Review Article

Uterine Serous Carcinoma: Clinicopathological features, Precursor lesions and Molecular Alterations

Sudeshna Bandyopadhyay, Adnan R. Munkarah and Rouba Ali-Fehmi*

Department of Pathology, Wayne State University School of Medicine, Harper University Hospital, USA

Abstract

Uterine serous carcinoma (USC), while only comprising 10-120% of all endometrial cases, accounts for nearly half the deaths caused by this disease. Its aggressive nature is highlighted by the high risk of recurrence seen even in patients with disease limited to the uterus. The biology of these tumors is underpinned by genetic and molecular features, which are clearly distinct from the endometrioid subtype. This dichotomy in clinical, pathological and molecular features validates a dualistic classification of endometrial carcinoma, which include Type I and Type II cancers. Type I lesions include endometrioid carcinoma and its subtypes, while serous carcinoma is a prototype of Type II. The clinical characteristics and biologic behavior of serous carcinomas generate constant interest and research to identify novel and potential therapeutic targets.

INTRODUCTION

It is estimated that approximately 52,630 endometrial carcinomas will be diagnosed in 2014 with 8,590 deaths [1]. USC, while comprising less than 10% of all endometrial carcinomas, paradoxically cause a high proportion of relapses and endometrial cancer related deaths, which is a testimony to its biologically aggressive nature [2,3]. Advanced stage disease (Stage III and IV) has a dismal prognosis with a 3-year survival of about 56% [4]. USC was first recognized by Lauchlan [5] and then described by Hendrickson as an endometrial carcinoma with histology similar to ovarian serous carcinoma [2]. Its defining histologic features and distinctive behavior have been validated in subsequent studies [6-8].

Clinico-pathological features

Uterine serous carcinoma (USC) usually occurs in postmenopausal women, in the milieu of an atrophic endometrium [9]. Although it was traditionally considered to be estrogen independent (as opposed to the endometrioid type), it has become increasingly evident that estrogen production continues after menopause from extra-ovarian sources, and therefore it is fair to say that USC are more likely estrogen deficient than estrogen independent (reviewed in [10]). High-grade histologic features characterize USC. These tumors exhibit severe nuclear pleomorphism, hyperchromasia, prominent nucleoli, increased mitotic activity and single cell apoptosis, akin to ovarian serous carcinoma. Additionally, the cells are dyshesive and lack cell polarity. Contrary to the high-grade cytology, these tumors tend to form glands (lined by these highly atypical cells). In addition, areas of papillary and solid architecture are also seen. Also seen are characteristic slit like spaces and budding/micropapillae. These tumors, diagnosed later in life, often arise in a background of atrophic endometrium [2,8,11]. Clinically, the aggressive biology of USC has been well established and this underlies the interest that has been generated in this disease. These tumors are biologically distinct with a poorer prognosis compared to stage-matched endometrioid carcinomas [3,12,13]. Sherman et al, had argued that a diagnosis of serous carcinoma is used when at least 25% of the tumor is serous in nature [8]; however, other investigators have reported that any serous component in mixed tumors will confer a worse prognosis compared to endometrioid carcinomas [14,15]. Also, it has been determined that the usual risk factors to predict recurrence in endometrioid carcinomas may not be useful to assess risk of recurrence in USC [15]. At clinical presentation, these tumors are more commonly diagnosed at a high stage with evidence of extra-uterine spread [16,17]. Slomovitz and colleagues have reported a significant frequency of extra-uterine disease (37%) and a poor prognosis [18] in patients with small endometrial lesions that

Ali-Fehmi et al. (2015)
Email: rali@med.wayne.edu

●SciMedCentral

do not invade the myometrium. Wheeler *et al* looked at a subset of "minimal USC" which included a cohort of EIC and superficial serous carcinoma, characterized as USC without myometrial or lymphovascular invasion [19]. In their experience, 25% of the EIC cases and 26% of the superficial serous carcinoma cases had extrauterine disease. In another series of patients diagnosed with "minimal USC", Hui *et al* found extra-uterine disease in 45% of the patients [20]. In a more recent study which included a cohort of USC without myoemtrial invasion, Semaan *et al* reported that 1.8% of the cases had Stage II disease, 1.8% had Stage IIIA and 16.4% of the cases had stage IVB disease [21].

