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Case Report

Management of leiomyosarcoma of the IVC, a rare vascular tumour, treated with adjuvant radiation therapy in a tertiary care hospital in India

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ABSTRACT

Leiomyosarcoma of the inferior vena cava (IVC) is an extremely rare malignancy, in an already rare subgroup of primary vascular malignancies, with nonspecific clinical presentation. The primary treatment modality is surgery and the disease outcome is dismal even after complete surgical resection. The role of adjuvant treatment (including Chemotherapy and Radiotherapy) is now being routinely considered. In this study, we have discussed a case of a 50 years old lady with good performance status, diagnosed with Leiomyosarcoma of the IVC. She was found to have a positive margin after extensive surgery and was treated with adjuvant External beam radiation therapy using VMAT technique in 2 phases. At 3 months after completing radiation treatment, her PET CT scan showed no evidence of disease and at 4 months follow up, she had good performance status with no major complaints. However, 5 months after completing treatment, she developed multiple liver metastases.

Keywords: Rare vascular malignancy, Leiomyosarcoma, IVC leiomyosarcoma, IVC tumor, Rare malignancies

INTRODUCTION

Sarcomas are connective tissue malignancies presenting with histologies like liposarcomas, clear cell sarcomas, rhabdomyosarcomas, angiosarcomas, leiomyosarcomas etc. The incidence of sarcoma has increased in the last few decades and varies across different geographical regions.[1]

Leiomyosarcoma is a common subtype, comprising 10-20% of all sarcomas, however, it is still relatively rare.[2] Leiomyosarcoma of the inferior Vena Cava (IVC) is an extremely rare malignancy. A registry established in 1991 reported just over 200 patients in literature.[3] These lesions arise from the tunica media of the blood vessels, with predominantly extra-luminal growth and can potentially infiltrate the hepatic or the renal veins.[4]

The management focuses on local control and prevention of recurrence. In this article, we reviewed the available literature and reported the management of a 50 years old

lady diagnosed with Leiomyosarcoma of the IVC, treated with an extensive surgery, followed by adjuvant External Beam Radiation Therapy in a tertiary care hospital in Mumbai, India. The literature with reference to India as a country is barely available, hence there are no specific guidelines for appropriate adjuvant treatment after surgery.

CASE REPORT

Our patient was a 50 years old lady, formerly healthy with controlled hypertension, no surgical history and no family history of malignancy. She was evaluated for severe abdominal pain, dizziness, acute loss of consciousness, massive swelling of both lower limbs, shortness of breath and orthopnoea.

A USG of the abdomen and pelvis demonstrated a thrombus in the IVC. Various hematological parameters were evaluated. Autoimmune etiology was ruled out using ANA immunofluorescence, C3 C4 levels, Lupus anticoagulant levels, Anti-cardiolipin IgG and IgM levels.

A CT scan with pulmonary angiogram and IVC Venogram showed a dilated IVC with a filling defect, extending cranially into the right atrium and caudally involving the infra-renal IVC, extending into the left renal vein and right hepatic vein, with no evidence of pulmonary embolism.

A wedge-shaped lesion was seen in the right lobe of the liver. The PET CT scan showed a dilated IVC with non FDG avid filling defect (thrombus) which was suspiciously secondary to disease arising in the IVC wall, and peripherally increased FDG uptake in the IVC at the commencement of the left renal vein (Figure 1, 2 and 3).

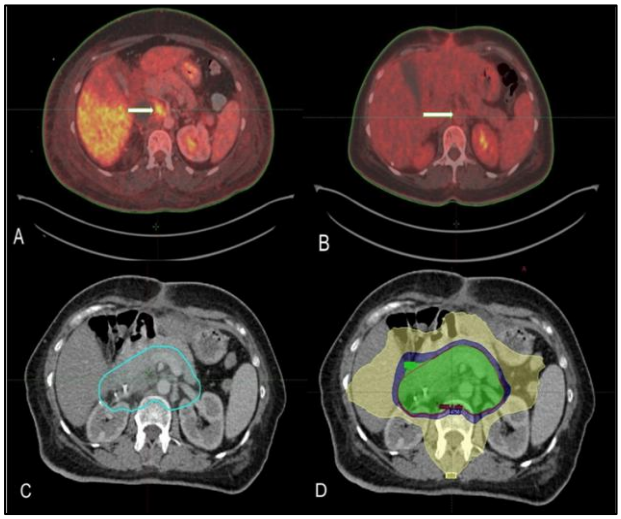

Figure 1: Axial views: A) pre-operative PET CT scan (white arrow showing FDG uptake), B) post-operative PET CT scan (absence of FDG uptake), C) treatment volume, D) dose distribution (yellow: 50% isodose of total dose, 3000cGy; blue: 95% isodose of total dose, 5700 cGy; green: 95% isodose of phase I, 4750cGy).

