ACTA SCIENTIFIC CANCER BIOLOGY

Volume 3 Issue 10 October 2019

Research Article

An Update on the Classification, Diagnosis and Treatment of Endometrial Carcinoma-A Systematic Review

Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]

[1]*Scientific Director, Centre For Human Reproduction, Nagar, Jalandhar, Punjab, India*

[2]*Scientific Director, Ex-Rotunda-A Centre for Human reproduction, Kalpak Garden, Bandra, Mumbai, India*

[3]*Consultant Neurologist, Swami Satyanand Hospital, Near Nawi Kachehri, Baradri, Jalandhar, Punjab, India*

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Centre For Human Reproduction, Nagar, Jalandhar, Punjab, India.

Received: August 27, 2019; **Published:** September 26, 2019

Abstract

Endometrial cancer (EC) is the most common gynecological cancer in post menopausal women in developed countries and the incidence is increasing in view of increased obesity and aging of the population. Multiple classifications have been developed right from the International Federation of Gynecology and Obstetrics (FIGO) Classification, those based on histopathology and recently advanced The Cancer Genome Atlas (TGCA), on the basis of molecular changes. Commonest histologic type is the endometrioid cancer and with use of micro classification one can use to prognosticate the treatment of these cancers and on basis of dedifferentiation and undifferentiated areas with differentiated areas. Further preoperative imaging helps in prognostication of the cases regarding myometrial invasion, lymph - vascular space invasion (LAVI) and thus prognosis after treatment. Treatment consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) with chemotherapy (CT) with or without radiotherapy (RT). Earlier the order used to be RT followed by CT but this trend has changed to CT followed by RT. Other biomarkers for increasing diagnosis are G –protein coupled receptor 64 (GPR64), besides carbohydrate antigen125 (CA125) alone or with human epididymis protein 4 (HE4), which further adds to the sensitivity. Further Death domain - Associated Protein 6 (DEXX). Further by doing uterine curettage in endometroid cancers and checking ER, PR, Ki 67 helped in predicting lymph node involvement. Also using SLB was helpful and not associated with any complications. Testing for GPR64 and connexins it was found that checkpoint inhibitors (PD1/PDL1 antibodies) might be used to treat the undifferentiated (UDE) and dedifferentiated endometrioid carcinomas (DDEC) which carry a poor prognosis. Thus in this review we have tried to summarize the update on the advances in the classification and management of endometrial carcinoma along with biomarkers that might be used.

Keywords: EC; FIGO Classification; GPR64; UDE/DDE; CT/RT; CA125; HE4

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in post menopausal women in developed countries and the incidence is increasing in view of increased obesity and aging of the population. In the US, EC is the 4th most common cancer in women with an estimated incidence of 61,880 new cases in 2019. Most women with EC are diagnosed between the ages of 60 and 80, and most are diagnosed at early stage of disease due to early symptoms like vaginal bleeding. This usually results in favorable prognosis and a relatively low number of cancer - related deaths (estimated 12,160 in 2019 in US) [1].

Methods

We carried out a pub med search for articles relating to endometrial cancer with Me SH terms “classification of EC” “Histological” “FIGO staging” and the newer molecular subclassification “treatment”.

Results and Discussion

We found a total of 137772 articles out of which we selected 50 articles for this systematic review. No meta-analysis was done.

Classification

Initially Uterine cancer was subclassified based on the anatomic site, separating those tumors arising from the endometrium from cervical cancers. Further subclassification of endometrial cancers based on cell type, and this was correlated with the Type 1 and Type 2 categories identified from the epidemiological studies of Bokhman, with endometrioid carcinoma corresponding (approximately) to Type 1 and serous carcinoma to type II. These histotype are not clearly separable in practice, however with considerable interobserver variability in histotype diagnosis especially for high-grade tumors. There followed studies of immunomarkers and then mutational studies of single genes, in attempts to improve subclassification. Although these have revealed significant differences in

protein expression and mutation profiles between endometrioid and serous carcinoma, there is also considerable overlap, so that there remain changes in subclassification of endometrial carcinoma. Gene panel testing, using next generation sequencing was applied to Endometrial cancers and highlighted that there are tumors that show genetic alterations intermediate between classic Type 1/endometrioid and Type II Serous carcinoma. The Cancer Genome Atlas studies of endometrioid and serous carcinoma offered revolutionary insight into the subclassification of endometrial carcinoma, i.e. that there are 4 distinct categories of endometrial carcinoma, rather than 2 based on the genomic architecture [2]. Murali., *et al.* told that on histopathological characteristics there were endometrial, serous or clear cell adenocarcinoma, besides that on clinical and endocrine features like Type I and type II. But substantial heterogeneity existed in biological, pathological, and molecular features within tumor types from both classification systems. Thus, they gave an overview of traditional and newer genetic classification of Endometrial cancer. They discussed how a classification system which incorporates genomic and histopathological features to define biologically and clinically relevant subsets of the disease would be useful. Such integrated classification might help in developing treatments tailored to specific disease subgroups and could potentially enable delivery of precision medicine to patients with Endometrial cancer [3]. In 2013 The Cancer Genome Atlas (TCGA) found that Endometrial carcinoma clustered into 4 prognostic molecular subgroups: POLE/ultramutated (POLE), Microsatellite-unstable Copy number-low and copy number-high). These results have laid the basis for a great improvement in the patient management [4].

