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Role of Adjuvant Radiation in Adrenocortical Carcinoma

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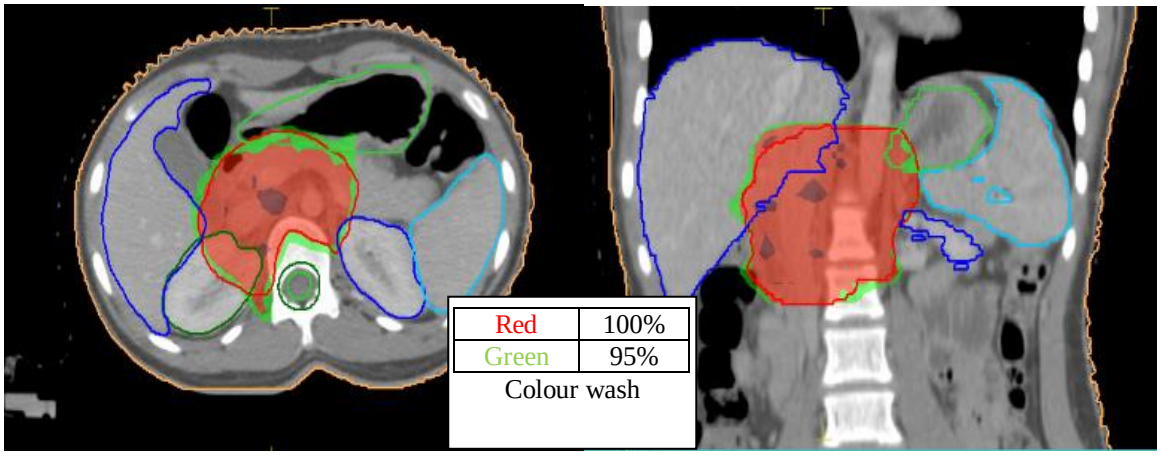
Abstract:-Adrenocortical carcinoma (ACC) is a rare and highly aggressive disease with higher rate of recurrence and poor survival. The main treatment is primary surgical resection with or without mitotane therapy. The role of radiation therapy is still controversial.Radiotherapy has limited role due to the risk of normal tissue toxicity, as the proximity of the adrenals to radiosensitive structures, like kidney, stomach, intestine, and spinal cord. However, newer techniques have made radiotherapy (RT) safe and effective for use in the management of adrenal carcinoma. Adjuvant radiation has shown a recurrence free survival by 18%. We hereby presenting the case series of 3 patients treated with adjuvant radiation that had good long term outcome.

