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ADRENOCORTICAL CARCINOMA

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Abstract: - Adrenocortical carcinoma (ACC) is a rare, heterogeneous cancer with a poor prognosis and an unclear origin. The incidence of adrenocortical carcinoma (ACC), a rare cancer, ranges from 0.7 to 2.0 incidences per million people per year. 15% of patients with ACC initially receive an incidental diagnosis, however the majority of patients present with excess steroid hormone or abdominal mass effects. Here we summarize the knowledge about diagnosis, epidemiology, pathophysiology, and therapy of ACC. Before surgery and after tumour excision, thorough examinations of clinical, biochemical, and imaging aspects are required for the diagnosis of malignancy. Different tools are suggested after the diagnosis in order to evaluate the prognosis for ACC and create a sound foundation for treatment choices. The total removal of the tumour is the primary option for treatment when the tumour is restricted to the adrenal gland. New targeted medicines, such as IGF-1 receptor inhibitors, have been researched in recent years, but their effectiveness is still restricted. We will have a better grasp of the pathophysiology thanks to the ongoing "omics methods" and next-generation sequencing, which should also result in better treatments.

Key words:- adrenocortical carcinoma(ACC), ENS@T staging, prognosis, mitotane, target therapy.

1. Introduction: -

Adrenocortical carcinoma (ACC) is a malignant tumour formed from the adrenal cortex that is uncommon, aggressive, and has a poor prognosis[1]. Although total surgical resection or treatment with mitotane are helpful for ACC patients, the 5-year survival rate is less than 40%[2-3]. In the meanwhile, prognosis varies according on age, the extent of surgery, the frequency of mitosis, and hormone secretion. Due to the diverse characteristics of ACC patients, the current tumour, lymph node, and metastasis (TNM) categorization approach is ineffective in predicting prognosis. ACC patients present with a variety of pathogenic variables, high heterogeneity, and poor prognosis, making precise prediction difficult. Therefore, it is essential to find more accurate biomarkers for predicting ACC patients' prognoses.

With its adrenolytic effect, the medicine mitotane (o, p'-dichlorodiphe nyldichloroethane (o, p'-DDD)) is the only adrenal-specific medication now used to treat ACC. However, its use and therapeutic efficacy are severely constrained by toxicity, a small therapeutic window, and adverse effects[4]. More efficient and targeted treatment approaches are required because to ACC's high mortality and aggressiveness. In recent clinical trials, monoclonal antibodies that target the insulin-like growth factor II (IGFII) receptor (IGF1R) were explored, however their efficacy in treating individuals who were resistant to treatment was limited[5].

Targeting IGF1R is justified by the finding that the IGFII gene is overexpressed in ACC[6]. We have recently shown that the oestrogen receptor alpha (ESR1), a gene overexpressed in ACC that promotes estrogen-dependent proliferative effects, can activate the IGFII/IGF1R pathway[7-8]. In fact, a recent study [8] that looked at a sizable cohort of people with advanced ACC verified the existence of a sizable number of molecules involved in the evolution of ACC[9]. These findings demonstrate that ACC is a highly heterogeneous illness, and that the integration of signals and the interaction of downstream pathways play a role in its development. Currently, it is believed that these alterations also involve a significant reprogramming of cellular metabolism[10].

Consequently, finding a shared downstream target of numerous pathways that can regulate the expression and activity of various bioenergetic variables represents one potential technique for creating a successful therapeutic for ACC. In the nuclear hormone receptor superfamily of transcription factors, the estrogen-related receptor (ERR) is an orphan member that has not yet been assigned an endogenous ligand despite sharing a high degree of sequence identity with the oestrogen receptor (ER)[11]. ERR controls the expression of genes involved in energy metabolism and mitochondrial biogenesis, such as those encoding enzymes and proteins of the tricarboxylic acid cycle, pyruvate metabolism, oxidative phosphorylation, and electron transport. ERR functions downstream of the peroxisome proliferator-activated receptor gamma coactivator-1 alpha and beta (PGC-1 and PGC-1)[12].

In recent years, research into how modifications in cell metabolism contribute to tumour formation has intensified[13]. As a result, research has concentrated on addressing the metabolic needs of cancer cells, a strategy that has the potential to significantly affect patient care. Notably, the development of cancer and dysregulated cell metabolism have lately been linked to ERR. As a result, it has been demonstrated that more ERR has been expressed in a number of malignant tissues, including the breast, ovary, prostate, and colon[14-15].