Du., *et al.* explored the molecular characteristics of Endometrial endometrioid cancer according to the The Cancer Genome Atlas (TCGA) based molecular classification of Endometrial carcinomas and to confirm simple and clinically applicable surrogate methodologies in pathological practice. 228 cases of Endometrial endometrioid adenocarcinomas (En Ac's) collected from august 2001 to august 2017 from Peking university Health Science Centre, Peking university Third Hospital were molecularly categorized by using Sanger sequencing of the exonuclease domain mutations (EDM) of POLE and by Immunohistochemistry for p53 and mismatch repair (MMR) proteins. The cohort was classified into polymerase-E exonuclease domain (POLE EDM), mismatch repair deficiency (MMR-D), p53 abnormal (p53-abn) and p53 wild type (p53wt) groups. The correlation between molecular subgroups and the clinical pathological features including prognosis were analyzed. The cohort was distributed as follows: 11 (4.8%) POLE EDM, 47 (20.6%) MMR-D,9 (4.0%) p 53-abn and 161 (70.56%) p53wt subgroup patients demonstrated significantly higher lymph node metastasis (p = 0.036) than those of somatic hypermutation group cases (POLE EDM and MMR-D). In the FIGO grade 2 - 3 En ACs cohort, TCGA molecular subtyping was significantly correlated with progression free survival and overall survival (p = 0.043). POLE EDM subgroup had the best survival, while p53 abn subgroup had the worst. Thus, concluding that the identification of POLE EDM and MMR-D subgroups provide independent and highly valuable prognostic information beyond identified histological classification. Based on Immunohistochemistry of MMR, p 53 and POLE mutation analysis, this pragmatic molecular classification scheme can be served as a reliable surrogate for TCGA molecular classification, which has potential to be used routinely in Chinese pathological practice [5].

Sentinel Lymph Node (SLN) Mapping has been proven to accurately stage Endometrial cancer (EC). But there have been lack of studies comparing the incidence of complications between different lymph node approaches in EC. Thus Accorsi., *et al.* tried to define the complication rates of SLN biopsy in EC patients. They conducted a retrospective cohort study in a tertiary referral hospital. All pts who were surgically treated for EC from April 2013 to march 2018. They evaluated intraoperative complications and 30 day complications using the Memorial Sloan Lettering Cancer Center's Surgical Secondary Events Grading System separating the patients into 4 groups: grpI, Hysterectomy (HT), grpII, Hysterectomy plus Sentinel Lymph Node biopsy (HT + SLN); grp III Hysterectomy plus pelvic lymphadenectomy, with or without para aortic dissection (HT + LND); and grp IV. Hysterectomy plus lymphadenectomy and Sentinel Lymph Node biopsy (HT + SLN + LND). They identified a total of 150 cases. As compared with the HT group, the HT + SLN group did not show any increased risk of complications in terms of intraoperative complications (0 vs 1; p = 1.0) and 30 day complication (8 vs 7; p = 0.782), but surgical time was approximately 20 minutes longer (p = 0,016). Performing LND was associated a greater risk of 30 days complications (hazard ratio [HR]: 3.11; 95% Confidence interval [CI]: 1.62 - 5.98), Intraoperative complications (HR: 14.25;95% CI: 1.85 - 19.63), and lower limb lymphedema (HR: 14.25; 95% CI: 1.01 - 65.27). Thus, concluding that SLN mapping does not increase morbidity in the surgical treatment of EC patients, and compared with comprehensive lymphadenectomy, it has lower risk of complications. Their findings supported the use of SLN algorithm in EC patients [6].

Histology and risk factors

The most common histologic type of EC is endometrioid adenocarcinoma (EEC), that accounts for roughly 70 - 80% EC. Non - endometrioid adenocarcinoma(NEC) mainly comprise serous and clear cell cancers, that account for roughly 5 - 10% and 1-5% of EC, respectively, and the other aggressive subtypes are undifferentiated and dedifferentiated EC and uterine carcinosarcomas. Well established clinicopathological risk factors, used in the current treatment guidelines are, age, histological type, tumor grade, International Federation of Gynecology and Obstetrics (FIGO)-stage, depth of myometrial invasion, and presence and extent of lymph - vascular space invasion (LVSI). EEC is graded using the FIGO grading system as low grade (grade I), intermediate (grade 2), or high grade (grade 3) based on the proportion of solid growth and nuclear atypia, while the NEEC are high grade by definition. Using combination of these risk factors, risk groups have defined based on data from randomized trials, with each risk group hav-

ing a distinct prognosis and adjuvant treatment recommendations have been determined for these risk groups [7].

Treatment

Women with EC are primarily treated with surgery, consisting of abdominal or laparoscopic hysterectomy and bilateral salpingo-oophorectomy with or without lymph node evaluation. The indication for adjuvant treatment has been based on the presence of clinicopathological risk factors. Women with low -intermediate risk EC are treated with surgery alone [8]. Women with high-intermediate risk (HIR) EC usually receive adjuvant radiotherapy, mainly vaginal brachytherapy [9]. Women with high risk EC (HR), being at higher risk of recurrence, receive pelvic external beam radiotherapy (EBRT) with or without adjuvant chemotherapy. Especially in the case of substantial LVSI,EBRT is preferred over VBT alone or maximum pelvic nodal control in HIR EC [10]. The role of adjuvant chemotherapy, most often given in combination with EBRT has been the subject of recent randomized trials, which showed increased relapse free survival rates with combined adjuvant treatment at the cost of increased toxicity, and this is mainly recommended in stage III disease and for serous cancers [11].

Molecular and genetic characteristics of EC and molecular risk factors

The extensive molecular-genetic characterization of EC by the TCGA has been pivotal in understanding the molecular pathways involved in EC development and their prognostic complications. By full genomic analysis of 373 EC cases 4 different molecular subclasses, were identified based on mutation rates and somatic copy number alterations (SCNA). The multiregulated subclass, characterized by mutations in the exonuclear domain of DNA polymerase-epsilon (POLE), is associated with a very favorable prognosis. The hypermutated subclass based on microsatellite instability (MSI) has been shown to have intermediate prognosis. The copy number low subclass with low mutation frequency (also known as subclass with no specific molecular profile or NSMP) has also been associated with an intermediate prognosis. The copy number high subclass, characterized by TP53 mutations, with mainly serous-type EC, has a very high degree of SCNA and a low mutation rate and is associated with the most unfavorable prognosis [12]. Various research groups have reproduced and validated the 4 TCGA subclasses in formalin fixed, paraffin embedded tissues in different EC cohorts by using their surrogate markers [10,13].