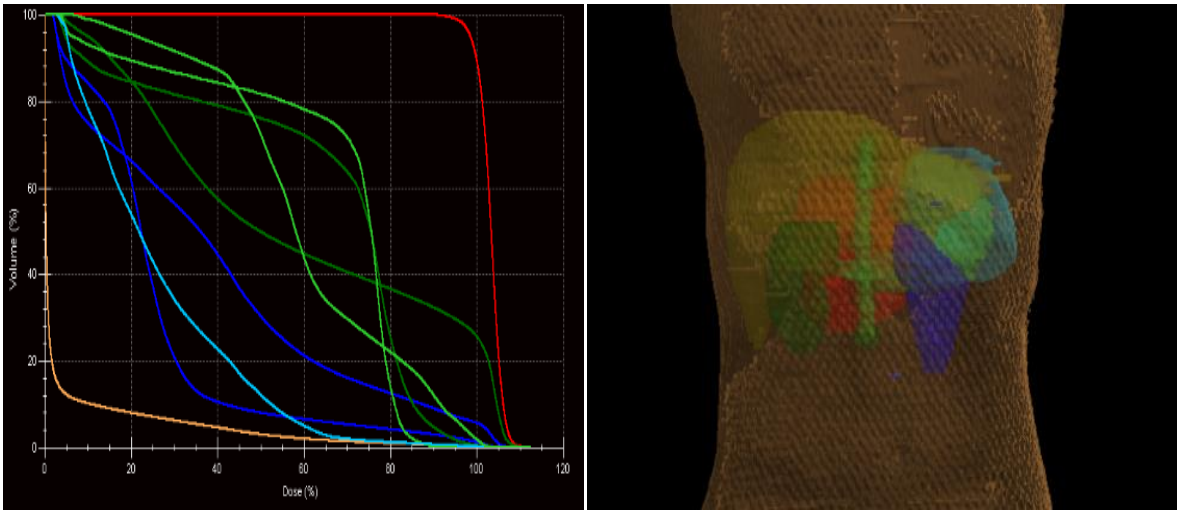
I. INTRODUCTION

Case-1

14 years aged girl with no co-morbidities presented with complaint of change in voice since 1 year, increased body and facial hair since 1 year and absent of menarche. She visited a local hospital and evaluated her T3 level was 162.7,T4-4.8, TSH- 1.3, Prolactin-13.9,Testosterone-7.21 and on USG done on 09/11/2020 ,found to have heterogeneous suprarenal mass with significant vascularity, ?adrenal hyperplasia with B/L polycystic ovaries with small sized uterus . On MRI-10.7 X 7.5X 7.4 cm round solid mass above kidney-in right adrenal gland. She was referred to urology department in MS Ramaiah medical college. On examination, per abdomen there was mild tenderness over right lumbar region, no organomegaly. External genitalia-ambiguous genitalia; there were no systemic findings on examination. Endocrinology reference was sought ,she was advised to check hormonal status: DHEA sulphate which was 71500,S.testosteone-7.57,S.cortisol-0.7 and after endocrinology clearance patient underwent laproscopic guided right adrenalectomy under GA on 03/12/2020.Post operative HPE- suggestive of adrenal cortical carcinoma,weiss criteria-tumor necrosis–present,mitotic rate>5/50 hpfpresent,atypical mitosis-present,high nuclear grade –present,diffuse architechure-present ,<25% clear cells –present,sinusoidal invasion –present,capsular invasion present , stage pT3N0-stage III and patient advised for IHC(immunohistochemistry) markers of Inhibin,chromgranin,Vimentin and calretinin and Ki-67. Medical oncology reference was sought and adviced for metastatic work up and given a option of Mitotane therapy for 2-5 years but patient refused for the same because of non affordability. After multidispilnary tumor board decision,patient was planned adjuvant radiation.After taking informed consent, patient was planned for IMRT to a dose of 45Gy/25fr/5 Fr week followed by boost 5.4 Gy/3 Fr on 6MV. PET-CT (29/12/2020)- 4.6X 1.5X 1.2 cm hypo dense well defined lesion in suprarenal region suggestive of residual disease. Prior to RT planning, DTPA (diethylenetriaminepantaacetic acid) scan for renal function assessment, patient refused for the same. Endocrinology reference sought and advised for genetic testing and repeat hormones level. After immobilization with pelvic thermoplastic, CT simulation done and images were transferred to planning system. Target volumes: Gross tumor volume (GTV) was contoured as per PET-CT uptake which was expanded by one cm margin including post op bed, draining lymph node (aorto-caval) and renal hilum to give clinical target volume (CTV).Planning target volume (PTV) was given by expanding 5 mm margin to CTV. Dose constraints were given to organ at risk (OAR) as per QUANTAC data: Left and right kidney (each) D33 <30,D67<50,mean dose to both kidneys 15 Gy, stomach max dose<45 Gy, liver V20<30 Gy with priority 1 given to kidneys. On plan evaluation,coverage of around 90% with mean dose to bilateral kidneys 12 Gy,maximum dose to Stomach 46 Gy. Plan was accepted in view of acceptable coverage and limited dose to OARS. Treatment verification was done with electronic Portal Imaging devices (EPID) (picture 1A,1B and 2A,2B).There was absolute no toxicity. Patient tolerated treatment well. She still on follow up.Long term can not comment.



Picture 1A- Coverage(axial plane) Picture:1B Coverage (Sagittalplane)



Picture 2A- DVH (Dose volume histogram) Picture 2B- BEV(Beam eye view)

Case-2

A 55 years aged lady known diabetic and hypertensive on medication for the past one year presented with history of vomiting and nausea since 1 month in October 2013.She had history of fall causing collapse of L2 vertebrae for which she was evaluated. On examination there were no mass findings, ultrasonography revealed mass per abdomen in suprarenal region. Biopsy from L2 vertebrae –negative for malignancy .She underwent left adrenalectomy with lymph node dissection on 27/11/2013.Post operative HPE revealed adrenocortical carcinoma;size -16X 15 cm; capsule breach;node positive; margins not evaluated.Patient referred for adjuvant radiation. Endocrinology reference was sought and patient's hormone levels were checked: S.testosterone,dihydrotestosterone,s.cortisoletc) and advised was followed.

After multidisciplinary tumor board decision patient was planned for adjuvant radiation to the dose of 45Gy in 25 fractions/5 fr/week followed by 5.4 Gy/3 Fr(Boost) using IMRT technique on 6 MV LINAC.Prior to radiation planning DTPA (diethylenetriaminepantaacetic acid) scan was done to assess renal function which was found to be normal.After RT planning, PET CT detected lesion was contoured as gross tumor volume(GTV) and clinical target volume was contoured by expanding GTV by 1 cm including tumor bed with extensions to include preoperative tumor volume and draining lymph nodes (aorto- caval) and it was trimmed from left kidney and liver. Planning target volume(PTV) was created by giving seven mm margin to which 45Gy/25Fr was prescribed.PTV boost was created by expanding five mm margin to GTV. Coverage of 94% Vs 92% was accepted which reduced the mean dose to right kidney from 24 Gy to 15Gy Patient withstood the treatment well with grade I enteritis. She is on regular follow up and at 6 years years, there is no evidence of any disease.

Case-3

A 37 years aged lady with no co-morbidities presented with complaint of pain abdomen and increased facial hair since 3 months in august 2014. On examination there were mass felt in left side of abdomen, ultrasonography revealed mass per abdomen in suprarenal region.She underwent left adrenalectomy with lymph node dissection on 12/10/2014. Post operative HPE revealed adrenocortical carcinoma; size -16X 15 cm; capsule breach; node positive; margins positive. Patient referred for adjuvant radiation. Endocrinology reference was sought and patient's hormone levels were checked: S. testosterone, dihydrotestosterone, s.cortisoletc) which were high and advised was followed.