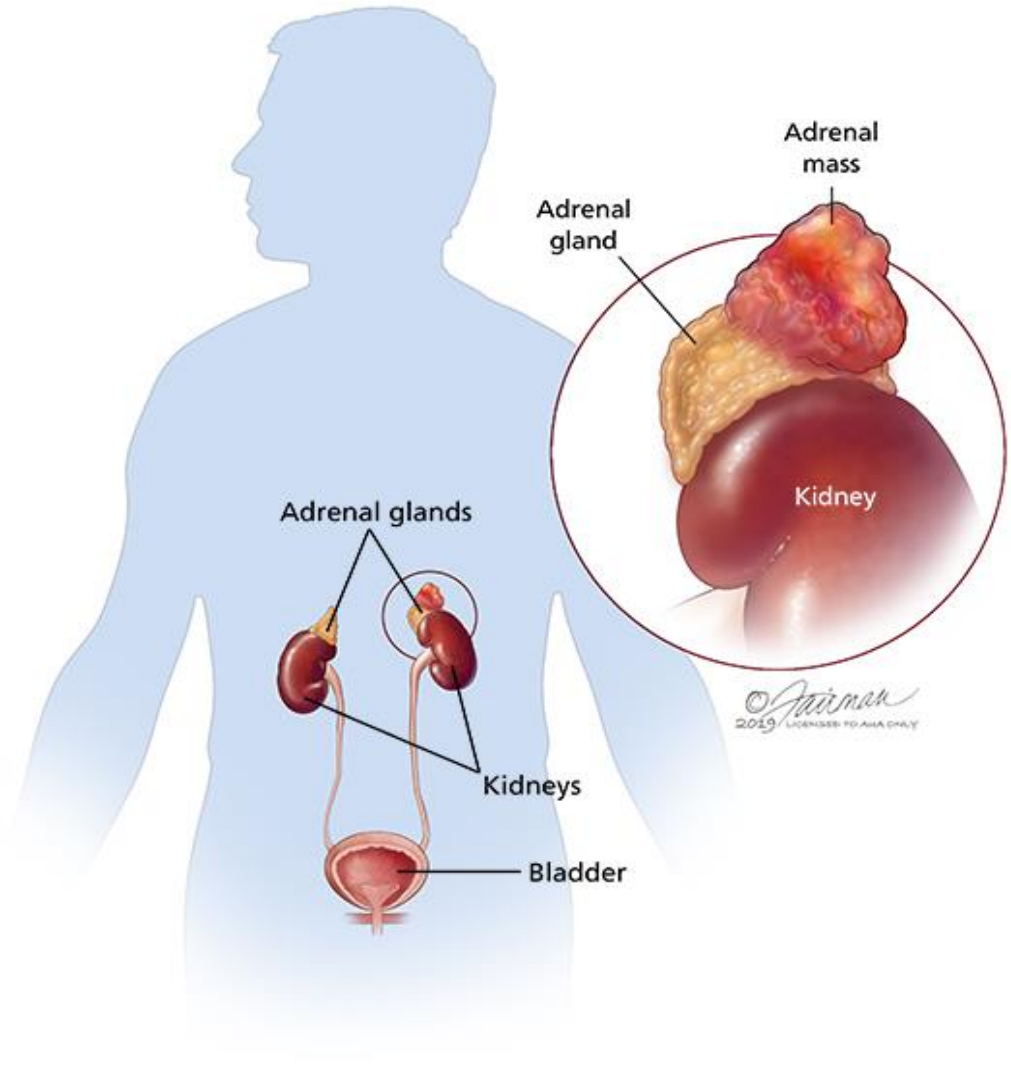

Fig.1: - Adrenocortical Carcinoma

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3. Scope of the work: -

Adrenocortical carcinoma (ACC) is an uncommon kind of endocrine cancer that frequently has a poor prognosis. Here, we provide a summary of our understanding of the pathogenesis, epidemiology, diagnosis, and treatment of ACC. Multidisciplinary clinics have been established recently, and the first global therapy studies have been carried out.