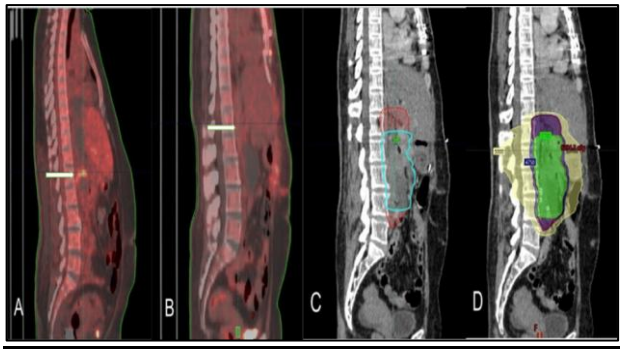

Figure 2: Sagittal views: A) pre-operative PET CT scan (white arrow showing FDG uptake), B) post-operative PET CT scan (absence of FDG uptake), C) treatment volume, D) dose distribution (yellow: 50% isodose of total dose, 3000cGy; blue: 95% isodose of total dose, 5700 cGy; green:95% isodose of phase I, 4750cGy).

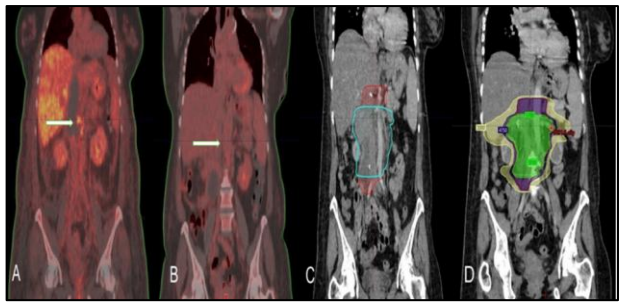

Figure 3: Coronal views: A) pre-operative PET CT scan (white arrow showing FDG uptake), B) post-operative PET CT scan (absence of FDG uptake), C) treatment volume, D) dose distribution (Yellow: 50% isodose of total dose, 3000cGy; blue: 95% isodose of total dose, 5700 cGy; green:95% isodose of phase I, 4750cGy).

The liver was enlarged with a large ill-defined lesion involving segment V, VI, VII and VIII. Normal AFP ruled out hepatocellular disease. Serum CEA and CA 19.9 were also within normal limits and CA125 was raised. After assessment for feasibility of surgery, she was operated by a team of surgical oncologist, urologist, vascular surgeon, cardiac surgeon and hepato-biliary and liver transplant surgeon. The IVC tumour with fresh clots was excised through a combined laparotomy and sternotomy approach using cardio-pulmonary bypass.

Intra-operatively, the thrombus was seen in the IVC up to the right atrium, extending into the right and left renal veins and right hepatic veins. A 3×3 cm tumor was found below the insertion of the left renal vein into the IVC, involving the IVC-renal vein junction. Frozen section histopathology was unremarkable. Surgical clips were placed to identify the target volumes for radiation therapy. Final histopathological assessment (Figures 4) revealed a high-grade spindle cell sarcoma, with large areas of tumor necrosis and high mitotic count (12-15/hpf). On

immunohistochemistry, the tumor cells expressed the smooth muscle markers h-caldeson and smooth muscle actin (SMA).

The tumor was adherent to the IVC wall and cut margins were positive. Further revision of the positive margin was ruled out and adjuvant treatment options with radical/curative intent were considered.