After multidisciplinary tumor board decision patient was planned for adjuvant radiation to the dose of 45Gy in 25 fractions/5 fr/week followed by 5.4 Gy/3 Fr (Boost) using IMRT technique on 6 MV LINAC. Prior to radiation planning DTPA (diethylenetriaminepantaacetic acid) scan was done to assess renal function which was found to be normal. After RT planning, PET CT detected lesion was contoured as gross tumor volume(GTV) and clinical target volume was contoured by expanding GTV by 1 cm including tumor bed with extensions to include preoperative tumor volume and draining lymph nodes (aorto- caval) and it was trimmed from left kidney and liver. Planning target volume (PTV) was created by giving seven mm margin to which 45Gy/25Fr was prescribed.PTV boost was created by expanding five mm margin to GTV. Coverage of 89 % was accepted with mean dose to left kidney 14.4 Gy, mean dose to combine kidney (left and right) was 14 Gy. Patient withstood the treatment well with grade I enteritis. She is on regular follow up and at 5years, there is no evidence of any disease with no long term toxicity.

II. DISCUSSION

ACC may present differently in children and adults. In children virilization the most common presenting symptom, followed by Cushing syndrome with androgen overproduction and precocious puberty .Among adults presenting cushing syndrome is most common.Most common symtoms are weight gain,musclewasting,excess facial and body hair,acne,enlargement of clitoris and voice change.[(1)] Out of two, our 1 patient had a lesion in left suprarenal lesion presented with above symptoms usually diagnosed in advanced stages with overproduction of steroid hormones due to tumor secreting excess hormones where as other patient presented with nausea vomiting and it was incidental founding in USG scan. Since it is rare and if above symptoms are not present are not present, they are diagnosed incidently in 15% cases[(2)].

Surgery remains the main modality for ACC ,however even R0 resection,30% patients fail loco regionally[(3)(4)(5)]. Which is associated with poor long term survival[(6)]. With this background, adjuvant radiation with or without mitotane (adrenolytic agent) has been tried ,has showen significant improvement in overall survival with adjuvant radiotherapy[(7)].

ACCs are rare tumors and have been considered a radio resistant tumor and adjuvant RT has often been omitted in ACC patients. In the Metaanalysis by JiaweiZhu ,results showed showed that compared to only surgical resection, adjuvant RT is an effective postoperative treatment for ACC[(7)].

Fassnacht et al. compared adjuvant RT with no adjuvant treatment after surgical resection in ACC in Germany database. According to tumor stage, margin status, and tumor size, 14 patients submitted to RT and 14 were included in control arm (only surgery without adjuvant RT).The results showed a significant impact of adjuvant RT on local recurrence, but with no effect on disease survival and overall survival[(8)].

Retrospective study of 32 patients done in 2012 by M.D Anderson concluded that there was no benefit with adjuvant RT in outcome. Although they managed to balance the groups according to tumor size, adjuvant mitotane, and margin resection, the main bias of the study was the referral bias, most of the patients were treated outside MDACC[(9)]. Authors from Michigan Cancer Center analyzed compared 20 patients treated with adjuvant RT versus 20 patients with the only surgery. In this study, they showed significant impact of adjuvant RT on the local control, but with no effect on disease recurrence in other sites or survival[(10)].The Germany study treated their patients with conformal RT on Linear accelerator using 6-18 Mev with median dose 50.4 Gy (range 36–59.4 Gy) in 25 fractions (range: 20–30)[(8)]. The study from Michigan used intensity-modulated RT (IMRT) in 15 patients, and conformal RT to the others.The median dose was 55 Gy (range 41.4-56)[(10)].Srougi et al. only also reported the median dose used (54 Gy median, range: 45–54 Gy) with no information about treatment technique, target volume, or treatment machine[(11)]. In present study we treated both patients with IMRT technique using the dose of 45 Gy in 25 fractions followed by boost to residual disease or post op bed with positive margins (R1/R2 resection) or capsule breach during surgery to the dose of 5.4 Gy in 3 fractions.

The Germany study reported the acute toxicity as per common toxicity criteria (CTC) criteria in 14 patients. In this study, the authors observed 8 patients had nausea Grade I or II, and 4 patients had dermatitis Grade I. Late toxicity was also reported with 1 case of impaired kidney function and 1 case of partial Budd–Chiari syndrome[(12)(13)]. MDACC study, authors observed 9 patients nausea Grade I or II, 5 patients presented fatigue Grade I or II, and 1 abdominal pain. They did not provide any information on late toxicity[(9)].We observed grade 1 enteritis in two patient ,rest one patientdid not show any toxicity .On 5 year follow up, two patients survived.2 year disease free survival was 100%,none of patient presented with local recurrence. Hence, given a rarity of tumor; adjuvant radiation is very effective and safe modality in ACC in adjuvant setting, however larger scale study required to comment on survival.

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