4. Epidemiology: -

Between 3% and 10% of people have an adrenal tumour, and the majority are tiny, benign, non-functioning adrenocortical adenomas (ACA)[16]. Contrarily, ACC is a fairly uncommon disease. Less than 200 000 Americans are affected by uncommon diseases, according to the National Institutes of Health Office of Rare Diseases Research[17].This definition could lead one to believe that ACC is an ultrarare condition. Though there are no reliable data, the incidence is thought to be between one and two per million each year[18].

According to the Surveillance, Epidemiology and End Results (SEER) database, the incidence of cancer is estimated to be 0.72 per million cases annually, accounting for 0.2% of all cancer-related fatalities in the United States[19].In comparison to the anticipated global incidence of 0.2 to 0.3 per million children per year, the incidence throughout childhood in Southern Brazil ranges from 2.9 to 4.2 per million per year[20]. This is mostly explained by the high prevalence of the TP53 allele with limited penetrance p.R337H[21-23].The German ACC Registry reports a median

age at diagnosis of 46 years, indicating that the median age of diagnosis is in the fifth to sixth decade[24]. According to a large single centre series in France, the median age was 46 years old[25].

The SEER database analysis results in a somewhat older mean age of 55 years[26].The presence of regional predisposing factors and biases seems to determine whether a second peak of increasing incidence during childhood may be identified[27-28].A brief analysis of case series described and the SEER data both unequivocally revealed a bimodal distribution[28-29].Other than a person's genetic makeup (see below), no risk factors have been conclusively shown. An analysis of data from the 1986 National Mortality Follow Back Survey found contraceptive use, particularly before the age of 25, and smoking as risk factors for men[30].It's interesting to note that recent in vitro experiments on the ACC cell line NCI-H295 have confirmed the growth-promoting effects of oestrogen[31].

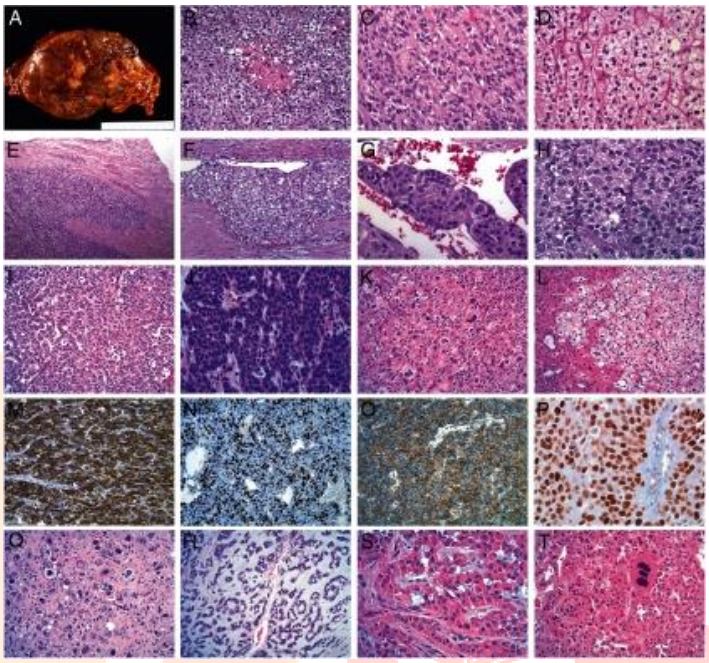


fig.2:- A, ACC gross.

5.Molecular Pathogenesis: -

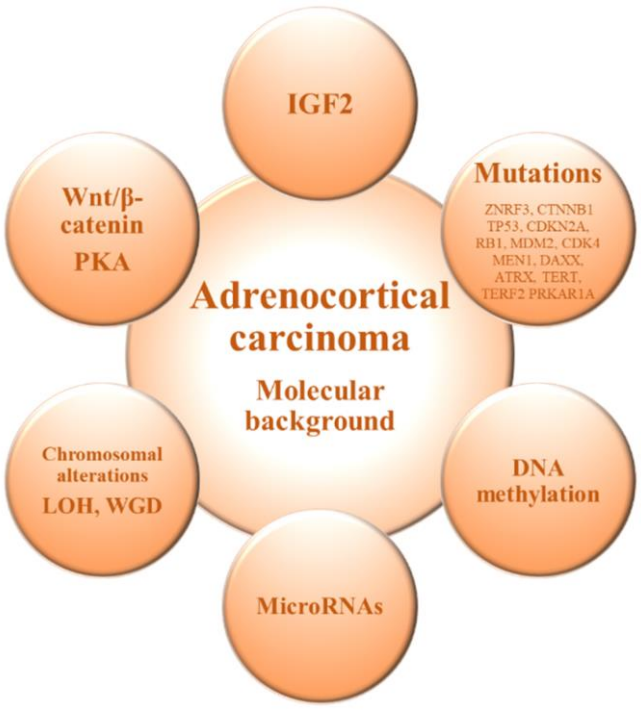


Fig.3: - Molecular pathogenesis of adrenocortical carcinoma.

