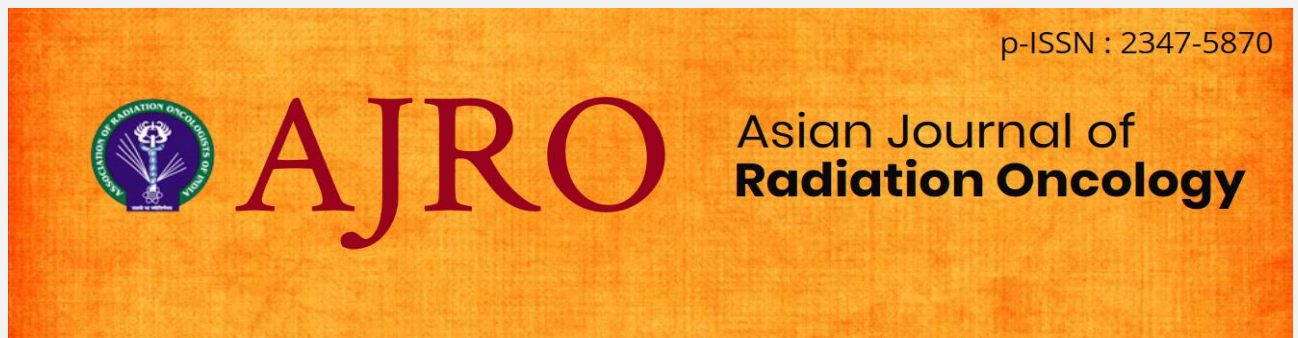




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Probing into Pancreatic Adenocarcinoma

Anil Kumar Dhull, Diptajit Paul, Rajeev Atri, Rakesh Dhankhar, Ashok Chauhan, Vivek Kaushal

Department of Radiation Oncology,

Pt. B. D. Sharma Post Graduate Institution of Medical Sciences, Rohtak-124001, INDIA

Corresponding author: Anil Kumar Dhull, PO Box 100, GPO Rohtak,

E-mail: anilkdhull@gmail.com; Facsimile: +91-1262-299999

Abstract Overall newly diagnosed cases of pancreatic carcinoma per year is 0.5 to 2.4 per 100,000 in men and 0.2 to 1.8 per 100,000 in women in India, 85% to 90% being adenocarcinoma. A number of previous studies, in different regions worldwide, have investigated the demographic profile, different treatment options and survival outcomes in patients with pancreatic cancer. The current study also focuses on same in our institute. **Aim:** Our aim is to analyse demographic profile of pancreatic adenocarcinoma along with survival. **Materials and Methods:** We retrospectively reviewed records of the pancreatic adenocarcinoma patients, who presented in Department of Radiation Oncology PGIMS Rohtak from the year 2013 to 2017 for analyzing demographic profile and survival of these patients. **Results:** Total 58-patients of pancreatic adenocarcinoma were identified, which constituted approximately 0.35% of total cancer patients. The median age at presentation was 58-years, 6th decade of life was the commonest presentation. At the time of initial presentation, 45% patients had Karnofsky performance status >70 and 12% had very poor general condition i.e. KPS <30. The most common presentation was weight loss in 55% patients. 62 % patients had metastatic disease (stage IV) and most common metastatic site was liver (48%). 33% patients were post-operative at the time of initial presentation. Majority of the patients were treated with palliative intent. Overall average survival was 5-months. **Conclusions:** Pancreatic adenocarcinoma as concluded have aggressive behaviour and only a fistful patient survived after intended treatment. More research protocols & clinical trials should be explored to improvise survival in these patients.

Keywords: Adenocarcinoma pancreas; Aggressive behaviour; Poor prognosis

Background: Pancreatic cancer is intractable malignancy with overall poor prognosis.¹ It has ranked 11th most common cancer in the world and seventh leading cause of global cancer death, more in developed countries.² Incidence in India is somehow less than worldwide data. Overall newly diagnosed cases of pancreatic carcinoma per year is 0.5 to 2.4 per 100,000 in men and 0.2 to 1.8 per 100,000 in women in India, 85-90% being adenocarcinoma.^{3,4} Pancreatic adenocarcinoma has very poor prognosis with 1-year and 5-year survival rates of 24% and 9% respectively.⁵ Numeral previous studies, in different regions worldwide, have

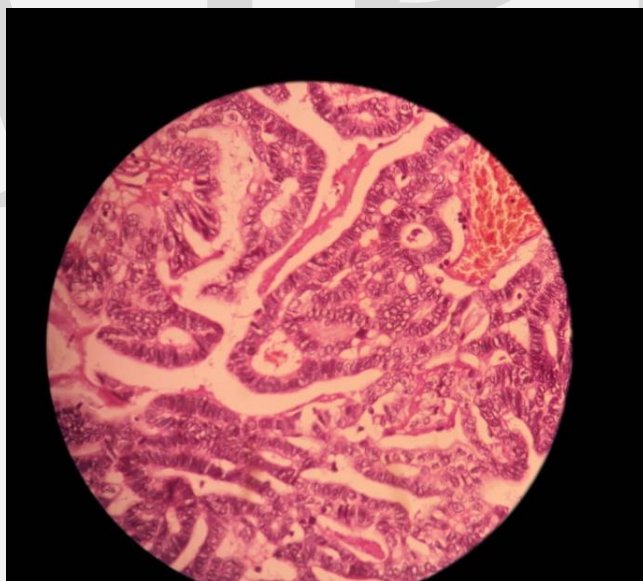
investigated the demographic profile, different treatment options and survival outcomes in patients with pancreatic cancer. The current study also focuses on same in our institute.

Aim: Our aim is to analyse demographic profile of pancreatic adenocarcinoma along with survival.

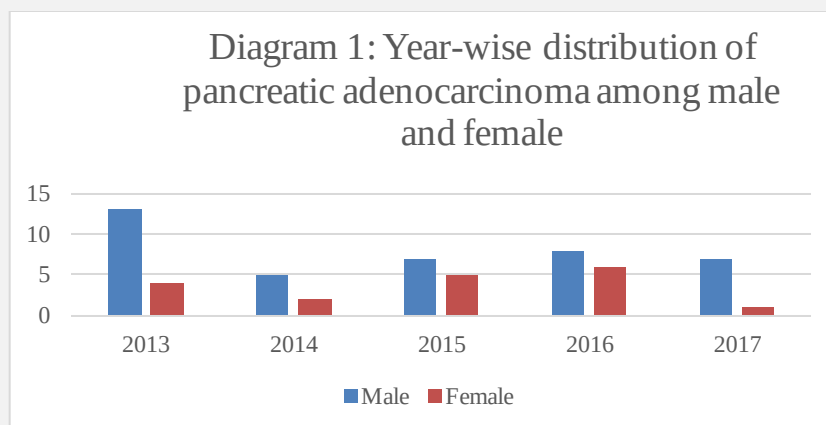
Materials and Methods: We retrospectively reviewed records of the pancreatic adenocarcinoma patients, who presented in Department of Radiation Oncology PGIMS Rohtak from the year 2013 to 2017 for analyzing demographic profile and survival of these patients. Statistical analysis was carried out using Stata 9.0 (IBM SPSS Statistics version 16.0, Chicago, IL, United States) and Microsoft Excel 2013 (15.0.5172.1000).