The current guidelines for diagnosis and treatment of EC are based on the clinicopathological factors, age, FIGO stage, histologic type and grade, myometrial invasion, and the presence of LVSI, but do not include molecular alterations. The current question is if and how these molecular risk factors can be used to guide.

Thus Wortman., *et al.* provided an overview of common molecular risk factors in EC with the possibility to improve adjuvant treatment selection. Recent studies have discovered and confirmed 4 different molecular subclasses in EC, with each having a distinct prognosis: POLE ultramutated (POLE), Microsatellite-unstable/hyper mutated (MSI), Copy number-low, and Copy number-high. Subsequent studies have shown that combining both molecular with clinicopathological risk factors can potentially improve adjuvant treatment selection for women with high-intermediate risk EC. For high risk and advanced stage EC, several molecular alterations are being explored for targeted therapy. Thus, summarizing that molecular alterations are frequently found in EC and have currently not been implemented in the treatment guidelines for EC. Assessment of molecular alterations can distinguish patients that require less or more intensified adjuvant treatment. Trials investigating targeted therapies in EC are ongoing and have shown some promising results, however more evidence is required and results of randomized trials have to be awaited [14].

While women treated with stage III EC are often treated with chemotherapy and external beam radiation, the optimal sequence of these modalities is unknown. Hence Latham., *et al.* examined the association between the sequence of chemotherapy (CT) and external beam radiation therapy (RT) on survival with Endometrial carcinomas. They utilized National Cancer Database to identify women with Stage IIIc Endometrial carcinomas treated with adjuvant CT and RT from 2004 - 2015, Patients were stratified based on the sequence of therapy: RT before CT, CT before RT, or concurrent therapy. The association between treatment sequence and mortality was examined through a weighted propensity score analysis. A total of 6981 patients were identified, including 5116 (73,3%) who received CT before RT, 696 (10.0%) who received RT before CT and 1169 (16.7%) who received concurrent therapy. The use of CT-RT increased from 39.9% in 2004 to 75.5% in 2015, while use of RT-CT decreased from 34.0% to 4.4% and concurrent therapy decreased from 26,1% to 20.2% over the same period ($p < 0.001$). Compared to CT - RT, there was no difference in risk of mortality with RT before CT (HR = 1.01; 95% CI, 0.86 - 1.19) while concurrent therapy was associated with a 47% increased risk of mortality (HR = 1.47; 95%CI, 1.31 - 1.66). In a sensitivity analysis combining the groups that received RT first (RT before CT or concurrent RT-CT), mortality was 25% higher (HR = 1.25; 95% CI, 1.13 -1.39) compared to a strategy of CT followed by RT.

Thus, concluding that among women with stage IIIC Endometrial carcinomas treated with combination chemotherapy and external beam radiation, a strategy employing chemotherapy 1st is associated with improved survival compared to concurrent therapy [15].

Although EC is staged according to FIGO surgical system, early and accurate diagnostic assessment of disease status of gynecological malignancies is important for optimal treatment planning and outcome prediction. Preoperative imaging might assist in evaluation of local extent and detection of distant metastatic disease guiding the optimal course of treatment. Various imaging techniques like transvaginal ultrasound, computed tomography, and magnetic resonance imaging have been used as tools for preoperative staging of EC. Positron emission tomography/computed tomography and most recently Positron emission tomography/magnetic resonance imaging have also been used in the management of EC. Cross-sec-

tional imaging, especially MRI, may detect gross myometrial invasion or extension of tumor to the cervical stroma which can alter management. Imaging studies can also evaluate the presence of lymph nodal involvement and detect local and distant metastatic disease at diagnosis. Additionally imaging also plays a role in the monitoring of treatment and surveillance of the patients for detection of early recurrent diseases. Thus Faria., *et al.* reviewed the role of imaging and staging in EC [16].

Gil., *et al.* evaluated the added value of diffusion-weighted imaging (DWI) in the preoperative assessment of myometrial invasion in EC, in comparison with T2 -weighted imaging (T2WI) and dynamic contrast-nhanced magnetic resonance imaging (DCE-MRI). This was a retrospective study involving 44 women with EC who underwent preoperative 1.5 T MRI, 2 radiologists, both of whom were blinded to the histopathology reports, performed a consensus interpretation of the depth of myometrial invasion and of the stage of the cancer, considering 3 sets of sequences: T2WI, DCE - MRI + T2WI and DWI + T2WI. Accuracy, sensitivity, specificity, positive prediction value, and negative prediction value were calculated in each set. The accuracy was compared with p-value adjustment by the Benjamini-Hochberg procedure. Of the 44 patients evaluated, DWI + T2WI demonstrated better diagnostic performance in assessing deep myometrial invasion and correctly staged more patients (n = 41) than did DCE - MRI + T2WI (n = 34) and T2WI (n = 22). The superior diagnostic accuracy of DWI + T2WI was statistically significant in comparison with T2WI ($p < 0.05$) but not in comparison with DCE-MRI + T2WI ($p > 0.05$). Thus concluding that the addition of DWI apparently improves the diagnostic accuracy of MRI in the preoperative assessment of the depth of myometrial invasion in EC, which maybe especially helpful in patients for whom contrast agents are contraindicated [17].