Recent reviews have discussed the ACC molecular pathogenesis; however, it is still not well understood[32-35]. After a second impact paradigm, it is unknown if ACCs develop from adrenal adenomas. Even if this pattern has

occasionally been seen, long-term follow-up data of accidentally found adrenal neoplasms suggest otherwise[36-39].

It is common to see TP53 tumour suppressor gene inactivating mutations at the 17p13 locus and changes at the 11p15 locus that cause IGF-II overexpression. In vitro research indicates that the proliferation of adrenal cancer cells may be influenced by excessive IGF-II working through the IGF-I receptor[40-42].

In light of this, the IGF-II IGF-I receptor pathway is a possible therapeutic target for ACC[43]. The primary cause of IGF-2 overexpression in sporadic ACC is paternal allele duplication (paternal unidisomy), which is linked to abnormal epigenetic imprinting at 11p15[44]. ACC cell proliferation was decreased in vitro by inhibiting IGF-1 receptor drugs that inhibited IGF-2 signalling[45].

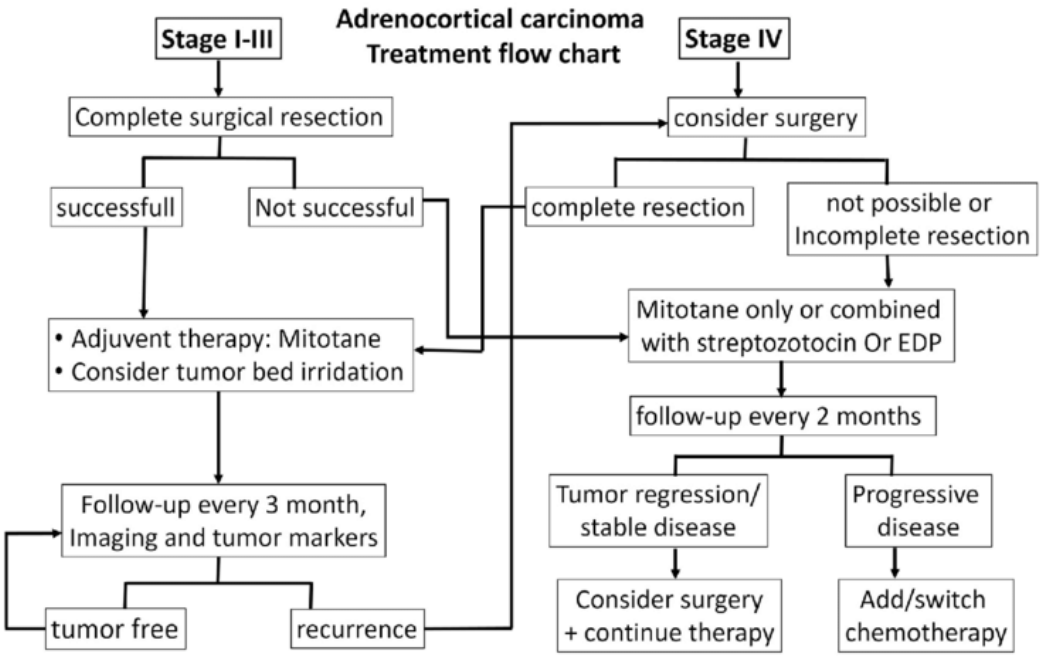
The association between beta-catenin activity and reduced overall survival in ACC patients, which is demonstrated by the presence of beta-catenin nuclear staining, suggests that this staining provides significant clinical information[46-47].Adrenal tumours were caused by activating the Wnt/beta-catenin pathway in the adrenal cortex, but few of these tumours were malignant[48].

6. Sign and symptoms: -

ACC forms on the outermost part of the adrenal gland.