Results

Total 58-patients of pancreatic adenocarcinoma were identified, which constituted approximately 0.35% of total cancer patients in our department. The median age at presentation was 58-years (Range 35-85) and 6th decade of life was the commonest presentation. The overall male to female ratio was 2.2:1. The year-wise distribution of disease among both sexes is shown in diagram 1.

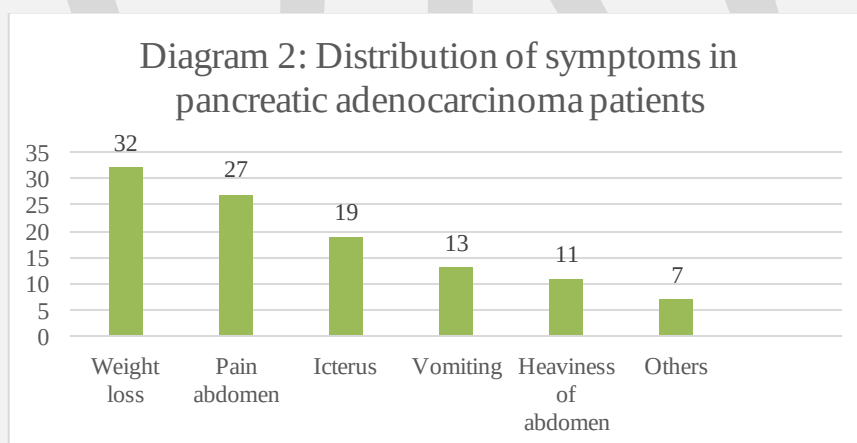


Microphotograph of adenocarcinoma pancreas ×100 magnification



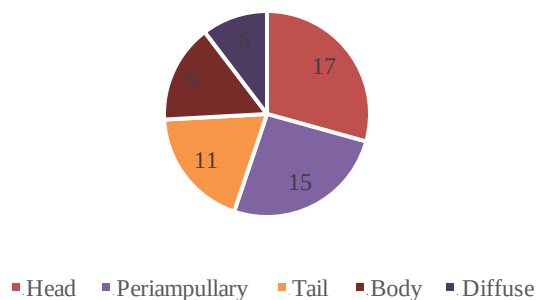
Rural to urban patients were 4.8:1. At the time of initial presentation, 45% patients had fair to good general condition i.e. Karnofsky performance status (KPS) >70 and 12% had very poor general condition i.e. KPS <30. Among all patients, 62% had a history of tobacco intake, while 40% were alcoholic.

Mean duration of symptoms were 10-months. The most common presentation was weight loss (55%), followed by pain abdomen (48%) and jaundice (33%) either alone or in combination with each other. Others symptoms included heaviness of abdomen, vomiting and dyspnoea; where presenting complaint of one patient was frequent seizure episodes. Distribution of different symptoms among patients was plotted in diagram 2.



Head of pancreas was the commonest site of presentation (29%) followed by periampullary region and tail in 26% and 17% respectively. 6 among 58-patients had a diffuse pancreas involvement. Site wise distribution is shown in diagram 3.

Diagram 3: Site wise distribution



62% patients had metastatic disease (stage IV). Liver was the most common metastatic site, others being lung and lymph nodes; two patients were presented with atypical site metastasis being brain and abdominal wall respectively. 33% patients were post-operative at the time of initial presentation. Whipple procedure is the most common surgery done in these subsets of patients.

Majority of the patients were treated with palliative intent. Gemcitabine based chemotherapy was given to most patients along with platinum compound (cisplatin or carboplatin). Erlotinib, a tyrosine kinase inhibitor (TKI), was given to some patients with variable outcomes. Radiation therapy was mainly reserved for metastatic lesions, with 3-patients received palliative radiation to chest (for lung metastasis) and one patient received whole brain radiotherapy for brain metastasis. 15-patients (26%) were lost to follow-up after initial assessment, whereas overall average survival was 5-months. Only 3-patients have complete response with average follow-up of 3.5-years.

Discussion

Pancreatic cancer is a major cause of cancer-associated mortality, with a dismal overall prognosis that has remained virtually unchanged for many decades. Pancreatic cancer is a highly lethal disease, and survival rates are worst of any tumor. Mortality closely parallels incidence i.e. mortality to incidence ratio is 98%. About 95% of cancers of the exocrine pancreas are adenocarcinomas. These cancers usually start in the ducts of the pancreas. Most patients with pancreatic cancer remain asymptomatic until the disease reaches an advanced stage, hence prevention or early diagnosis at a curable stage is exceedingly difficult. Further, these patients rarely exhibit symptoms and tumors do not display sensitive and specific markers to aid detection. There is no standard programme for screening high risk patients of pancreatic cancer. Pancreatic cancers also have few prevalent genetic mutations; the most commonly mutated genes are KRAS, CDKN2A (encoding p16), TP53 and SMAD4 - none of which are currently druggable. Although its etiology still remains unknown, many risk factors have been recognised, and among them, smoking is a known and dominating factor.^{6,7}

The improvement in overall survival with systemic chemotherapy with 5-fluorouracil plus folinic acid shown in the ESPAC-1 trial represented a step change in survival after resection for pancreatic cancer, doubling the estimated 5-year survival to 21.1% (95% CI 14.6–28.5) compared with 8.0% (3.8–14.1) for surgery alone or 10.8% (6.1–17.0) for chemoradiation.^{8,9} The ESPAC-3 trial showed that adjuvant gemcitabine is the standard of care based on similar survival to and less toxicity than adjuvant 5-fluorouracil/folinic acid in patients with resected pancreatic cancer. Other clinical trials have shown better survival and tumour response with gemcitabine and capecitabine than with gemcitabine alone in advanced or metastatic pancreatic cancer.¹⁰

Assessment of quality of life (QOL) in patients with pancreatic cancer is important because the disease is often incurable and survival is short. Pancreatic cancer in advanced stage commonly causes severe pain that requires opioid treatment and can obstruct the bile duct, causing obstructive jaundice, or the duodenum, causing anorexia, nausea and vomiting. In addition to these physical symptoms, patients with advanced-stage incurable cancer face psychological and social encounters.¹¹

Emerging treatments

Despite these challenges, innovative strategies currently in clinical trials include PEGPH20 (a pegylated hyaluronidase for stromal modulation)¹², ruxolitinib and momelotinib (inhibitors of Janus kinase (JAK) and STAT)¹³, ibrutinib (an inhibitor of the tyrosine-protein kinase BTK)¹⁴, MM-141 (an IGF1R inhibitor) and palbociclib (a cyclin-dependent kinase 4 (CDK4) and CDK6 inhibitor), among others. One of the emerging interests in pancreatic cancer therapy is immunotherapy (BOX 3) because these tumours generally escape immune surveillance through various mechanisms, including the secretion of immunosuppressive factors such as TGF β , their immunosuppressive microenvironment that is depleted of effector T cells, and less commonly their low immunogenicity due to the expression of the immune checkpoints PD-L1 and PD-L2.^{15,16} Indeed, immune checkpoint blockade to activate T cell function, is being investigated in pancreatic cancer.¹²⁻¹⁶

Conclusions

Pancreatic cancer remains a deadly disease; however, the next decade holds promise to substantially change the current dismal outlook for most patients. Key areas for basic and clinical research are advances in our understanding of the molecular pathophysiology, precision medicine. Pancreatic adenocarcinoma as concluded have aggressive behaviour with mortality to incidence ratio of 98% and only a fistful patient survived after intended

treatment. Although its etiology still remains unclear, however smoking is the main dominating factor. Most patients with pancreatic cancer remain asymptomatic until the disease reaches an advanced stage, hence more emphasis should be given for early diagnosis at a curable stage.