Dedifferentiated Endometrial carcinomas (DDEC) is a rare and more aggressive type of endometrioid carcinomas than high grade endometrioid carcinomas [18]. In 2006 DeSilva., *et al.* reported cases of Endometrial carcinomas in which low grade endometrioid carcinoma was combined with undifferentiated carcinomas and designated them as Dedifferentiated Endometrial carcinomas [18]. A total of 50 - 58% of patients with DDEC present with advanced stage disease, and 40% of these patients die within half a month to 20 months from the disease [18,19]. Because of that it is urgently needed to develop therapies, such as immunotherapy, that fit molecular subgroups. DDEC was suggested to be related to the deficiency of MMR proteins, mutL protein homolog 1 (MLH1), post meiotic segregation increased 2 (PMS2), mutS protein homolog 2 (MSH2) and mutS protein homolog 6(MSH6), resulting in microsatellite instability (MSI) [19]. MMR deficiency has been reported in 58% of cases by Immunohistochemistry (IHC) and occurs more frequently than in common Endometrial cancer, with 25 - 30% of cases showing mismatch repair deficiency [19]. MMR-deficient tumors are burdened with somatic mutations are more immunogenic and have immune escape mechanisms like the programmed cell death-1 (PD1) and PD1 ligand1 (PDL1) pathways [20], Clinical trials of immune checkpoint inhibitors for MMR deficient tumors have been studied in many carcinomas including colorectal cancer and melanoma [21]. As a biomarker for the effectiveness for immune checkpoint inhibitors, PD - L1 expression on IHC, cytotoxic T lymphocyte ($CD8^+$ T cells), and neoantigen (mutation burden rich) are shown in existing reports [22,23]. Specifically when assessing the anti- PD1 antibody for melanoma, infiltration of $CD8^+$ T cells correlate with response to them [18]. It has been suggested that immune checkpoint inhibitors may be effective when there is a high infiltration of $CD8^+$ T cells into the tumor [24]. Thus immune checkpoint inhibitors are thought to be effective for MMR deficient tumors. But the relationship between MMR deficiency and the expression of PD - L1 and $CD8^+$ T cells tumor infiltration remains poorly understood in DDEC with MMR deficiency and the expression of PD - L1 and $CD8^+$ T cells tumor infiltration remains poorly understood in DDEC. Hence Ono., *et al.* analyzed the immunophenotype (MM)of 1R-deficient and expression of PDL17 DDEC cases. In the undifferentiated component, 9 cases (53%) expressed PD-L1, PD-L1 expression was significantly associated with MMR deficiency ($p = 0.026$). In addition, the presence of tumor-infiltrating lymphocytes ($CD8^+$) was significantly associated with MMR deficiency ($p = 0.026$). In contrast, none of the cases showed PDL1 expression in the well differentiated component. Their results showed that DDEC could be a target of immune checkpoint inhibitors (PD1/ PD-L1 antibodies), especially in the well undifferentiated component. As a treating strategy for DD EC, conventional paclitaxel plus carboplatin and cisplatin plus doxorubicin therapies are effective for those with the well differentiated component. However, by using immune checkpoint inhibitors in combination with other conventional treatments, it may be possible to control the undifferentiated component and improve prognosis [25].

Guiseren., *et al.* investigated the estrogen receptor (ER), progesterone receptor (PR), and Ki 67 receptor levels in endometrial curettage material for their ability to predict lymph node (LN) involvement in patients with endometrioid type Endometrial cancer (EEC). The retrospective study was based on a review of the records of patients who were diagnosed with EEC and underwent both hysterectomy and systematic retroperitoneal lymphadenectomy at the Gynecologic Oncology Clinic of Tepic Training and Research Hospital Turkey between January 2008 and august 2017. The curettage materials of 138 EEC patients were analyzed for ER, PR and P53 and Ki67. According to the pathology results, the median pelvic LN count was 20 (range: 12 - 49) and the para-aortic LN count was 14 (10 - 46). Retroperitoneal LN involvement was present in 18 patients (13.0%). The association of LN involvement with all receptors was significant. The combined ratio of the 2 groups of markers ([IP53 + Ki67]/[ER + PR]) (> = 0.71) was an independent risk factor for LN involvement. In addition, in a univariate logistic regression analysis all receptors were significant predictors of LN involvement. Thus, concluding that in the detection of LN involvement, determination of the receptor status in curettage materials can be evaluated to detect LN involvement preoperatively [26].

The most common type of Endometrial cancer is endometrioid adenocarcinoma, that originates from endometrial epithelial cells [27]. The development of endometrial hyperplasia, a proliferative process in the epithelium, is the abnormal thickening of the lin-

ing of the uterus due to an increase in the number of endometrial glands. It is a critical risk factor for endometrioid Endometrial carcinoma [25]. Despite most cases being diagnosed in the early stage of Endometrial cancer, a subset of these patients have poor outcomes and high rates of recurrence and metastases [28]. Many studies have focused on targeted molecular therapies for controlling Endometrial malignancies [29], but still they are not sufficient. Thus it is important to find out the molecular mechanisms that are involved in the development and of Endometrial cancer.

G-protein coupled receptor 64 (GPR64) is a member of the GPCR subfamily, that is key for male fertility [30,31]. Additionally, GPR 64, was expressed in the proximal epididymis and efferent ductule regions, that are responsible for spermatozoa maturation, along with rete fluid reabsorption [30,31]. The level of GPR 64 was higher in Ewing sarcoma than other mesenchymal neoplasms, and GPR64 induces placental growth factor (PGF) and metalloproteinase (MMP1) expression [32]. Loss of GPR64 in ewing sarcoma cell line = > reduced PGF and MMP expression, with decreased cellular growth factor with induced TRAIL, dependent apoptosis. GPR64 knockdown in an ewing sarcoma tumor model in immune deficient mice, decreased metastasis and invasiveness to the liver and lung [33].