Symptoms of adrenal cancer might include weight gain, muscle weakness, trouble sleeping, deepening voice, and increased hair growth, pain in abdomen or lower back, weight loss or loss of appetite.

7. Treatment: -



A. Surgery: -

Complete tumour excision by a skilled surgeon offers by far the best chance for recovery in stages I through III[49]. A better prognosis is specifically linked to a R0 resection. Invasive organs must frequently be removed all at once during comprehensive surgery, which frequently includes lymphadenectomy. It is crucial to preserve the tumour capsule to prevent tumour spilling and lower the likelihood of a local recurrence[50].Although the use of cardiac bypass technology is not always necessary, the presence of a tumour thrombus in the inferior vena cava or the renal vein is consistent with total tumour removal[51].

The use of laparoscopic adrenalectomy for ACC is up for dispute. Due to less postoperative pain and a shorter hospital stay, minimally invasive adrenalectomy, which was first used in 1992, has become the preferred treatment for benign adrenal lesions with a diameter of less than 6 cm[52-53].Currently, there is agreement that

open adrenalectomy is still the preferred procedure for ACC patients who have tumours greater than 10–12 cm in size, invasion of nearby organs, or enlarged regional lymph nodes[54-55].

There is disagreement over the function of tumour debulking in the presence of metastatic illness. A very poor prognosis is linked to incomplete excision of the primary tumour or metastatic disease that cannot be surgically treated. The median survival time in most trials is fewer than 12 months[56-57]. Debulking a tumour, however, might be able to reduce excessive hormone production and, in some situations, make other therapeutic approaches easier.Retrospective studies have shown that surgery for local recurrences or metastatic disease is a beneficial therapeutic choice and increases survival.

B. Radiofrequency thermal ablation:-

This method has demonstrated potential in the treatment of individuals with liver, kidney, and lung solid tumours.Evidence suggests that in some patients with metastatic ACC and tumours smaller than 5 cm in size, this procedure may be used instead of surgery, although its utility and worth have not yet been established, and the potential benefits must be balanced against the risks[58-59].

C. Radiation Therapy:-

Radiotherapy has frequently been seen as ineffectual for treating ACC[60].Tumor response rates as high as 42% have been reported in numerous reports, nevertheless[61].These results show that ACC is not resistant to radiation therapy, despite the fact that the techniques and response criteria in these studies did not meet modern standards and despite the fact that the number of patients was small. As a result, we advise taking into account radiation therapy to treat localised conditions that cannot be treated with surgery[62].

An expert radiotherapist using cutting-edge treatment techniques, including CT planning, high-voltage radiation, and numerous fields is necessary for the best outcomes.Even little is known about adjuvant radiation given after surgery.For the first time, radiation treatment was applied after (apparently successful) surgery by Stewart et al.[63].

D. Medical therapy:-

Mitotane:-

The only adrenal-specific medication for ACC therapy is mitotane.The only medication still recognised by both the European Medicine Executive Agency and the U.S. Food and Drug Administration as effective for treating ACC is mitotane[64].We still don't fully understand the pharmacological mechanism by which mitotane produces its adrenolytic effect.Mitotane causes the inner zones of the adrenal cortex, the zona fasciculata, and the zona reticularis to be destroyed in a somewhat particular manner.

Ex vivo adrenal perfusion studies have demonstrated that mitotane can be taken from the adrenal gland and metabolised further[65].A considerable portion of mitotane is transported to fatty tissues after approximately 40% of it is absorbed from the GI tract.Plasma levels vary from 0 to 90 mg/L after a typical daily intake of 5 to 15 g.The effectiveness of mitotane as an adjuvant therapy or for advanced ACC as a single treatment or in combination with chemotherapy has been examined in several trials.

I. Mitotane for adjuvant therapy:-

Within three months of surgery, adjuvant therapy is usually initiated.Recent mice trials verified the benefit of beginning mitotane as soon as feasible after surgery. Mitotane was substantially more effective at preventing the growth of xenotransplants when given at the time of tumour cell inoculation rather than at the time of obvious tumour growth[66].

II. Mitotane for recurrent and advanced disease:-

Mitotane therapy has a proven track record of success when used to treat ACC that has metastasized, returned, or is not fully resectable.After receiving treatment with mitotane, 30% of patients have stable disease or a partial remission.The therapeutic mitotane level has been determined by the majority of research, including a significant retrospective analysis, to be 14 to 20 mg/L[67].