The association of serous carcinoma with endometrial polyps was first described by Silva and Jenkins [22]. In their study, they described 16 patients with USC involving a polyp with minimal or no myometrial invasion. Six of these 16 (37.5%) patients also had extra-uterine disease. Involvement of an endometrial polyp was also found in 30.9% of cases in series of USC limited to the endometrium, reported by Semaan *et al*; and of these 29.4% had stage IVB disease [21]. Numerous studies have also identified a high risk of lymph node metastasis (ranging from 13% to 36%) in patients with uterine serous carcinoma without myometrial invasion [12,18,23]. These findings underline the fact that the traditional risk factors associated with endometrial carcinomas may not be applicable in USC.

Precursor lesions

Serous endometrial intraepithelial carcinoma (EIC) also known as "endometrial carcinoma in situ", "surface serous carcinoma", "minimal USC", is considered to be the precursor to USC, first recognized as intraepithelial carcinoma present adjacent to serous carcinoma [6,8,24]. This lesion is described as composed of cytologically malignant cells, similar to those seen in USC, lining the surface of the endometrium or endometrial glands without invasion of endometrial stroma, myometrium or lymphovascular spaces [25]. It is often seen in conjunction with USC, which raises the possibility that this might be a precursor lesion. Pure EIC is a rare disease. Although technically noninvasive in appearance, these tumors have been associated with extra-uterine disease, reflecting their aggressive biology [17-19,23]. Identical p53 mutations in EIC and the pelvic serous component have been described by various studies [26,27]. One of the mechanisms of spread that have been postulated is that there is dissemination of dyshesive neoplastic cells shed from the surface of the endometrium and glands through the fallopian tubes into the peritoneal cavity [28,29]. Another possibility is development of multifocal disease, as synchronous primaries involving various foci in the Mullerian epithelium [30].

Molecular signature

The concept of a dualistic model of carcinogenesis for endometrial carcinomas was first introduced by Jan Bokhman in 1982 [31] based on the widely varied clinical presentation and behavior of various types of endometrial carcinoma. This hypothesis has subsequently been validated by various studies, which have identified varying molecular aspects underlying the morphological and clinical differences between Type I, and Type II carcinomas. Type I endometrial carcinomas comprise close to 80% of all endometrial cancers and are related to unopposed

estrogen stimulation. Common molecular alterations seen in those tumors are PTEN mutations, microsatellite instability, K-ras and β-catenin mutations [32-37]. Type II tumors include serous and clear cell carcinomas. Chromosomal instability, characterized as extensive genetic alterations which include loss or gain of chromosome arms and /or whole chromosomes [38], is frequently seen in serous carcinoma [39], while microsatellite instability is reportedly uncommon [11]. The most frequently detected genetic alterations are p53 mutations, Her-2/neu amplification, negative or reduced E-cadherin expression and inactivation of p16. Below is a review of these common genetic alterations encountered in USC.

a) TP53: The most common mutations seen in uterine serous carcinoma are those involving the p53 gene and include mis-sense mutation followed by insertion mutation. Majority of the mutations in the p53 gene occur in exons 5-8 [40]. These mutations lead to an accumulation of abnormal intra-nuclear protein, which is more stable than the normal protein and therefore easily identified by immunohistochemistry. Rarely, a nonsense mutation may result in a truncated protein, which is not compatible with immunohistochemistry and therefore results in a negative staining pattern [41,42]. Loss of the normal protein prevents apoptosis and promotes tumor progression[43]. Mutations in the p53 gene have been reported in up to 90% of serous carcinomas [42]. Additionally, these mutations have also been documented in EIC adjacent to uterine serous carcinoma and EIC without associated USC, implying that these mutations occur early in the pathogenesis. The similarity in mutations between EIC and co-existent USC supports the hypothesis that EIC is linked to the development of USC. It has been postulated that the p53 mutation occurs early in one gene resulting in EIC; this is then followed by loss of heterozygosity affecting the remaining wild-type gene and resulting in progression to USC [42]. There exists a strong correlation between strong p53 protein expression (strong immunohistochemistry) and p53 mis-sense mutations. Rarely insertion mutations may result in a more unstable protein, which may not be stained by immunohistochemistry. Identical mutations have also been reported in USC and extra-uterine serous carcinoma, supporting a monoclonal origin for these tumors [26,27].

There are reports in the literature, which have attempted to establish "pre -precursors" of USC. Zheng *et al* have reported an entity, "endometrial glandular dysplasia" (EmGD), composed of single or a group of atypical appearing glands or surface epithelium, with enlarged, hyperchromatic nuclei and rare mitoses. The nuclear atypia described is less than that seen in EIC. These glands have an "intermediate' level of p53 and Ki-67 expression [44]. In subsequent molecular studies [45], approximately a third of the foci of EmGD identified showed LOH at TP53 in a pattern concordant with the co-existent EIC and USC. Concordant p53 mutations have also beed reported in EmGD and co-existing EIC and USC lesions [46].