Connexin 43 (Cx43) is a member of the large family of gap junction proteins [34]. Gap junctions are intracellular plasma membrane proteins that provide for the exchange of ions and small molecules between adjacent cells [35]. Some studies have indicated that the Cx43 channel was localized in the plasma membrane, but not involved in gap junction formation [33]. The Cx43 channel might regulate cell growth by transportation of calcium ions or other ions between intracellular cytoplasm and the extracellular environment [36,37]. Other studies suggest that Cx43 can regulate cell growth and death by direct interaction with regulated cell cycle proteins including cyclin A, Cyclin d 1, p21 and p27 [36]. Dysregulation of gap junction intercellular communication was linked to various human diseases like in cancer, cardiac ischemia, Charcot Marie Tooth (CMT) and visceral heterotaxia syndrome(VAH) [38]. Cx43 is ubiquitously expressed in human tissues and controls cell growth and differentiation through multiple mechanisms. Attenuation of Cx43 is commonly observed in cancers, causing loss of gap junctional intercellular communication [39]. Activation of Cx43 in cancers cells derived from various tissue types has been shown to cause restoration of normal cell growth and differentiation [40]. Small interfering RNA (si RNA)-mediated knockdown of Cx43 results in a more aggressive growth of breast cancer [41]. There is an inverse correlation between Cx43 expression and tumor grade in Endometrial cancer [42]. These suggest that Cxx43 has a tumor suppression function and is a potential target in cancer therapy.

Thus Ahn., *et al.* examined the levels of GPR64 in human endometrioid Endometrial carcinoma by immunohistochemistry analysis. To determine the tumor suppressor role of GPR64 in Endometrial cancer, they used a siRNA loss of function approach in human Endometrial adenocarcinoma cell lines. GPR64 levels were remarkably lower in 10 out of 21 (47.62%) of Endometrial carcinoma samples compared to control. Depletion of GPR64 by siRNA transfection revealed an increase in colony formation ability, cell proliferation, cell migration and invasive activity of Ishikawa and HEC1A cells. The expression on Cx43 was decreased through activation of AMP-activated protein kinase (AMPK) in Ishikawa cells with GPR64 deficiency. Thus, concluding that these results suggest that GPR64 plays an important tumor suppressor role in Endometrial cancer [43].

Huang., *et al.* 2019 tried to evaluate the overall diagnostic value of human epididymis protein 4 (HE4) combined with carbohydrate antigen 125 (CA125) in Endometrial carcinoma based on a meta-analysis of all eligible studies. The PubMed, Cochrane, Embassy, CNK1, VANFUN, and VIP databases were searched by index words to identify eligible studies and also to search for relevant literature sources that had been published by January 2019. Eligible studies included prospective cohort studies or cross-sectional studies. The heterogeneity of the included studies was used to select appropriate effect models to calculate summary weighted sensitivity, specificity and diagnostic odds ratio (DORs). The summary receiver operational characteristics (SROC) analysis was summarized for the EC. In total, 25 studies that had explored the diagnostic accuracy of HE combined with CA125 for Endometrial carcinoma were as follows: 66% (95% CI: 60 - 72) and 92% (95% CI: 88 - 95), respectively. The global positive likelihood ratio and global negative likelihood ratio of HE4 combined with CA125 for Endometrial carcinoma were as follows: 8.03 (95%CI: 5.36 - 12.04), and 0.37 (95% CI: 0,31 - 0.44). respectively. The global DOR was 19.59 (19.59 (95%CI: 12.25 - 31,32) for IL-6.The area under the SROC was high for HE4 combined with CA125 (AUC = 0.86; 95%CI: 0.83 - 0.89). Thus concluding that this study provided a systematic review and meta-analysis of the diagnostic accuracy of HE4 combined with CA125 for Endometrial carcinoma. The results indicate that HE4 combined with CA125 is highly accurate for the diagnosis of Endometrial carcinoma [44].

Death domain-Associated Protein 6 (DAXX) is involved in regulating apoptosis via subcellular localization. The presence of DAXX point mutations correlates well with the loss of nuclear expression patterns on immunohistochemistry(IHC). Jin., *et al.* sought to determine i) whether DAXX expression patterns is same across different uterine carcinoma subtypes, and ii) which uterine carcinomas show loss of nuclear DAXX IHC. They studied 65 uterine carcinomas of the following histologic types: 30 endometrioid (12 FIGO grade 1, 12 FIGO grade 2, and 6 FIGO grade 3). 8 serous, 14 clear cell and 13 undifferentiated/Dedifferentiated (UEC/DDEC). Nuclear DAXX IHC was assessed in each tumor and was graded semi quantitatively as follows: 0% to 50%, 50% to75% and > 75% of lesion cells react. A total of 61% (25/41) of high grade carcinomas (FIGO grade 3, serous, clear cell and UEC/DDEC) showed retained DAXX nuclear staining in >75% and of lesioned cells, compared with only 4.2% (1/24) of the low grade carcinomas (FIGO grades 1 and 2) (p = 0.001), where DAXX expression was cytoplasmic. In addition, in the 11 DDEC cases, all the differentiated components showed loss of nuclear DAXX compared with the undifferentiated components

that retained DAXX expression. Thus, concluding that that loss of nuclear DAXX is present in low grade Endometrial carcinomas and the differentiated components of the UEC/DDEC, but not in high grade ones, suggesting DAXX's role in tumor progression and its potential as a therapeutic target in high grade Endometrial carcinomas [45].