III. Mitotane management:-

It takes practise and effort to manage mitotane therapy, which is a rather intense process.The dose is started at 1 g twice day and raised by 0.5 to 1 g/d every 4 to 7 days until it reaches a daily dose of 5 to 7 g.Additionally, a low-dose loading protocol has been outlined, which is likely to produce fewer adverse effects while maintaining effectiveness and boosting patient compliance.Most GI, neurological, and metabolic/endocrinological side effects are manageable when they are modest.

Mitotane has a limited therapeutic window, and it frequently causes side effects that are dose-limiting. Over 80% of patients report at least one negative side effect.

E. Cytotoxic chemotherapy:-

There is still little cytotoxic chemotherapy experience in ACC.The information that is now available suggests that cisplatin alone or in combination with etoposide has some activity in ACC. Several combinations of cytotoxic drugs have been used.The overall response rate in 72 patients, using WHO standards, was 49%, with five individuals achieving a full response[68].This achievement comes with a heavy price in terms of toxicity.

In 36% of patients with detectable illness, full or partial responses were seen.It's noteworthy that Khan et al. recently reported the failure of streptozotocin plus mitotane in 11 patients and the use of a second-line cytotoxic chemotherapy regimen[69].

With a median survival of 21 months from the beginning of second-line chemotherapy, they saw a partial response in two patients and stable illness in seven patients using a combination of vincristine, cisplatin, teniposide, and cyclophosphamide.High expression of the multidrug-resistant gene mdr-1, which results in high amounts of p-glycoprotein serving as a drug efflux pump, has been linked to the limited response to cytotoxic therapy in ACC[70].

Combining cytotoxic therapy with mitotane is based on in vitro data that mitotane may overcome multidrug resistance and the possibility that p-glycoprotein antagonists may increase the effectiveness of cytotoxic therapy[71].

F. Treatment of hormone excess:-

The burden of the disease is typically increased by the over secretion of hormonal steroids in ACC, and this can significantly lower quality of life.Mitotane therapy alone is frequently insufficient to effectively control hypersecretion in all individuals because of its late onset of action and dose-limiting effects.

Ketoconazole, metyrapone, aminoglutethimide, and etomidate are examples of adrenostatic medications that have been used successfully to inhibit steroidogenic enzymes and bring circulating cortisol into the normal range.The most used dosage is ketoconazole (400–1200 mg/d), which can be coupled with mitotane.

All adrenostatic medications must be closely monitored by a qualified endocrinologist to keep cortisol within the therapeutic range and prevent adrenal insufficiency.

8. Diagnostic Workup:-

A. Hormonal Workup:-

Before undergoing surgery in ACC, a thorough endocrine examination is required.The pattern of hormone production may indicate the lesion's potential for malignancy (e.g., estradiol in males, high serum DHEA-S concentrations, or the release of steroid precursors), which may have an impact on surgical approach (open instead of minimal invasive surgery).

An extensive hormonal work-up is required to identify tumour markers for monitoring tumour recurrence.

B. Imaging:-

When they first appear clinically, ACCs are often big tumours, frequently measuring more than 6 cm in diameter[72].As a result of internal bleeding, necrosis, and calcifications, these tumours frequently exhibit heterogeneous enhancement and can have a variety of appearances.In 2% to 10% of cases, they are bilateral.

There may be invasion of neighbouring organs or venous extension into the renal vein and/or inferior vena cava, as well as metastases to the liver, lungs, or lymph nodes.Differentiating between benign and malignant lesions has traditionally relied on the size and appearance of an adrenal tumour on computed tomography (CT), magnetic resonance imaging (MRI), and more recently 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).One of the best indications of malignancy continues to be the size of the adrenal tumour as determined by CT or MRI.

Tumors greater than 6 cm are highly suspected of being cancerous and will be removed, according to the National Institutes of Health consensus conference.Therefore, the primary diagnostic difficulty is with tumours between 3 and 6 cm.

C. Thin Collimation (CT):-

Advanced ACC frequently has local invasion or tumour extension into the inferior vena cava, as well as lymph node or other metastases (lung and liver).It is quite useful to distinguish between benign and malignant adrenal lesions by measuring the Hounsfield units (HU) in unenhanced CT.In a meta-analysis of 10 trials, the sensitivity and specificity for classifying an adrenal lesion as a benign adenoma in unenhanced CT were 71 and 98%, respectively.