The identification of the "p53 signature" in the fallopian tube in association with in situ carcinoma [47] has generated a search for a similar lesion in the endometrium. Jarboe *et al* reported the increased expression of p53 in cytologically benign appearing glands adjacent to EIC involving endometrial polyps and in benign

endometrial polyps. The Ki-67 labeling index in these foci ranged from 0-20% (often <5%), akin to the p53 signature described in fallopian tubes. Concurrent mutation analysis of the p53 gene from both the "p53 signature' and the adjacent EIC, showed similar mutations in a subset of cases, suggesting biological clonality [48]. Based on these findings, the authors suggest that there might exist a latent precursor of EIC in the endometrial lining, similar to the "p53 signature" lesions seen in the fallopian tube. Multiple such events with varying mutations might occur early on with only a subset progressing to malignancy [48].

It has been postulated that the hypoxic environment of atrophic endometrium promotes selection of cells able to overcome apoptosis, thereby selecting for cells with p53 mutations.

b) Her-2/neu: Her-2 receptor is membrane bound protein encoded by the Her-2/neu gene, located on chromosome 17p. It belongs to the Her family of tyrosine kinase receptors which include Her-1, Her-3 and Her-4. It is a tyrosine kinase receptor with an extra-cellular ligand binding domain, a trans-membrane component and an intracellular component related to tyrosine kinase enzyme [49,50]. There is no known ligand for the Her-2 receptor; activation occurs by homodimerization or heterodimerization with other her family receptors with Her-2/Her-3 heterodimer forming the most potent combination for mitogenesis [51]. Her-2 receptors are normally present on the cell membrane of non-neoplastic epithelial cells, but not in enough numbers to result in dimerization and activation of the tyrosine kinase enzyme. Her-2/neu gene amplification results in over-expression of the receptors with homo and hetero-dimerization and ultimately in activation of the tyrosine kinase enzyme and related pathways resulting ultimately in increased cell proliferation, survival and migration [52].

Variable levels of Her-2/neu protein expression have been reported in uterine serous carcinomas [53-56] and the concordance level with Her-2/neu gene amplification by Fluorescent in Situ Hybridization (FISH) assay has also been variable. While Santin et al found a high level of concordance between protein expression and gene amplification [53], Mentrikoski and colleagues reported concordance between protein expression and gene expression in about 1/3rd of the cases. This is far short of the concordance level of > 95%, that is mandated in breast carcinoma for this marker to be clinically relevant. The heterogeneity of Her-2/neu protein expression reported in the above studies might be attributed to small sample size, lack of standardized Her-2/neu scoring system, different histologic subtypes of cancer included and variation in the antibodies used.

Over expression of Her-2 protein has been associated with poor prognosis and shorter overall survival [54,57,58]. Santin and colleagues have also reported a significantly shorter survival in patients with Her-2/neu gene amplification, compared to those without [59]. However, other studies have failed to show such a correlation [60]. One of the explanations for this could be that the cases included in this study were already high stage or recurrent.

Interest in the role of Her-2/neu gene in endometrial carcinoma increased after the discovery of successful targeted therapy in patients with Her-2/neu positive breast carcinoma.

The same efficacy has not been established in endometrial carcinoma yet. The utility and therapeutic efficiency of Her-2/neu targeted therapy in endometrial carcinoma may follow accurate and optimal patient selection.

c) EGFR: Epidermal Growth Factor Receptor (EGFR/Her-1) is a trans- membrane tyrosine kinase receptor (belonging to her family receptors). Similarly composed of an extracellular ligand binding domain, intracellular tyrosine kinase activity and a portion spanning the cell membrane. Ligands associated with EGFR are EGF and transforming growth factor α. Mutant variants of EGFR, while do not bind a ligand have activated tyrosine kinase resulting in increased cell progression and inhibition of apoptosis. Although the studies are limited in the literature, EGFR over-expression has been reported in a significant subset of serous carcinomas; however, concomitant EGFR mutations in these cases were not documented [61,62]. Down-stream PIK3CA mutations were identified in a small proportion of these cases [62].