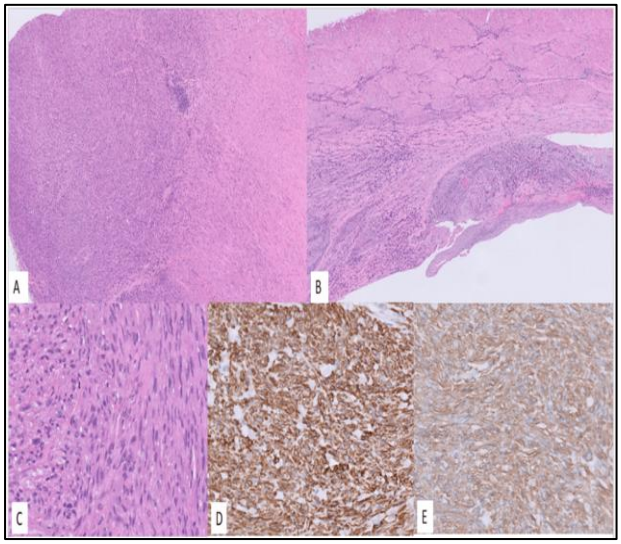

Figure 4: A) Histopathology of the specimen: Hematoxylin and Eosin (H&E) section (10X) of the tumor showing a spindle cell morphology (left side) and large areas of necrosis (right side); B) the tumor arises from and infiltrates into the wall of the inferior vena cava (10X); C) tumor showing atypical spindle cells arranged in fascicles (40X); D and E) on immunohistochemistry the tumor cells express the smooth muscle marker (SMA and h-caldesmon respectively).

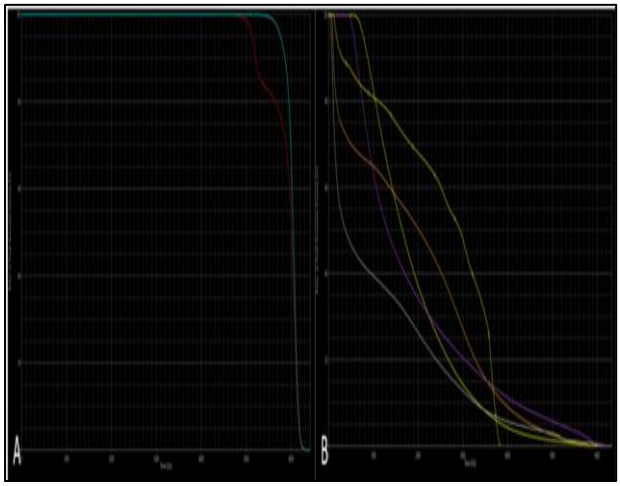

Figure 5: Dose-volume Histogram (DVH): A) treatment volumes (red: phase i; blue: phase ii); and B) organs at risk (orange: bowel; purple: right kidney; yellow: left kidney; grey: liver; green: spinal cord).

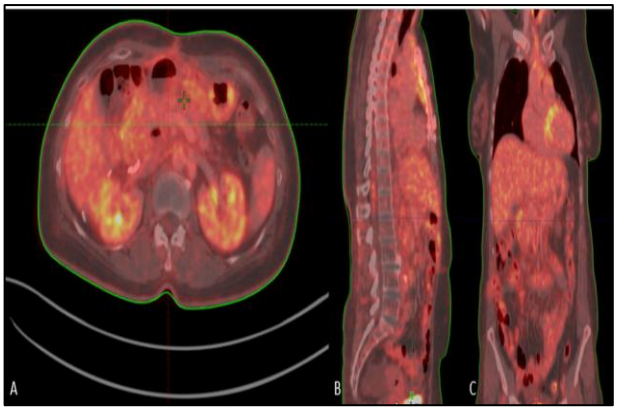

Figure 6: Follow up PET CT scan at 3 months (showing no abnormal FDG uptake): A) axial images; B) sagittal images; C) coronal images.

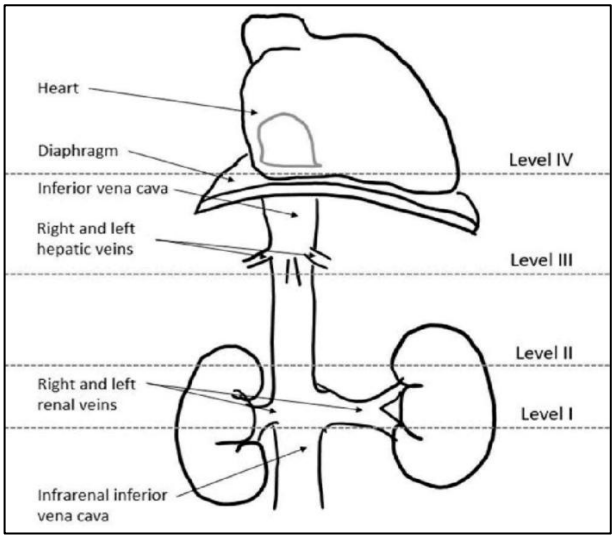

Figure 7: Different levels of origin of Leiomyosarcoma of the IVC.[8]

Post-operative PET CT scan demonstrated postoperative collection in the abdominal wall with no evidence of metastases (Figure 1, 2 and 3). She was scheduled for adjuvant radiation therapy. She was immobilized in supine position using a vacuum cushion device (vacloc) and knee rest. A planning CT scan (with contrast) was acquired in 2 mm slices using siemens somtatum scope power and was co-registered with the pre- and post-surgery PET CT scans.