In identifying malignant from benign lesions, modern MRI with dynamic gadolinium enhanced- and chemical shift method is just as successful as CT[73].Once more, the presence of fat aids in the distinction between benign and malignant adrenal tumours.Between 81 and 89% and 92 to 99%, respectively, of benign and malignant adrenal tumours could be distinguished by MRI[74-75].Because the inferior vena cava and invasion into nearby organs may best be identified via MRI, it is also helpful in surgical planning.Compared to CT, MRI is more expensive and less standardised.

Currently, each centre should employ these techniques in accordance with the local radiologist's experience.The attending endocrinologist should additionally study images of a potential ACC.

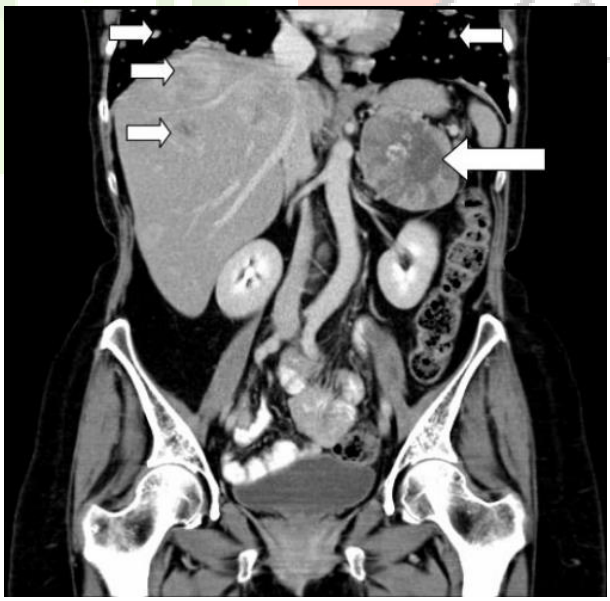


Fig 4:- CT of a large inhomogeneous ACC of the left adrenal gland with multiple pulmonary and hepatic metastases.

D. Pathological Assessment:-

An expert pathologist should carry out the pathological diagnosis. The most used tool, the Weiss score, is used to differentiate between benign and malignant adrenal lesions based on macroscopic criteria (tumour weight, haemorrhage, breached or unbroken tumour capsule), as well as a microscopic diagnostic score.[76]

Broad fibrous bands are another distinguishing characteristic that distinguishes ACC from benign tumours. Immunohistochemistry provides significant new information.

E .Staging:-

Different staging systems, most frequently the Sullivan version of the Macfarlane system, were used prior to 2004 because there was no official tumour nodes and metastasis (TNM) categorization for ACC.Localized tumours 5 cm or less and bigger than 5 cm are classified as stages I and II, respectively.

Stage III tumours are those that are locally invasive or have metastases to local lymph nodes, while stage IV tumours have metastases to distant organs or have invaded nearby organs. However, there has never been a direct comparison of the prognostic usefulness of the various staging systems in a large patient sample.Staging categories' primary goal is to simplify information sharing between treatment facilities.

9. Future Perspective:-

Our understanding of the pathology of the condition has substantially improved as a result of current fundamental scientific and clinical ACC research, which has also established criteria for clinical therapy. However, the prognosis for ACC remains bleak. Our knowledge of the genetic and epigenetic alterations underpinning ACC pathogenesis will hopefully grow as a result of the current large-scale, high-resolution analysis.

The anticipated outcomes should also provide fresh ideas for potential targeted treatments. In large-scale clinical trials like the FIRM-ACT and GALACCTIC study, the principal international knowledge centres have collaborated, offering a special platform for further trials. Future trial objectives should focus on two things: Specifically, adjuvant mitotane and radiation therapy are being evaluated prospectively. Of course, novel treatment options are also being looked into.

We will, however, wait for upcoming talks on this subject from a scientific and ethical standpoint.

Abbreviations:-

ACC- Adrenocortical Carcinoma.

CNS- Central Nervous System.

CT- Computerized Tomography.

DHEA-S- Dehydroepiandrosterone Sulphate.

FDG-PET- ^{18}F-Flourodeoxyglucose Positron Emission Tomography.

HU- Houns field Unit.

MRI- Magnetic Resonance Imaging.

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