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RADIOTHERAPY ROLE IN SOFT TISSUE SARCOMA:

AUTHORS: Dr Pardeep Garg, Dr Raja Paramjeet Singh Banipal, Dr Manraj Singh, Dr Romi Kant Grover, Dr Sonali Karnwal.

CORRESPONDING AUTHOR: Dr Pardeep Garg.

KEY-WORDS: Radiotherapy techniques, Soft tissue Sarcoma.

ABSTRACT: Soft tissue Sarcoma are huge group of tumors arising from mesenchymal cells. Radical dose Radiotherapy alone and along with the Surgery is the standard treatment modality now a days. Whereas, due to various histological subtypes and its grading and prognostic factors, the treatment outcome can vary along with its local recurrence and overall survival rate. Treatment modality team consist of experience pathologists, radiologist, surgical oncologist, orthopedician, radiation oncologist, medical oncologists. Various Radiotherapy techniques are available to get a good control on the disease depending upon the patients choice to get surgery or not. Different sophisticated radiotherapy techniques consist of proper casting for immobilization, using different treatment planning for determining the necessity for wedges or compensating filters in the radiation field and utilizing secondary collimation. After these optimal techniques good response can be achieved.

INTRODUCTION:

Soft tissue Sarcoma are the tumors arising from mesenchymal tumors. Soft tissue sarcoma can arise from :

1. Viscera i.e. from (Gastro-intestinal tract, Genitourinary organs and Gynecological organs).
2. Non- Visceral organs i.e. muscle, tendon, adipose tissue, connective tissues, pleura).

Soft tissue sarcoma can arise at any site but the most common site are according to mentioned below in their descending order i.e. Upper extremity(43%) > trunk > lower extremity > head and neck. There are more than 50 histological subtypes of soft tissue sarcoma according to their origin from tissues, according to IHC staining. Proper history and physical examination should be taken in details as many of the subtypes have co-relation with genetic inheritance. The basic core biopsy is the important for the diagnosis of soft tissue sarcoma with IHC (Immuno- histochemistry) to get the proper diagnosis. Other basic investigation includes: MRI scan , CECT scan, PET CT scan, to rule out metastasis.

Earlier it was thought that soft tissue sarcoma are radioresistant tumors. The main treatment modality at that time was surgery by an experienced surgical oncologist. But because of preserving the extremity in cases with extremity sarcoma radiotherapy techniques were introduced that mainly comprises of External beam radiotherapy (EBRT) and the treatment was virtually always given postoperatively. Over the last decade, there has been increase trends in other techniques such as the use of preoperative radiation therapy, the use of concurrent chemotherapy combined with radiation, and the use of interstitial implant techniques i.e. brachytherapy, Intensity modulated radiotherapy (IMRT), Dose painting.

RADIATION ALONE:

The basic idea is to have a quite high local and good response by giving high dose to microscopic residual disease left after surgical dissection. External beam radiotherapy dose given for radical treatment is about 5000 cGy in pre-operative cases whereas in post-operative cases we can give up to 6600 cGy to 7000 cGy to the tumor bed along with margins. This combination of EBRT along with surgical resection of disease gives an excellent overall survival result and decreases the local recurrence rate.

There are three basic radiotherapy modalities : i.e. either radiating the tissue pre-operatively, intra-operatively and post-operatively.

1. Pre-operative irradiation helps in inactivating the 99% of cells even in a bulky lesion, the changes of tumor seeding is also reduced leading to good treatment modality overall. However, pre-op patients have good response also due to good blood supply as no tissue stress has been given by surgical intervention.

2. Intra-operative irradiation mainly includes : electron beam radiotherapy and brachytherapy. Intra-op EBRT (IOERT) mainly consists of electron therapy has good response in low grade sarcoma. Whereas, IOERT as well as Brachytherapy (BRT) have equally effective response in both high grade and low grade sarcoma. For lesion more than 5cm we prefer IOERT followed by post-op RT. Main advantage is short treatment time with cost effective. We can use HAM applicator (Harrison Anderson Mick applicator), composed of silicone, silicone-plastic, foam, or delcrin materials for the tumor bed.

Delcrin is the most rigid material and more suitable for flat surfaces, whereas foam has the most flexibility, and the silicone or silicone-plastic applicators have intermediate flexibility. The implant is secured to the tumor bed with sutures without intervening air gap or fluid.

3. Post-operative irradiation: has an advantage of evaluating full pathological panel without radiating the tissue. Main disadvantage is larger treatment volume.

RADIOTHERAPY TECHNIQUES :

SIMULATION & FIELD: Optimal positioning of patient is very important for proper irradiation. This mainly involves proper positioning of extremities according to their involvement.

Basic principles includes:

1. Maximum sparing of adjacent normal tissues.
2. For proximal thigh lesions cover genitals, perineum.
3. Spare a Strip of limb so as to prevent lymphedema and pain in that extremity.
4. Avoid treating whole thickness of bone to high doses as it leads to bone fractures in long term.
4. Avoid treating entire joint to high doses so as to prevent joint stiffness.

TECHNIQUES:

INTENSITY MODULATED RADIOTHERAPY (IMRT): mainly done to spare the adjacent normal tissues as much as possible. IMRT dose differ for post-op and pre-op patients.

Fig.1. Dose prescribed:

PRE OP RT	POST OP RT
GTV= Gross tumor	GTV = No such gross tumor.
CTV = GTV + 3 cm margin (longitudinal) +1.5 cm radially +Peri-tumoral edema.	CTV = Initial GTV+ Margins to encompass mic spread + incision site/ drain site & surgical clips. GTV to CTV margin = 2-4 mm (longitudinal) and 1.5 – 2mm (radial)
PTV = CTV + 5-10 mm	PTV = CTV + 5-10mm.

BRACHYTHERAPY(BRT): includes use of silicone applicators, foam, silicon-plastic applicator. BRT delivers high precised dose to the selective tissue which has to be irradiated. Most commonly used for retroperitoneal sarcoma, as the adjacent organs are very sensitive to lower doses. BRT was used either as single modality or as boost to EBRT in either radical or post-operative cases. Most common mode of BT delivery was interstitial brachytherapy (ISBRT).

Most commonly we use Cobalt 60 and Iridium 192 as High dose rate BRT. Basic principles of BRT are: Catether should be placed 1-2 cm away from the lateral edge of CTV and 2-5 cm in longitudinal direction. In retroperitoneal sarcoma we can also use peritoneal slings or expander to keep the small bowel away from the tumor bed. Total dose which can be given high dose rate(HDR) is 1400cGy – 1600cGy as about 3000cGy- 4000cGy twice a day for microscopic residual disease and 1800cGy- 2400cGy for gross residual disease.