Target volumes were delineated after discussion with the surgical team. The clinical target volume (CTV) incorporated the postoperative bed, contoured using postoperative changes and surgical clips and the planning target volume (PTV) was generated by giving a 5 mm margin to the CTV, (shown in Figure 1, 2 and 3). A VMAT (Volumetric Modulated Arc Therapy) plan was generated with Rapid Arc, using Varian Eclipse TPS, Version 17.0.1, with a single iso-center, 3 full arcs and 10 MV FFF (Flattening Filter Free) photons. Dose was prescribed to

100% of the PTV and target coverage was achieved with 95% iso-dose line (Figure 1, 2 and 3). The planned dose was prescribed in two phases: phase I was 50 Gy in 25 fractions, once daily, 5 fractions in a week, to the post-operative bed with adequate margins, Phase II (reduced volumes to spare kidneys and other organs at risk) was 10 Gy in 5 fractions, delivered after ensuring that phase I was well tolerated. Dose distribution is shown in figure 1, 2 and 3 respectively. Cumulative DVH (Dose Volume Histograms) for both Phase I and Phase II are shown in figure 5. 95% of total dose (50 Gy) was delivered to 100% of the Phase I PTV volume and 95% of escalated dose (10 Gy) was delivered to 100% of Phase II PTV volume. Normal tissue constraints as per standard guidelines were considered (Table 1).[5] Slightly higher doses to the kidney were accepted due to the involvement of renal vein in the treatment volumes. The treatment was well tolerated, with minimal requirement of antiemetics after the 4th week of treatment and no requirement of Steroids. She had good performance status (KPS 90%) throughout, good appetite and overall excellent general condition. A FDG PET CT scan done after 3 months of completing adjuvant treatment showed no metabolically active disease (Figure 6). However, 5 months after completing treatment, she developed multiple liver metastases and was referred for palliative systemic therapy.

Table 1: Normal tissue tolerances and achieved Dose constraints:5 V45: Volume receiving 45 Gy; D mean: Mean dose; V 20: Volume receiving 20 Gy; V30: Volume receiving 30 Gy; D max: Maximum dose received by the organ.

Organs	Dose Constraints	Constraints achieved
Bowel	V 45 Gy<195 cm3	V 45 Gy=88.2 cm3
Kidney	D mean<18 Gy	Right Kidney D mean=19.02 Gy
		Left Kidney D mean=19.06 Gy
	V 20 Gy=33%	Right Kidney V 20 Gy=34.21%
		Left Kidney V 20 Gy=36%
Liver	D mean<25 Gy	D mean=11.97 Gy
	V 30 Gy=33%	V 30 Gy=12.8%
Spinal canal	D max<45-50 Gy	D max=38.56 Gy

Table 2: Various studies utilizing adjuvant and neoadjuvant treatment modalities for management of Leiomyosarcoma of the IVC.

S. no.	Authors	Type of study	No. of patients	Year of publication	Metastases at presentation	Other treatment modalities	Ref
1	Kieffer et al[10]	Case series	22	2006	Liver metastases at presentation in some patients	Adjuvant chemotherapy and radiation therapy	10
2	Hines et al[22]	Observational study	14	1998	None	Preoperative systemic therapy and pre and/or postoperative Radiation Therapy	22
3	Reddy et al[28]	Case report	1	2010	None	Postoperative radiation therapy	28
6	Yoshizawa et al[29]	Case report	1	2023	Liver metastases at presentation	Postoperative systemic therapy for metastases	29
7	Kim et al[30]	Case series	6	2012	None	Adjuvant chemotherapy and radiation therapy	30
8	Dew et al[31]	Case series	8	2005	None	Adjuvant chemotherapy	31
9	Munene et al[33]	Case series	4	2010	None	Preoperative radiation therapy	33

DISCUSSION

Leiomyosarcomas of the IVC are more common in females as compared to males (3:1) and are common in the 5th-6th decade of life. Despite being extremely rare, Leiomyosarcomas are the most common tumors of the IVC.[6] Based on the anatomical level of IVC involved (Figure 7), they can be classified as level I (lower): infra-renal segment (IVC below the entrance of the renal vein), level II (middle): IVC located between the end of the hepatic veins and the renal veins, level III (Upper): Hepatic segment (IVC located between the Right Atrium and the