AlHilli M, 2019 evaluated survival, prognostic features for survival, and treatment outcomes associated with undifferentiated Endometrial cancer. The National Cancer Database was queried to identify patients with undifferentiated Endometrial cancer who underwent definitive primary surgical treatment. Patients with all other histologic subtypes or incomplete treatment data were excluded. Univariable and multivariate Cox proportional hazard analysis were used to determine independent prognostic factors for survival. Points for each prognostic factor were assigned from regression coefficients in the final multivariate model and summed for a total score. Recursive partitioning analysis was used to determine cut-offs and the score to identify unique prognostic groups. Among 349404 women diagnosed with Endometrial cancer from 2004 - 2013, 3994 (1.1%) met the criteria for diagnosis of undifferentiated Endometrial cancer and 3846 had survival data. Median age at diagnosis was 65 years (interquartile range [IQR] 57 - 74) and 58% of patients had early stage disease. Median interval from diagnosis to surgery was 3.7 weeks (IQR 2.0 - 5.7). 5 year overall survival was 57% (standard error [SE] 1%). Stage was the strongest predictor of survival, with a 15 - 20% decrease in 5 yr survival for each advance in stage. Stage, age race, and the presence of comorbidities were independent predictors of survival and were used to categorize patients into 5 prognostic groups. Adjuvant therapy was associated with improved survival across most disease stages and prognostic groups. Multimodal Adjuvant therapy was superior to unimodal treatment especially in advanced stage unfavorable and very unfavorable groups. Thus concluding that in women with undifferentiated Endometrial cancer, survival is primarily driven by age. Despite the overall prognosis of undifferentiated Endometrial cancer, multimodal Adjuvant therapy is a crucial component of treatment [46].

Bi., *et al.* 2019 investigated the expression of SMARC4 (BRG1) and SMARC B1 (INI-1) protein in endometrial dedifferentiation carcinoma (DDC) and undifferentiated carcinoma (UDC), and their correlation with clinicopathological features. Clinicopathological information was collected for 26 cases of DDC and UDC and consulting hospitals from January 2006 - December 2018 in Fudan University Shanghai Cancer Center, including 10 cases of DDC and 16 cases of UDC. Morphological features and diagnosis were reviewed by 2 pathologists. Immunohistochemistry for expression of BRG1 and IN1 was performed. The correlations with clinicopathologic features were analyzed.. BRG1 and IN1 were present in 14/26 cases of DDC/UDC, including 12 BRG1 deficient cases respectively. 6 cases showed variable amounts of rhabdoid cells in 14 BRG1/IN1-deficient cases and only 1 case showed rhabdoid cells in the 12 intact expression cases. However no statistically significant difference ($p = 0.060$). Age, invasive depth, lymph node status and FIGO Stage were not associated with the expression of BRG1 and IN1($p = 0.437$, $p = 0.672$, $p = 0.348$). Remarkably the BRG1/IN1- deficient cases had worse survival than those with intact expression (4.7 vs 22.9, $p = 0.003$). Thus concluding that BRG1/IN1-deficient is observed in approximately half of DDC and UDC. Identification of these tumors is clinically relevant due to their more aggressive behavior and poor prognosis. Hence BRG1 and IN1 Immunohistochemical stains should be done for DDC and UDC in order to help the pathologists to differentiate these tumors from other carcinomas, and to predict the clinical prognosis [47].

Tichy M., *et al.* tried to do accurate stratification of risk relative to body mass index (BMI) in Endometrial adenocarcinoma with the increasing incidence of malignant tumors of uterine body. The study population included 376 women of Caucasian race diagnosed with Endometrial adenocarcinoma, with BMI measured simultaneously in 2005 - 2017. A control group consisted of an equal number of age –matched women not diagnosed with any oncological or gynecological disease. These 2 files were statistically processed. Odds (OR,95% CI)relative to normal weight represents same risk for the development of Endometrial adenocarcinoma, and women with obesity were at 5.18 - 8.67, and 24.70 - times higher odds, depending on the severity of obesity. Thus, concluding that the hypothesis that overweight represents same risk for the development of Endometrial adenocarcinoma, as lower degrees of obesity was not verified. However overweight is a serious risk for Endometrial adenocarcinoma development. The odds of Endometrial adenocarcinoma is correlated with increasing BMI and the population studied is higher than the population studied is higher than reported previously for Endometrial carcinoma subtypes [48].

Micro RNA-589-5p (miR9-5p) has been recently reported to be aberrantly regulated in hepatocellular carcinoma, but its functional role and molecular mechanisms still remains unknown in the Endometrial carcinoma (EC) as one of the most common female malignancies. Wang., *et al.* collected EC tissues and adjacent tissues for determining the expression of mi R-589-5p and thyroid interacting protein 6 (TRIP6) using quantitative real time PCR, Subsequently, 2 EC cell lines HEC -1B and AN3CA were transfected with miR-589-5p to achieve miR-589-5p overexpression. Using cell counting kit-8 (CCK-8), wound healing assay and Trans well assay, they analyzed cell proliferation, migration and invasion. Dual luciferase reporter assay confirmed that thyroid interacting protein 6 was a direct target of miR-589-5p. They 1st observed that mi R -589 - 5p was downregulated in EC tissues compared with normal endometrial tissues. MiR-589-5p, overexpression significantly suppressed EC cell proliferation, migration and invasion. TRIP6 was a direct target of miR-589-5p. Besides TRIP6 knockdown presented similar effects on cell proliferation, migration and invasion to miR-589-5p overexpression. Furthermore, TRIP6 knockdown efficiently enhanced the effects of miR-589-5p on the above cellular function. Moreover, miR-589-5p upregulated E-cadherin expression but downregulated N-Cadherin and Vimentin by targeting TRIP 6.Thus they concluded that miR-589-5p might function as a tumor suppressor by targeting TRIP6,hich will provide new insights into the molecular mechanisms underlying the development of EC [49].