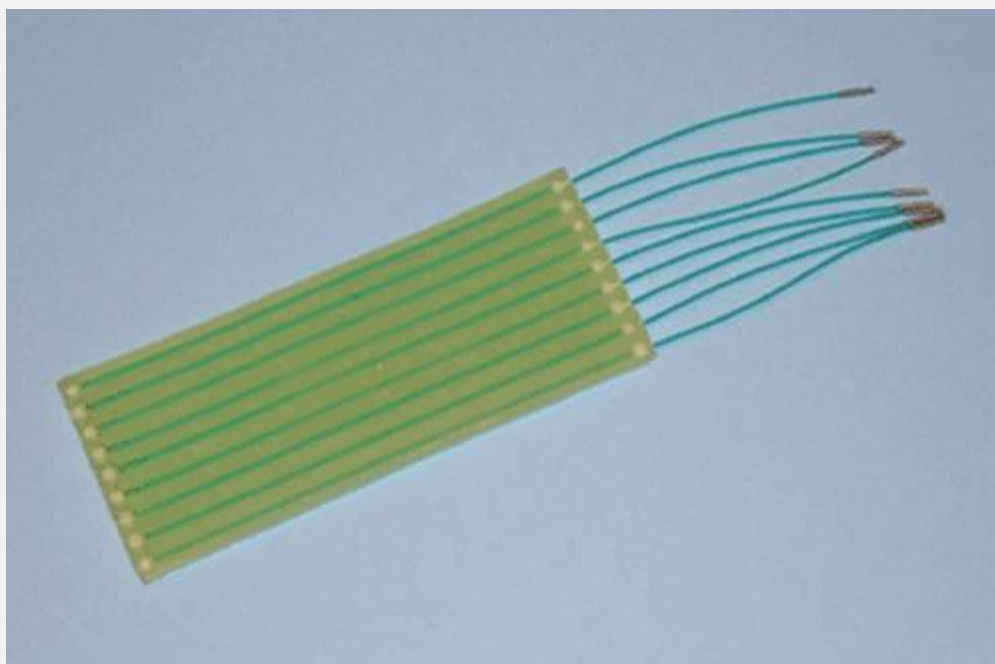


Fig.2. HAM applicator (Harrison Anderson Mick)

EXTERNAL BEAM RADIOTHERAPY(EBRT): with this techniques we can give upto 5000cGy in pre-op cases whereas for post-op cases we can irradiated upto 6600cGy to 7000cGy. In post-op cases if the margins are positive then after 5000cGy we can boost the site with microscopic residual disease upto 1600cGy to 1800cGy , and for gross residual disease we can boost upto 2000cGy to 2600cGy. Patients are generally treated with post-op radiotherapy.

DOSE PAINTING: is the technique of selectively increasing the prescribed dose to specific region within the tumor. Mainly achieved in IMRT or other conformal techniques. Dose prescribed is 45 – 50 Gy/ 25-28 # to CTV simultaneously with integrated boost to total dose of 57.5 Gy/ 25 # to high risk retroperitoneal sarcoma. By dose painting , we basically improves the biological effective dose(BED) for most radioresistant tumor by hypofractionating the area.

STEREOTACTIC BODY RADIOTHERAPY(SBRT): is the form of radiotherapy where focused photons are delivered to extracranial lesion. In soft tissue sarcoma SBRT has specific role in the treatment of oligometastatic lesion. Dose prescribed is 6000cGy -3000cGy per fraction which can be given in 1- 5 courses.

PROTONS AND HEAVY PARTICLE: photons and protons are used mainly for highly precised tumor location. Many single institute studies are published only which shows good use of Braggs' peak for treating tumors. Examples are chondrosarcoma, chordomas, paraspinal and sacral bone tumors. This technique helps in sparing adjacent normal structures as well as safe dose escalation.

IMAGE GUIDED RADIOTHERAPY(IGRT): refers to serial imaging of patient stup prior to the treatment so that accurate position adjustments can be made beforehand. Also known as “Adaptive radiation therapy” as if there is change of patients cast during treatment due to weight loss then one can go for secondary radiation plan. In short set-up errors are reduced by this technique.

CONCLUSION: Soft tissue sarcoma are wide range of tumor arising from viscera and non-visceral structures. Radiotherapy addition along with surgery have a very good response rate. With new techniques patient can have limb sparing procedure these days.

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Cutaneous Angiosarcoma of Infra-auricular Region: A Treatment Challenge

Authors : Sinha A, Garg P, Banipal RPS

Corresponding Author : Garg P

ABSTRACT

Introduction – Cutaneous Angiosarcoma is a rare, highly malignant vascular tumour. It needs to be differentiated from other common condition making the diagnosis and thus its treatment difficult. **Case report** – 74 year old male patient presented with complaints of nodular mass in the preauricular region progressively increasing in size. Histopathological diagnosis came out to be low grade angiosarcoma of the skin. Patient was treated with radical XRT. Now follow up CECT shows no residual lesion. The patient is being kept on close follow up. **Conclusion** – Angiosarcoma constitutes only 1 per 10,000 of all patients with malignant neoplasms. Owing to this, no randomized phase III trials have been performed for guiding treatment. Here we present a case of cutaneous angiosarcoma of infra-auricular region presenting as a treatment challenge.

Keywords – Cutaneous angiosarcoma, rare , XRT angiosarcoma, infra-auricular

Case report

74 year old male patient named Tarlok Singh presented to Guru Gobind Singh Medical hospital on 11/01/2019 with complaints of swelling over right side of face in front of the ear since last 6 months. There was no history of fever, vomiting, loss of weight or appetite.

On examination the swelling was present on the infra-auricular region, nodular on inspection; measuring 4 cm x 3 cm with overlying skin showing a purple-red hue. There was no palpable cervical and pre-& post auricular lymph nodes.

Fine needle aspiration cytology of the swelling performed on 14/01/2019 which showed singly scattered epithelial cells. In view of clinical suspicion, patient was subjected to biopsy on 26/02/2019. The histopathological report revealed that the entire dermis showed presence of elongated, arborizing blood vessels lined by monomorphic bland endothelial cells with prominent apical nuclei and scant cytoplasm. The above features were suggestive of a vascular neoplasm possibly low grade angiosarcoma of skin.

CECT neck (from base of skull to clavicle) was done on 13/03/2019 which showed an enhancing thickening of skin and subcutaneous region 6mm over a length of 3.5 cm in right infra-auricular region. No involvement of underlying muscles was seen. No nodal involvement was seen.

Patient was planned for XRT. Patient received Phase I – 30 Gy / 15# followed by Phase II – 22 Gy / 11 # from a period of 18/03/2019 – 25/4/2019. Patient had grade I skin reactions during radiotherapy which were managed conservatively.

Patient developed bleeding from local site one month after completion of RT. He was given 6 Gy/# on 21/05/2019 for the same.

Patient was examined at 2 weekly basis and thereafter kept on monthly follow up. The skin on examination showed post RT changed with no palpable mass.

CECT neck was done on 3/08/2019 which showed no residual lesion with post RT skin changes.

Patient is being kept on close follow up.