Hepatic veins).[7] A fourth segment (Level IV) may be seen in the IVC after it drains into the right atrium. Segment II (middle segment) is the most commonly affected.[4] Involvement of more than one segment is also seen. The clinical presentation can be non-specific or even asymptomatic. Most common presenting symptoms are abdominal pain, distension and deep venous thrombosis.[9] Majority patients present with pain in the right flank.[10] Other symptoms include malaise, weight loss, nausea and vomiting. Symptoms depend on the segment of the IVC involved, bulk and extent of the disease.[11] Infra-renal segment disease presents with right lower quadrant pain, back or flank pain and edema of the lower limb.[12]

The middle segment disease presents with pain in the epigastrium or right upper quadrant of the abdomen. In case of renal vein involvement, nephrotic syndrome or arterial hypertension may be seen.[12] Upper segment IVC lesions commonly present with nausea and vomiting. Cardiac symptoms may be seen in disease extending into the right atrium.[13] Some cases may present with acute Budd-Chiari syndrome due to the obstruction of hepatic venous outflow.[14]

Ultrasonography of the abdomen and pelvis is usually the first investigation and is easily available, affordable and sensitive. On ultrasound, these masses are lobulated, heterogeneously hypoechoic, with cystic components.[6] The ultrasonography also shows any gross abnormalities of the abdominal or retroperitoneal structures or gross ascites. A contrast enhanced CT scan helps in determining the tumor origin, size and invasion and shows these tumors as lobulated and heterogeneous due to hemorrhage and necrosis.[15]

The CT scan of thorax and abdomen will also assist in metastatic work up and may be accompanied by an abdominal venogram to see the filling defect and the extent of disease in the IVC. It will also demonstrate any extension into renal veins or extension into the right atrium. MRI scans are more accurate regarding tumor's location, extent and adjacent structures compared to a CT scan, conventionally using Gadolinium contrast. Gadobutrol is a high concentration gadolinium-based contrast agent which visualizes small vessels even better than conventional Gadolinium.[16] A PET CT scan is utilized in differentiating the background thrombus from an actual tumor. It also helps in determining the actual tumor extent. If the clinical picture favours a procoagulant state (thrombus) as an etiology rather than a malignancy, an FDG PET CT scan helps in diagnosing the latter.[17] Tissue diagnosis may be done through either percutaneous biopsy or trans-venous biopsy.[18] Histopathologically, these tumors demonstrate a spindle shaped bundle of cells, with high mitotic activity and positive staining for smooth muscle actin (SMA), h caldesmon, desmin and vimentin, originating from the smooth muscle cells of the media of the IVC and demonstrate three growth patterns: extraluminal, intraluminal or both.[7,19] The prognosis of leiomyosarcomas is related to the location, size and grade of the tumor. The grade grossly includes tumor differentiation, mitotic count and tumor necrosis and the chances of distant metastases increases with grade.[20] A review article concluded that radical tumor resection, presence of abdominal pain at presentation and tumor location in the middle segment of the vena cava were good prognostic factors. Factors associated with bad prognosis were inferior vena cava occlusion, lower limb edema and tumor location in the upper segment of vena cava. The worse survival in upper segment lesions was due to the technical difficulty of complete excision in upper segment tumors.[21] The surgical margins are also predictive for survival, with positive surgical margins having poorer outcomes as compared to negative surgical margins.[22]

The management is predominated by surgery. Studies utilizing adjuvant treatment modalities (radiation and systemic therapy) are limited. Majority of the literature is in the form of case reports that have demonstrated poor disease outcomes even after treatment.[23-25] In their registry Mingoli et al, in 1996 have shown the actuarial malignancy-free survival rates at 10 years to be less than 8% after wide surgical resection. They concluded that radical tumor resection was the only long-term cure.[3] The operative management of these tumors is challenging, complex, technically demanding and requires experience in vascular and visceral surgical aspects.[26] Wide tumor resection with safe distance from the tumor is the most suitable approach, to be followed by prosthetic replacement of the IVC and creating an arterio-venous fistula to ensure patency.[9,10]

Adjuvant treatment includes radiotherapy and systemic therapy. In the early 1990s, adjuvant treatment following surgical management was considered unnecessary and ineffective.[3,27] A case report where the surgical management of IVC leiomyosarcoma was not followed by radiotherapy or chemotherapy (due to low grade) reported no recurrence after 1 year follow up.[26] In another case report, no form of adjuvant treatment (chemotherapy, radiotherapy or radio-chemotherapy) was offered after en bloc surgical resection with clear surgical margins.[24]