Many women have undergone both resectoscope and non resectoscope (or global) endometrial ablation (EA) during the past 20 yrs. These women are now approaching their sixth and seventh decades of life, a time frame in which Endometrial carcinoma (EC) is most frequently diagnosed. In many reports, surgeons have expressed concerns that EA artifact does not hinder the evaluation and treatment planning in the presence of EC. Data bases used are from Medline and Pubmed. Worlman., *et al.* introduced 6 new cases of post ablation Endometrial carcinoma (PAEC). 4 of which occurred after the introduction of global Endometrial ablation (GEA) techniques. In addition they examined important crucial questions regarding the impact of EA on the subsequent development of EC, including the manner in which PAEC presents, the efficacy of traditional diagnostic modalities, the ablation-to-cancer interval, and the stage of PAEC at the time of diagnosis. Ultimately, they explored the use of hysteroscopic surgery (RHS) as a diagnostic modality and address the possible role ultrasound surveillance as a screening method for women at risk of EC [50].

Conclusions

Thus in this review we have tried to update the classifications used for EC, with addition of imaging studies like CT, MRI, PET and diffuser tensor imaging helping in prognosis. Further we have considered the treatment modalities in the commonest EC namely the endometrioid cancer, be it differentiated, UDC, or DDE. The surgical modes of treatment and use of various lymph node biopsies have been considered as well. Further the biomarkers that are getting developed like GPR64, HE4, DAXX might be of use in prognosis or aid with the use of CA125. Moreover role of immune checkpoint inhibitors in UDC or DDEC is considered.

Bibliography

1. Siegel RL., *et al.* "Cancer statistics ,2018". *CA Cancer Journal for Clinicians* 69.1 (2019): 7-30.

2. Goebel EA., *et al.* "The evolution of endometrial carcinoma classification through application of Immunohistochemistry and molecular diagnostics: past, present and future". *Virchows Archiv* 472.6 (2018): 885-896.

3. Murali R., *et al.* "Classification of endometrial carcinoma: more than two types". *The Lancet Oncology* 15.7 (2014): e268-e278.

4. Raffone., *et al.* "Clear cell Endometrial carcinoma and the TCGA classification". *Histopathology* (2019).

5. Du NN., *et al.* "Clinical application of TCGA molecular classification in endometrial endometrioid carcinoma". *Zhonghua Bing Li Xue Za Zhi* 48.8 (2019): 596-603.

6. Accorsi GS., *et al.* "Sentinel Lymph Node Mapping vs Systematic Lymphadenectomy for Endometrial cancer: Surgical Morbidity and Lymphatic Complications". *Journal of Minimally Invasive Gynecology* (2019): S1553-4650.

7. Colombo N., *et al.* "ESMO –ESGO-ESTRO Consensus Conference on Endometrial cancer: diagnosis, treatment and follow up". *Annals of Oncology* 27.1 (2016): 6-41.

8. Keys HM., *et al.* "A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynaecological Oncology Group Study". *Gynecologic Oncology* 92.3 (2004): 744-751.

9. Blake P., *et al.* "Adjuvant external beam radiotherapy in the treatment of Endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomized trials): pooled trial results, systematic review and meta-analysis". *Lancet* 373.9658 (2009): 137-146.

10. Wortman BG., *et al.* "Ten year results of the PORTEC-2 trial for high intermediate risk endometrioid carcinoma: improving patient selection for adjuvant therapy". *British Journal of Cancer* 119.9 (2018): 1067-1074.

11. De Boer SM., *et al.* "Adjuvant chemotherapy versus radiotherapy alone for women with high risk Endometrial cancer (PORTEC 3): final results of an international, open label, multicentric randomized phase 3 trial". *The Lancet Oncology* 19.3 (2018): 295-309.

12. Kandoth C., *et al.* "Integrated genomic characterization of endometrial carcinoma". *Nature* 497.7447 (2013): 67-73.

13. Kommoss S., *et al.* "Final validation of the Pro Mis E molecular classifier for endometrial carcinoma. In a large population based case series". *Annals of Oncology* 29.5 (2018):1180-1188.

14. Wortman BG., *et al.* "Selecting treatments for endometrial carcinoma. Using Molecular risk factors". *Current Oncology Reports* 21.9 (2018): 83.

15. Latham AH., *et al.* "Sequencing of therapy in women with Stage III endometrial carcinoma receiving Adjuvant combination chemotherapy and radiation". *Gynecologic Oncology* (2019): 31410-31416.

16. Faria SC., *et al.* "Imaging and Staging of Endometrial cancer". *Seminars in Ultrasound, CT and MRI* 40.4 (2019): 287-294.

17. Gil RT., *et al.* "The added value of diffusion –weighted imaging in the preoperative assessment of Endometrial cancer". *Radiologia Brasileira* 52.4 (2019): 229-236.

18. Silva EG., *et al.* "Association of low grade-endometrioid carcinoma of the uterus and the ovary b with undifferentiated carcinoma: A new type of dedifferentiated carcinoma? A Review". *International Journal of Gynecological Pathology* 25 (2006): 52-58.

19. Tafe LJ., *et al.* "Endometrial and ovarian carcinomas with undifferentiated components: Clinically aggressive and frequently under recognized neoplasms". *Molecular Pathology* 23 (2010): 781-89.

20. Le DT., *et al.* "PD1 Blockade in Tumors with Mismatch Repair Deficiency". *The New England Journal of Medicine* 372 (2015): 2509-2520.

21. Basile D., *et al.* "Immunotherapy for colorectal cancer: Where are we heading?" *Expert Opinion on Biological Therapy* 17 (2017): 709-721.

22. Ma., *et al.* "Current status and perspectives in translational biomarker research for PD1/PD-L1 immune checkpoint blockade therapy". *Journal of Hematology and Oncology* 9 (2016): 47.