DISCUSSION

Cutaneous angiosarcoma is a rare, aggressive & vascular tumour. There are three clinical types of angiosarcomas – angiosarcoma of head, neck and face of the elderly and post irradiation angiosarcoma. More than 50% are limited to skin of head and neck.^[1] Angiosarcoma of the infra auricular ear is a very rare tumour.^[2-4] It is predominantly seen in white races and rarely dealt with among the coloured races.^[5]

This condition can present mimicking other common conditions like squamous cell carcinoma, basal cell carcinoma, malignant melanoma and lymphomas.^[6-8]

After histopathological diagnosis, the staging is done using TNM staging system of the American Joint Committee on Cancer. The tumour based on the pathological features is included in the staging. Localized disease is stage I or II; nodal involvement or T2 tumour with histologic grade 3, as stage III; distant metastasis as stage IV. As there is no standardized treatment algorithm for each stage, staging has little clinical benefit in the treatment decision.^[9]

Surgical resection is considered the standard treatment in sarcoma and the same is extended to angiosarcoma management. R0 resection is the goal. In a study by Shin et al,^[10] absence of surgery was shown to correlate with poor survival. In case under discussion, ENT consult was taken and after detailed discussion patient was taken up for radiotherapy instead in view of T1 stage with low grade on histopathology.

Radiotherapy alone is usually taken up as adjuvant after surgery as most patients present with advanced lesions leading to incomplete resection.^[11-13] Ogawa et al,^[14] reported that in their cohort of 25 patients who received radiation monotherapy with curative intent, 11 of 14 patients (79%) who received >70 Gy achieved local control, whereas only 3 of 11 patients (27%) who received <70 Gy did. Scott et al.^[15] did a study of 41 patients who were treated with radiation. This study recommends at least 60-65 Gy for the post-operative tumour bed and 70-75 Gy for patients treated with XRT. Other studies^[16] revealed that with improved delivery of radiation one might achieve higher efficacy.

Chemotherapy is advocated in T2 lesions in view of subclinical metastasis but trials with anthracycline-based adjuvant chemotherapy did not show any survival benefit in soft tissue

sarcomas.^[17] Similarly taxane based adjuvant chemotherapy did not reveal any clear benefit.^[18]

Chemo-RT can achieve the task to eradicate the subclinical spread after surgical resection and act as a radiosensitizer that will enhance the effect of radiation; but there is added toxicity. Although neoadjuvant and adjuvant chemotherapy may also achieve this task, no study has shown a definite benefit for this line of treatment.^[9]

Cutaneous angiosarcoma is a rare malignant vascular tumour and is predominantly seen in white skinned people.^[2] There have been very few records of cutaneous angiosarcoma in Indian patients.

Here we would like to report this case for its rare occurrence in dark-skinned people, its uncommon site of presentation and it presenting as a treatment challenge.

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Hemangiopericytoma : Rare case report

Authors : Sinha A, Garg P, Banipal RPS

Corresponding Author : Garg P

ABSTRACT

Introduction – Haemangiopericytoma is a rare, highly malignant tumour arising from pericytes around capillaries . It constitutes <1 % of all central nervous system malignancies. It needs to be differentiated from meningioma as the presentation is similar. It's rarity makes its treatment difficult as there are no guidelines for this tumour Here we present 2 cases of intracranial haemangiopericytoma presenting to our hospital as a treatment challenge. **Case report** –We report 2 cases of haemangiopericytoma- presented to us in 2018 and 2019. Both were treated with adjuvant radiotherapy. One patient is in remission whereas the other shows signs of progression. Patient with disease progression has been started on chemotherapy with Temozolomide & Bevacizumab. Patient is being evaluated for response subjectively while currently on chemotherapy. **Conclusion** –Intracranial haemangiomas are rare aggressive neoplasms. This case report depicts the rarity of this tumour & trial of chemotherapy in cases with residual disease post adjuvant radiotherapy. More cases need to be reported to further evaluate treatment.

Keywords – Intracranial Haemangiopericytoma, chemotherapy, radiotherapy

Introduction

Hemangiopericytoma is an extremely rare and unusual tumor with an aggressive natural history, accounting for <1% of all intracranial tumors.^[1-3] These are highly vascular dural-based neoplasms^[2] with a propensity for local recurrence and distant metastasis.^[3] They arise predominantly in soft tissues and very rarely in central nervous system (CNS).^[2] With radiographic resemblance to meningioma and histological similarity to soft tissue tumors, it poses a diagnostic dilemma and a therapeutic challenge. Here we present two such cases that reported to our hospital and their management.

CASE 1

A 55y old female presented to our hospital with complaints of headache for 3 years which was gradual in onset and progressive in nature. Patient a CECT head was done on April 2018 which showed an enhancing lesion measuring 3.2*2.4 cm arising from posterior one-third of falx cerebri. Patient underwent left posterior sagittal craniotomy and Simpson's Grade I excision on 2/4/2019. Histopathology report revealed (1350/2018) 16/04/2018- possibilities of Atypical Meningioma Or Hemangiopericytoma. IHC was performed which was CD34+, CD99+, Bcl-2 + & Vimentin +. The final diagnosis was Hemangiopericytoma Grade II. Patient was given 56 Gy/ 30 # with Three Dimensional Conformal Radiotherapy from 17/05/2018-26/6/2018. The MRI brain done on 09/02/2019 shows no neurological finding. Patient is stable and kept on monthly follow up.

CASE 2

A 36y old female presented with complaints of multiple episodes of focal motor seizures with on episode of Generalised tonic clonic seizure since February 2019. Patient also complained of weakness in Right lower limb weakness. A CEMRI was done on February 2019 which showed a 3.1*2.3*2.3 cm post one third falcine meningioma. Patient underwent left parietal para sagittal craniotomy & excision on march 2019. Post operative period was normal. Power in right lower limb improved after surgery. Histopathology & IHC revealed a tumour positive for CD34 & STAT6 and negative for EMA. A diagnosis of Hemangiopericytoma Grade III was made. A follow up CEMRI was done on 11/04/2019 which revealed ill defined, round to oval extra axial mass lesion seen involving left fronto-parietal / left parietal para sagittal region adjoining the falx and adherent to superior sagittal sinus measuring 2.1*1.8*1.3 cm. Patient was treated with 54 Gy / 30 # Intensity Modulated Radiotherapy from 20/05/2019-04/07/2019. In view of recurrent headaches , MRI Brain was done which showed residual disease. Patient is currently on treatment with Bevacizumab & Temozolomide. Patient is responding well to treatment subjectively.

Discussion

The term hemangiopericytoma was first described by Schmidt in 1937 and name was coined by Stout in 1942. Guthrie *et al.* gave the term angioblastic meningioma; however, WHO in 1993 changed the name to hemangiopericytoma and classified it as a distinct pathologic entity mesenchymal nonmeningothelial tumor in 2000. Most common location of intracranial HPCs is frontal, middle, and posterior fossa.^[4] They are highly vascular, occur at an earlier age than other meningeal tumours. Hemangiopericytoma occurs equally in males & females i.e. it shows no sex predilection.

There is a role of RT as definitive modality in case of surgically unresectable and inaccessible tumor or as adjuvant therapy, since this tumor tends to recur even after complete excision.^[5-7] Postoperative RT has been associated with decreased local recurrence and increased overall survival (OS).^[8] in cases of malignant HPC, the addition of radiation therapy or chemotherapy may be indicated, especially in high-grade lesions, large tumors, +ve surgical margins

In our case one patient was successfully treated with RT. The second case showed residual disease for which we have started the patient on Bevacizumab & Temozolomide. Patient is showing improvement subjectively.

Conclusion

Intracranial HPCs are rare neoplasms. The diagnostic & treatment part remains a challenge. This case report emphasises the need to explore more into various modalities for better treatment outcome.