The approach has since changed and radical resection followed by adjuvant treatment is now considered for patients without a metastatic disease.[10] In postoperative patients, adjuvant radiotherapy has shown survival benefit in various case series. Hines et al, have shown that radiotherapy did not statistically impact the overall survival ($p=0.18$), but there was significant improvement in median survival. Since this was not a randomized study, the efficacy of any particular treatment was not ascertained, but there was a trend of improved survival with chemo-radiotherapy as compared to radiotherapy alone. They concluded that aggressive surgical management combined with adjuvant therapy offers the best treatment for such patients, especially with positive resection margin.[22] The dose and treatment fields for radiation therapy have not been standardized and postoperative doses of 45 to 50 Gy have been commonly

used with conventional fractionation.[22] However, based on the nature of leiomyosarcomas of other subsites, dose escalation respecting normal tissue tolerance limits may be considered for better tumor control, with due consideration given to the performance status of the patient and distance from critical structures. A case report found dose escalation upto 60 Gy in 30 fractions to be well tolerated, with no major side effects of the skin or Gastro-intestinal system. At 5 years, the patient was found to be free of disease.[28] There is no established chemotherapy for leiomyosarcoma of the IVC. There are reports that suggest that chemotherapy does not improve survival.[29] In a case report, a postoperative pediatric patient was offered surgical resection (of the primary tumour along with liver metastasectomy), followed by multiple lines of systemic therapy after she was found to have new metastases on post op day 51.[29]

Overall, the prognosis of the disease is poor even with treatment. The 5 and 10 year actuarial malignancy-free survival rates after wide surgical resection (only) are 31.4% and 7.4% respectively in a 3 decade old registry.[3] Lately, small case series and reports have shown better disease outcomes with adjuvant therapy. A case series of 6 patients concluded that long term survival was achieved with adjuvant treatment, even if the tumors had poor pathology features. In this case series, 1 patient received only chemotherapy, 2 patients received only radiotherapy and 3 patients received radiotherapy and chemotherapy both. The 3 and 5 year survival rates were 80% and 60% respectively.[30]

Metastases are common with these tumors, commonly lungs and liver. Liver metastases may present upfront at the time of diagnosis.[32] In a small retrospective series of 4 patients, Radiation therapy was adopted as a neoadjuvant treatment modality. Patients received preoperative radiotherapy to a total dose of 45-50 Gy in 25 fractions, in 1.8-2 Gy per fraction. Prior to radiation therapy, saline filled tissue expanders were placed to displace the small bowel from the radiation fields and protect other adjacent organs. Following radiotherapy, definitive resection was performed after 6-8 weeks and the IVC was reconstructed. They found microscopically negative resection (R0) in all patients. Postoperative CT scan was done in all patients at 6 month intervals for 6 years and then annually up to 5 years. At median follow-up of 37.5 months, one patient had developed distant metastases to the lung and liver. All patients were alive at 61 months.[33]

In our patient, 50 Gy in 25 fractions was delivered to the entire post-operative bed including the post-operative changes, surgical clips and pre-operative extent of the disease. The cranio-caudal length of the treatment volume was reduced to deliver the boost of another 10 Gy in 5 fractions. Volumes were not reduced anterior-posteriorly and laterally due to the presence of postoperative changes, extent of pre-operative disease and involvement of confluence of the renal vein with the IVC. Acutely, the treatment was well tolerated. At 4 months after completing adjuvant treatment, she was in good general condition with no major complaints. However, after 5 months after completing treatment, she developed multiple liver metastases and was offered palliative systemic therapy.

CONCLUSION

Leiomyosarcoma of the inferior vena cava (IVC) is a rare malignancy with undefined management algorithms. Surgery is the predominant treatment modality. adjuvant treatment in the form of radiotherapy to the post-operative bed has shown improved disease outcome in various small studies and case reports. In our patient, adjuvant radiotherapy was offered in view of positive margin and good performance status of the patient at a tertiary care hospital in Mumbai, India. At 3 months of completing adjuvant treatment, an FDG PET CT scan showed no evidence of disease and at 4 months after completing adjuvant treatment, the patient was in good general condition with no major complaints, suggesting a promising role of adjuvant treatment for better disease outcomes in such patients. However, after 5 months after completing treatment, she developed multiple liver metastases and was offered palliative systemic therapy.

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