23. Topalan SL., *et al.* "Mechanism driven biomarkers to guide immune checkpoint blockade in cancer therapy". *Nature Reviews Cancer* 16.5 (2016): 75-87.

24. Fader AN., *et al.* "Preliminary results of a phase II study: PD1 blockade in Mismatch Repair -deficient, recurrent or persistent endometrial cancer". *Gynecologic Oncology* 141 (2016): 206-207.

25. OnoR., *et al.* "Dedifferentiated Endometrial carcinomas could be a target for immune checkpoint inhibitors (Anti PD1/PD-L1 antibodies)". *International Journal of Molecular Sciences* 20.15 (2019): 3744.

26. Guiseren V., *et al.* "Do estrogen, progesterone, P53, and Ki67 receptor ratios determined from curettage materials in endometrioid type Endometrial carcinoma predict lymph node metastasis?" *Current Problems in Cancer* (2019): S147-0272.

27. DiCristano A and Ellenson LH. "Endometrial carcinomas". *Annual Review of Pathology* 2 (2007): 57-85.

28. Kumari RH., *et al.* "behavior of endometrial hyperplasia: A longterm study of untreated hyperplasia in 170 patients". *Cancer* 56.2 (1985): 403-412.

29. Dedes KJ., *et al.* "Emerging therapeutic targets in endometrial cancer". *Nature Reviews Clinical Oncology* 8.5 (2011): 261-271.

30. Thanapprapasr D and Thanapprapasr K. "Molecular therapy as a future strategy in endometrial cancer". *Asian Pacific Journal of Cancer Prevention* 4.6 (2013): 3419-3423.

31. Gottwald U., *et al.* "New approaches for male fertility control HE6 as an example of a putative target". *Molecular and Cellular Endocrinology* 250.1-2 (2006): 49-57.

32. Kirchhoff C., *et al.* "Role of epidermal receptor HE6 in the regulation of sperm microenvironment". *Molecular and Cellular Endocrinology* 250.1-2 (2006): 43-48.

33. Richter GH., *et al.* "G –protein coupled receptor 64 promotes invasiveness and metastasis in Ewing sarcoma through FGF and MMP 1". *The Journal of Pathology* 230.1 (2013): 70-81.

34. Sohl G and Willecke K. "An update on connexin genes and their nomenclature in mouse and man". *Cell-Cell Adhesion and Communication* 10.4-6 (2003): 173-180.

35. Saez JC., *et al.* "Plasma membrane channels formed by connexins: their regulation and functions". *Physiological Reviews* 83.4 (2003): 1359-1400.

36. DecrocE., *et al.* "Connexin-related signaling in cell death: to live or die?" *Cell Death and Differentiation* 16.4 (2009): 524-536.

37. DeVuyst N., *et al.* "Ca (2+) regulation of connexin 43 hemichannels in C6 glioma and glial cells". *Cell Calcium* 46.3 (2009): 176-187.

38. Sanchez-Alvarez R., *et al.* "Tolbutamide reduces glioma cell proliferation by increasing connexin 43 which promotes the upregulation of p21 and p27 and subsequent changes in retinoblastoma phosphorylation". *Glia* 54.2 (2006): 125-134.

39. Naus CC and Laird DW. "Implications and challenges of connexin connections to cancer". *Nature Reviews Cancer* 54.2 (2006): 125-134.

40. Liethe E., *et al.* "Downregulation of gap junctions in cancer cells". *Critical Reviews Oncogenesis* 12.3-4 (2006): 225-256.

41. Kardami E., *et al.* "The role of connexins in controlling cell growth and gene expression". *Progress in Biophysics and Molecular Biology* 94.1-2 (2007): 245-264.

42. Schlemmer SR., *et al.* "Changes in connexin 43 protein expression in human Endometrial carcinoma". *Experimental and Molecular Pathology* 67.3 (1999): 150-163.

43. Ahn JII., *et al.* "G –protein coupled receptor 64(GPR64) acts as a tumor suppressor in Endometrial Cancer". *BMC Cancer* 19 (2019): 810.

44. Huang GQ., *et al.* "Serum human epididymis protein 4 combined with carbohydrate antigen 125 for Endometrial carcinoma Diagnosis: A meta-analysis and systematic review". *Genetic Testing and Molecular Biomarkers* 23.8 (2019): 580-588.

45. Jin C., *et al.* "A Comparison of death domain –Associated Protein 6 in Different Endometrial carcinoma Histotypes". *Biomarker Insights* (2019).

46. Al Hilli., *et al.* "Undifferentiated Endometrial carcinoma:a National Cancer Database analysis of prognostic factors and treatment outcomes". *International Journal of Gynecology and Obstetrics* (2019).

47. Bi R., *et al.* "Expression of SMARCA 4(BRG1) and SMARCB1 (IN1) in Dedifferentiated and Undifferentiated Endometrial carcinoma and their correlations with clinicopathological features". *Zhonghua Bing Li Xue Za Zhi* 48.8 (2019): 590-595.

48. Tichy M., *et al.* "BMI and Odds of Endometrial Adenocarcinoma in Czech Women-a Case Control Study". *Klinicka onkologie Journal* 32.4 (2019): 281-287.

49. Wang Y., *et al.* "Targeting Thyroid Receptor Interacting Protein 6 by MicroRNA-589-5p Inhibits Cell proliferation, migration, and invasion in Endometrial carcinoma". *Cancer Biotherapy and Radiopharmaceuticals* (2019).

50. Wortman M., *et al.* "Post ablation Endometrial carcinoma". *Journal of the Society of Laparoendoscopic Surgeons* 21.2 (2017): E2017.00011.

Volume 3 Issue 9 September 2019