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VON HIPPEL- LINDAU SYNDROME – A CASE REPORT

AUTHORS: Sonali Karnwal , Pardeep Garg, Raja Paramjeet Singh Banipal, Manraj Singh, Romi Kant Grover, Savita

CORRESPONDING AUTHOR: Pardeep Garg

ABSTRACT:

Von Hippel Lindau disease(VHL) is a hereditary cancer syndrome characterised by development of multiple vascular tumors. It is a autosomal dominant hereditary tumor that arises due to germline mutation in VHL gene, located on the short arm of chromosome 3. It is believed that the VHL or hypoxia inducible factor(HIF) pathway plays a key role in the pathogenesis of VHL related tumors. Dysregulation of this pathway, leading to stabilization of HIF and transcriptional activation of the target genes, which has a important role in tumorigenesis and angiogenesis. Patient with VHL may develop multiple benign and malignant tumors which mainly includes retinal hemangioblastoma, central nervous system, pancreatic neuroendocrine tumors, pancreatic cystadenoma , renal cell carcinoma (clear cell), renal cysts, pheochromocytomas. Annual incidence is 2 cases in 100,000 people. The most common primary sites involved are the gastrointestinal and bronchopulmonary tracts. Routine genetic testing and surveillance using various diagnostic techniques are used to monitor disease progression and implement various treatment options accordingly. Despite recent advances in clinical diagnosis and management , life expectancy for these patients remain low at 40-52 years. This article provides an overview of major clinical, histological, and radiological findings as well as treatment modalities.

INTRODUCTION:

Von Hippel-Lindau syndrome is an autosomal dominant , multi-organ syndrome which is caused by genetic abnormality of tumor suppressor gene i.e. VHL gene. The most common VHL associated tumors are hemangioblastoma involving brain , spinal cord, retina, kidney i.e. clear cell carcinoma, pheochromocytoma, paraganglioma and pancreatic neuroendocrine tumors (PNET). VHL affects 1 in 36,000 live births and it is an autosomal dominant inherited syndrome. Cerebellar hemangioma is the most common presenting symptoms of VHL. Most common mortality is due to the complication related to Central nervous system tumors and kidney i.e. Renal cell carcinoma.

GENETIC AND MOLECULAR BIOLOGY:

VHL gene is a tumor suppressor gene, located on chromosome 3. It encodes for pVHL that is a tumor suppressor protein. There are two isoforms of pVHL i.e. pVHL 30 and pVHL 19, and both isoforms are important for tumor suppressor effects of the VHL gene.

While majority of VHL cases are familial, there are 20% cases of VHL occurs due to sporadic mutation. In affected individuals, germline mutations of gene are present in all cells of the body which is considered as first hit; however , only those cell types with a somatic

inactivation of normal allele are inclined to tumor formation which is the second hit. Thus VHL follows Knudson's two hit hypothesis of hereditary tumorigenesis as in retinoblastoma.

Management of VHL associated tumors requires multidisciplinary approach, and advances in genetic testing have led to early diagnosis of the syndrome.

VHL DIAGNOSIS:

A VHL diagnosis can be made clinically with the proper clinical history, family history and complete examination. The clinical diagnosis can be made in following circumstances:

- ❖ In a patient with family history of VHL and at least one of the characteristic presentation i.e. retinal HBs, CNS HBs, clear cell RCCs, pancreatic NETs and endolymphatic sac tumors.
- ❖ In the presence of two or more retinal or CNS HBs.
- ❖ In the presence of retinal or CNS HB, with at least one of the characteristic VHL related visceral tumors, excluding renal and epididymal cysts.

Genetic testing for heterozygous germline VHL mutation may also confirm the diagnosis. Current indications for genetic testing include:

- ❖ Patient with suspected clinical diagnosis of VHL.
- ❖ Patients with close relatives in an established VHL family.
- ❖ Patients with moderate suspicion for VHL who do not satisfy all criteria for clinical diagnosis, which include simplex cases with one retinal or CNS HB, pheochromocytoma or an endolymphatic sac tumor.

CASE REPORT:

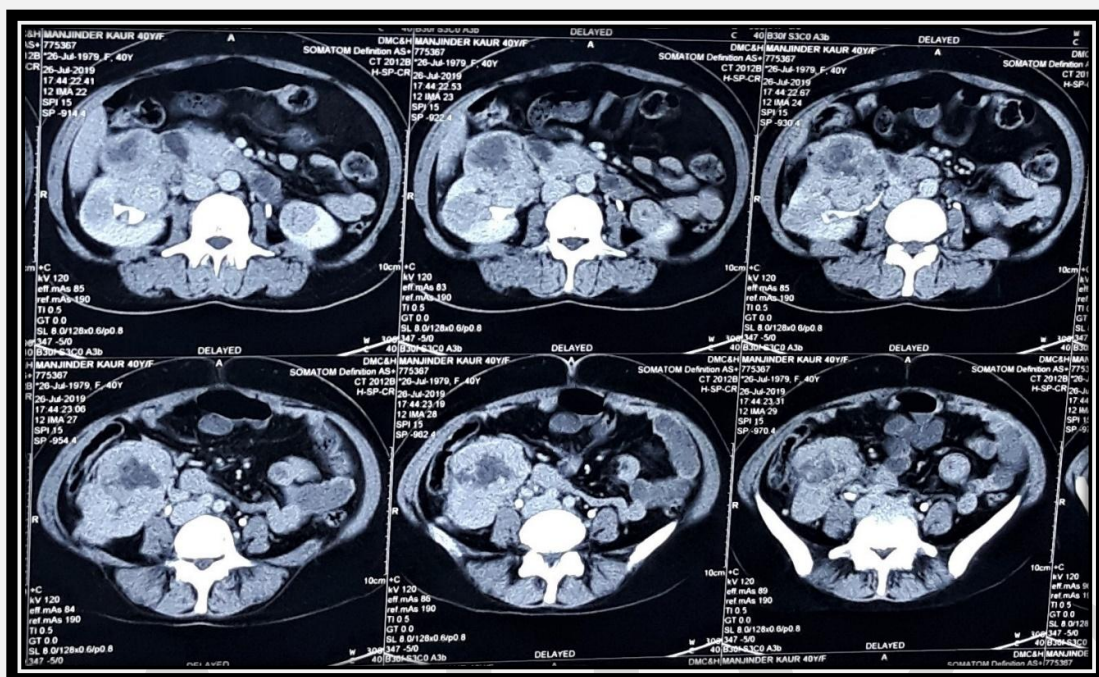
This case has been reported at GURU GOBIND SINGH MEDICAL COLLEGE HOSPITAL, FARIDKOT, with an informed consent was obtained from the subject.

