disease. The four most common types of liver tumours that often require palliative treatment are Hepatocellular Carcinoma (HCC), metastatic Colorectal Carcinoma (mCRC), Cholangiocarcinoma and metastatic Neuro Ectodermal Tumour (mNET). We have presented a case of a 33-year-old female with DLBCL refractory to systemic chemotherapy, symptoms not responding to stenting, and unamenable to surgical resection was taken up for palliative radiotherapy in form of partial liver irradiation for pain relief. Metastatic disease to the liver carries a poor prognosis with median survival of only 6 months [1].

Various modalities employed in palliative treatment of liver tumours include surgical resection, stenting, chemotherapy, radiation, ablation and general measures for liver failure symptoms. Surgery is reserved for a subset of patients with solitary or limited number of liver lesions. Due to chemotherapy and targeted therapy advances, significant improvement in outcome of patients have been observed for patients with CRC metastasis [2]. But unfortunately these results were not reproducible for liver secondaries of other malignancies. Radiotherapy is administered in a wide array of forms including external beam radiotherapy (EBRT), intraluminal brachytherapy (ILBT), intraoperative radiotherapy (IORT). Use of whole/partial liver RT is rare in clinical practice due to the belief that it inevitably leads to radiation induced hepatitis (RILD) (see Figs. 1 and 2).

RILD is observed in 5–10% patients after whole liver radiation to doses above 30–35 Gy. It is a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes between 2 weeks and 4 months after radiation. The pathological lesion in RILD is veno-occlusive disease with sparing of larger veins. There are very few data on partial volume liver tolerances of liver to radiation. Ingold et al. first reported on partial liver irradiation in 1965 who noted ascites and hepatomegaly in 1 of 8 patients who received 30–35 Gy versus 12 of 27 patients who received greater than 35 Gy [3]. Various other subsequent studies confirmed that doses higher than whole liver tolerance to radiation could be delivered to the liver without any adverse long term adverse effects as long as substantial amount of normal liver tissue is spared [4–6].

The first quantitative analysis of RILD as a function of dose and volume was performed by Austin et al. in 1986 and it was suggested that liver doses in excess of 35 Gy must be limited to 30% of liver [7]. Emami et al. published a paper on dose volume tolerances of all organs to radiation in which the estimated TD 5/5 for one third, two-third and whole liver were 50 Gy, 35 Gy and 30 Gy respectively [8]. These estimates were based only on 27 patients who received partial liver radiation, so tolerance levels were based primarily on clinical judgement. Following the review by Emami, many other reports have been published using photons, protons and Stereotactic Body Radiation Therapy (SBRT), the largest reported series of patients treated with partial liver irradiation is based on the experience at University of Michigan in which dose prescription was based on Dose Volume Histogram (DVH) of normal liver and it was a prospective study in which RILD was studied [9].

## Radiobiology

Liver parenchyma is arranged in parallel architecture which allows for high dose treatment to sub volume of liver as long as dose to the nontumorous region is low enough to minimize the risk of global functional compromise. Liver can regenerate as observed in surgical candidates for whom extensive resection of 78–80% have been safely performed [10].

Liver metastasis presents a unique opportunity for radiation oncologists in both palliative and curative settings. Whole Liver Radiation Therapy (WLRT) has been described in literature in various retrospective studies for symptomatic liver metastasis to relieve pain, discomfort, nausea and night sweats. Low dose WLRT can benefit these patients and relief may be prompt with very few side effects [11,12]. There are two different scenarios in which palliative radiation can be used. Firstly, for tumour ablation with a goal of improving Overall Survival (OS) and secondly, for the relief of symptoms. For the former, patients are generally in a relatively good prognosis group with longer survival expectancy and usually without local symptoms from metastasis. OS and Progression Free Survival (PFS) are the primary end points and Quality of Life (Q.O.L) is secondary end point in such cases. In the latter group, patients are generally nearing the end of their life. In these patients, symptom control and short term Q.O.L are the primary end points (see Tables 1 and 2).

A variety of ablative techniques have been developed [13]. The most commonly used technique is Radiofrequency Ablation (RFA). Though it is less invasive than surgery, it still requires placement of electrodes into the tumour either percutaneously or via laparoscope. The most serious limitation of RFA is that, it cannot be used in porta hepatic region which is extremely important in regard to survival and quality of life. Many studies have been done on palliative WLRT alone or in combination with systemic therapy. All studies have shown significant relief by WLRT [14–22]. The most commonly reported endpoint, pain relief ranged from 55 to 80%

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