HISTORY AND EXAMINATION

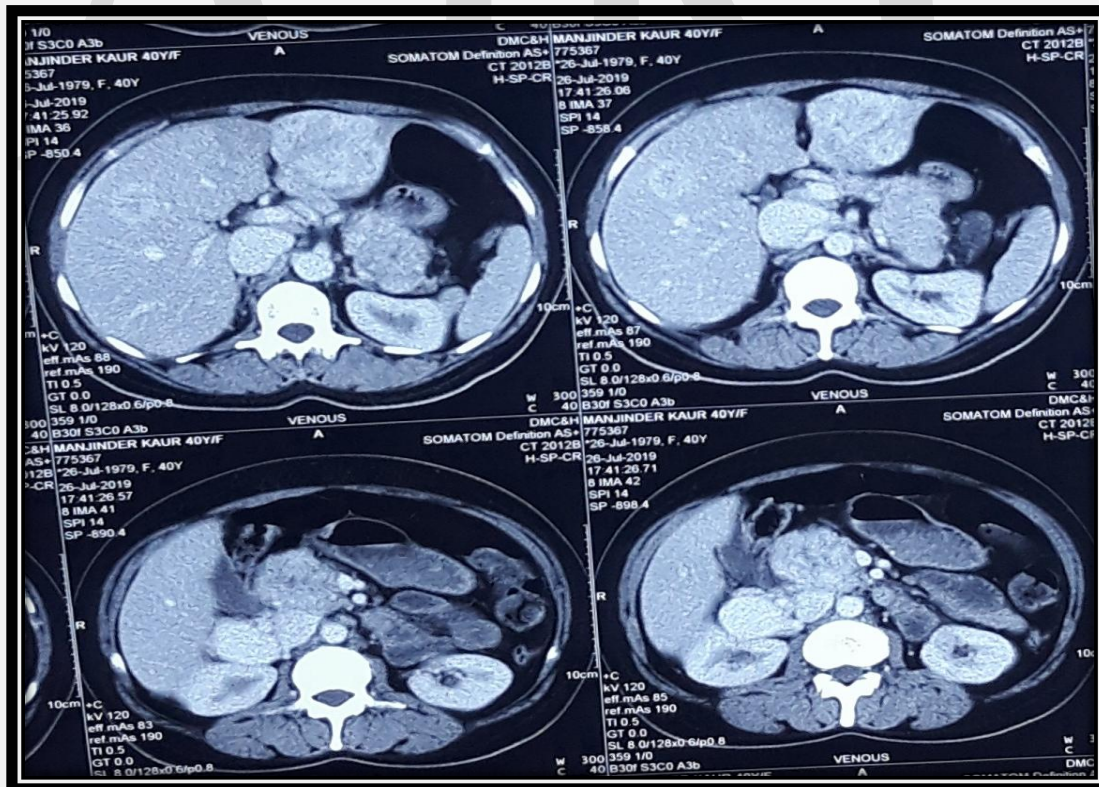
The patient is 43 years old female with history of sudden loss of weight (15-16kg in 3-4 months), intermittent fever from the past 3- 4 months, with non specific abdominal pain. There are also episodes of headaches, sweating.

Patient underwent a MDCT SCAN whole abdomen and chest reveals following lesion i.e. lobulated central non enhancing lesion in right kidney involving mid and lower poles and is bulging exophytically measuring 9.6 X 7.3 X 6.0 cm in size. Left kidney has 4.0 X 2.8 cm lesion at lower pole. Liver showed multiple non enhancing area in both lobes of liver with largest measuring 5.4 X 4.2 cm. Pancreas also has multiple arterial enhancing lesion involving head, neck, body measuring 6.3 X 3.5 cm. A lobulated right adnexal mass measuring 5 X 6 cm. Right lower lobe postero-basally 8.3 X 9.2 cm mass. Patient underwent USG guided FNAC from right renal mass revealing malignant pathology features suggestive of clear cell carcinoma. USG FNA Liver SOL dated 17-08-2019 shows positive for malignant

cells. CECT SCAN head reveals no signs of CNS HB's. Fundus examination reveals no Retinal HB's signs.



CECT SCAN Abdomen: Asymptomatic renal carcinoma in von Hippel-Lindau disease, with intravenous contrast from a 43-year-old female.



CECT ABDOMEN : Pancreatic mass in asymptomatic 43 year old female.

Patient is started on tablet SORAFENIB 400 mg BID after diagnosis and on regular close follow up.

DISCUSSION:

When a diagnosis of von Hippel-Lindau disease is made, it is recommended to screen all the at-risk members, such as first degree relatives, of the family throughout their lifetimes to get a early diagnosis. Asymptomatic parents, siblings and children of affected individuals were advised to have regular baseline investigation such as abdominal CECT scans, spinal and brain MRI, ophthalmologic examination once a year for lifetime. If a germline VHL mutation is detected, that individual should be periodically examined for manifestations of the disease taking the specific mutation into account, as well as the age specific incidence of VHL tumors. Genetic counselling, which includes explaining in detail the potential risk of getting detected with one of the manifestation of syndrome in the offspring are done. A guided reproductive options is appropriate for young adult patients who are affected or at risk.

CONCLUSION:

VHL is a multisystem cancer syndrome with common manifestations affecting the CNS and several visceral organs. Management of VHL syndrome is complex and requires a multidiscipline team. Routine surveillance for common VHL manifestations is used to monitor disease progression and help guide treatment for tumors that can possibly metastasize. As VHL has many endocrine manifestations, patients require regular follow-ups and interventions after undergoing treatment.

KEY WORDS: Von Hippel Lindau Syndrome, genetic counselling, targeted therapy.

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Malignant Intracerebral Nerve Sheath Tumors: A Case Report with Review of the Literature

Authours: Priyanka P¹, Garg P², Benipal RPS³, Kang M⁴, Grover R⁵

PG Resident¹, Associate Professor², Professor and head³, Assistant Professor⁴, Assistant Professor⁵, Department of Radiation Oncology, Guru Gobind Singh Medical College and Hospital Faridkot, Punjab, India

Email: parulpriyanka786@gmail.com

Abstract :

Background: MPNSTs are very rare tumors with incidents of approximately 0.001% in the population. surgery is the primary modality used to treat MPNSTs of the head and neck, with complete surgical excision of the tumor with negative margins. Given the relatively small space within the head and neck, the proximity to vital structures, and the potential for microscopic local spread, obtaining negative margins can be difficult to high rates of local recurrence and distant metastasis and thus a multimodality treatment approach is most favorable. In addition to surgery, many studies have cited the importance of radiotherapy as adjunctive treatment, especially for improving local control.

Case history: A 45yr old male presented with complain of nasal blockage, frontal headache. His CECT head revealed heterogenous mass in the left frontal lobe crossing mid line with mass effect. He underwent bifrontal craniotomy and gross total excision of the mass. His post operative histopathology report was suggestive of grade IV gliosarcome and further immunohistochemistry panel suggested malignant peripheral nerve sheath tumour. He recieved cumulative dose of 70Gy to frontal and ethmoid sinus. The patient is on regular follow up at our institution with recurrence free interval of 26 months. **Conclusion:** adjuvant radiation increases local control in high grade MPNSTs. **Keywords:** Excision, IHC, radiation.

Introduction:

Malignant peripheral nerve sheath tumors (MPNSTs) are rare high-grade sarcomas arising from peripheral nerves or cells of the peripheral nerve sheath [1, 2]. They account for approximately 5–10% of all soft-tissue sarcomas, with only about 8–16% occurring in the head and neck region [2–7]. They are commonly associated with neurofibromatosis type 1 (NF1), an autosomal dominant disorder resulting from the defective tumor suppressor protein neurofibromin, but can also arise through sporadic mutation [7, 8]. Based on historically high rates of local recurrence and rapid disease progression, the prognosis for MPNSTs is generally poor despite aggressive therapy [7, 8].

Clinical case:

A 45yr old male presented in our OPD on 03/07/2017 with complain of nasal blockage, frontal headache. The patient underwent through ENT examination but no suspicious finding was obtained and he was initially managed as a case of sinunasal headache. Patient got

symptomatic relief for two to three days after that his headache started worsening and he again presented with the above mentioned symptoms with increased severity. His CECT head revealed heterogenous enhancing 7×6 cm mass in the left frontal lobe crossing mid line containing multiple cystic areas within with mass effect on underlying cerebral sulci (Figure 1&2). The patient underwent bifrontal craniotomy and gross total excision of the mass on 02/09/2017 at the department of neurosurgery at our institute. His post operative histopathology report was suggestive of astrocytic neoplasm (possibly grade IV gliosarcoma) (Figure 3). A further immunohistochemistry panel suggested spindle cell sarcomatous neoplasm possible malignant peripheral nerve sheath tumour and the tumour cells were strongly positive for vimentin, CD99, EMA and MIB labeling was high (12-15%) and negative for CD34, cytokeratin and GFAP. Due to high grade adjuvant radiation therapy was recommended to improve local control. One month after surgical resection, five weeks of radiation therapy was delivered to the frontal and ethmoid sinuses at a cumulative dose of 70Gy. The treatment was well tolerated; complete remission was achieved. The patient is on regular follow up at our institution with recurrence free interval of 26 months. His last MRI brain on 28/08/19 showed post operative changes with gliosis and no recurrence or residual mass was identified (Figure 4). The patient is doing well and has no neurological deficit.

Discussion:

MPNSTs are very rare tumors with incidents of approximately 0.001% in the population [3, 9]. These tumors usually affect the proximal extremities and trunk and are very rare in the head and neck [6, 10–12]. They usually arise in adulthood, with most occurring around 20–50 years of age [13]. MPNSTs can occur sporadically or in patients with NF1. For patients with NF1, the lifetime risk of developing a MPNST is much higher at approximately 10% [12, 14]. Clinically, these tumors usually present as an enlarging palpable mass with or without pain [15, 16]. Based on the internal nature of our patient's head and neck MPNSTs, the presenting symptoms (severe headaches, diplopia, airway obstruction, etc.) are related to the tumor's anatomic location as it enlarged. Similar to most soft-tissue sarcomas, surgery is the primary modality used to treat MPNSTs of the head and neck, with complete surgical excision of the tumor with negative margins correlating with longer overall survival [2, 6, 7, 18–21]. However, given the relatively small space within the head and neck, the proximity to vital structures, and the potential for microscopic local spread, obtaining negative margins can be difficult. These factors have led to high rates of local recurrence (22% to 52%) and distant metastasis (18% to 33%) and thus a multimodality treatment approach is most favorable [2, 22–24]. In addition to surgery, many studies have cited the importance of radiotherapy as adjunctive treatment, especially for improving local control [2, 15, 18, 20, 24–27]. The radiation dose commonly administered in studies is 50–60 Gy. The oncology consensus group, as part of a uniform treatment policy for MPNSTs, recommends adjuvant radiotherapy for all “intermediate- to high-grade lesions and for low-grade tumors after a marginal excision” [18]. Though the consensus group states that radiotherapy only provides local control and has little effect on long-term survival, some more recent studies have also reported survival benefit [2, 15, 24, 28]. Based on the rarity of head and neck MPNSTs,

survival and prognostic data in the literature is mostly limited to case reports and smaller series. In the literature of the past 10 years, the 5-year overall survival and disease-specific survival rates for head and neck MPNSTs have ranged from approximately 28% to 40% and from 20% to 44%, respectively [2, 21, 23, 24, 35, 36]. In analyzing MPNSTs from all body sites, most studies agree that the significant prognostic factors for survival include surgical margin status and tumor size [2, 9, 20, 21, 27, 32, 37, 38]. Some also report that histologic grade is significant with high-grade status relating to a poorer prognosis [15, 20, 27, 32, 37].

A more controversial topic is whether NF1 status significantly affects prognosis, as there have been conflicting reports. Evans et al. and Sordillo et al. found 5-year overall survival rate differences of approximately 20% between their patients with NF1-associated MPNSTs compared to sporadic cases, with the NF1-associated group having the poorer rates [14, 34]. In more recent studies, Anghileri et al. and Lafemina et al. both reported no significant difference in the survival rate of their patients with NF1-associated MPNSTs compared to their sporadic MPNST patients [2, 38]. A recent large survival meta-analysis by Kolberg et al. also came to the same conclusion [32]. This convergence in rate over time could be due to improved early recognition and diagnosis of MPNSTs in NF1 patients as well as improved treatment strategies overall.

Our case series describes significantly better outcomes than those reported in the literature. These high rates of recurrence-free survival are most likely due to obtaining negative surgical margins as well as utilizing adjuvant radiotherapy. As stated previously, the increased radiation treatment dose delivered may also have contributed to decreased recurrence rates.

Conclusion:

This case series reports on three instances of MPNSTs of the head and neck. Since they are very rare neoplasms, literature remains sparse on the prognostic factors and ideal treatment methods to control these tumors. While surgical excision with negative margins and radiation therapy seems to be the current mainstay, the prognosis historically remains poor. Nonetheless, careful follow-up in patients with NF1 and timely diagnosis and treatment is necessary. Research into new therapies, including possible molecularly targeted therapeutics, needs further study in order to continue to improve local control and survival rates.

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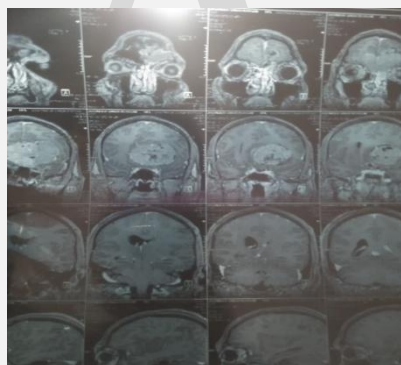


FIG 1

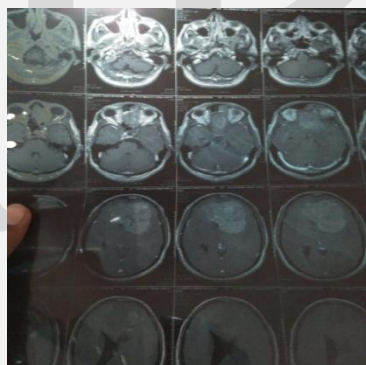


FIG 2

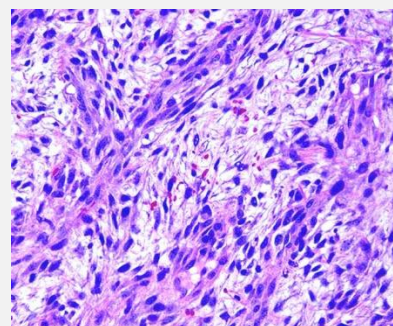


FIG 3

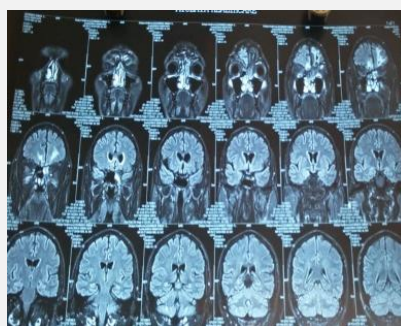


FIG 4



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