d) E-Cadherin: This is a cell-adhesion molecule, which is present on the cell membrane and is Calcium dependent. This molecule maintains the cell-to-cell adhesion by interacting with the actin cytoskeleton of the cell and β-catenin. Reduced or negative expression of E-Cadherin has been attributed to loss of heterozygosity of the CDH1 tumor suppressor gene in serous carcinomas [63]. Decreased or aberrant E-Cadherin function has been implicated in the epithelial to myoepithelial transformation pathway [64], which results in dyshesion of the affected neoplastic cells, increased invasive and metastatic potential with tumor dedifferentiation. Decreased E-Cadherin expression has been associated with higher grade endometrial carcinoma, increasing depth of invasion and increased lymph node metastasis [65]. Aberrant E-Cadherin protein also results in cytosolic accumulation of β-catenin with subsequent its translocation to the nucleus. β-catenin is a key player in the Wnt signaling pathway. By immunohistochemistry, E-Cadherin and β-catenin expression is membranous, in non neoplastic epithelium. Defective expression of the E-Cadherin protein results in aberrant staining pattern described as reduced and patchy or negative; while β-catenin is seen to be cytosolic or nuclear. In uterine serous carcinoma, authors have shown decreased E-Cadherin expression in at least a proportion of serous carcinoma [36,63,66,67], suggesting that dysfunction of this molecule may at least in part contribute to the aggressive behavior of these tumors. Increased expression of E-Cadherin in Stage I-III endometrial carcinomas has been associated with a better prognosis [63]. A concurrent nuclear localization of β-catenin is not observed in serous carcinomas, suggesting that the abnormalities of this molecule are more relevant in the Type I carcinogenesis.

e) P16 (INK4a): This is a tumor suppressor gene present on the 9p21 gene locus. It controls the G1-S transition of the cell cycle via the pRB pathway. Any damage to p16 by mutation or hypermethylation will result in defective tumor suppressor function of the pRB gene and this may result in over-expression of p16 protein, presumable due to an aberrant negative feedback mechanism. Loss of p16 function in various neoplasms has been well documented including head and neck squamous cell carcinoma, pulmonary neuroendocrine carcinomas and

pulmonary squamous and adenocarcinomas. High expression of p16 is also seen in cervical adenocarcinoma and adenocarcinoma in situ, in these cases being used as a marker for high risk HPV infection. Although limited, studies have shown that a significantly higher proportion of USC are diffusely positive for p16 by immunohistochemistry when compared to non –serous USC [68,69]. These studies also demonstrated a lack of high risk HPV DNA in these cases of USC, suggesting alternate molecular mechanisms might be involved in carcinogenesis.

Genomic characterization of USC

Most recently, The Cancer Genome Atlas Research Network published its findings from the genomic characterization of 373 endometrial carcinomas, which included 66 cases of USC. By unsupervised hierarchical clustering, they found that endometrial carcinomas could be grouped into 4 distinct clusters. USC (along with a subset of the FIGO 3 endometrioid carcinomas) formed a separate cluster which was characterized by a high frequency of TP53 mutations (90%), fewer PTEN mutations (11%) and MSI (6%). This cluster also included other gene amplifications, which included ERRB2, MYC, CCNE1, FGFR3 and SOX17. Tumors in this "serous-like" cluster had a worse prognosis compared to the "endometrioid –like" tumors [70].

CONCLUSION

USC is an aggressive variant of endometrial carcinoma with poor prognosis in even seemingly limited or early stage disease. This highlights the need to understand the pathogenesis of this disease and identify novel therapeutic treatments. Continued appraisal of its molecular alterations may help identify precursor lesions that may be easier to cure. Furthermore, such understanding will identify specific changes that can be targeted with novel approaches and drugs.

REFERENCES

1. ACS: Cancer Facts and Figures. American Cancer Society; 1-70 2014.

2. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982; 6: 93-108.

3. Slomovitz BM, Caputo TA, Gretz HF, Economos K, Tortoriello DV, Schlosshauer PW, et al. A comparative analysis of 57 serous borderline tumors with and without a noninvasive micropapillary component. The American journal of surgical pathology. 2002; 26: 592-600.

4. Sovak MA, Hensley ML, Dupont J, Ishill N, Alektiar KM, Abu-Rustum N, et al. Paclitaxel and carboplatin in the adjuvant treatment of patients with high-risk stage III and IV endometrial cancer: a retrospective study. Gynecol Oncol. 2006; 103: 451-457.

5. Lauchlan SC. Tubal (serous) carcinoma of the endometrium. Arch Pathol Lab Med. 1981; 105: 615-618.

6. Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. Hum Pathol. 1995; 26: 1260-1267.

7. Lachance JA, Everett EN, Greer B, Mandel L, Swisher E, Tamimi H, et al.The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecologic oncology. 2006; 101: 470-475.

8. Sherman ME, Bitterman P, Rosenshein NB, Delgado G, Kurman RJ.

9. Kurman RJ, Ellenson LH, Ronnett BM. (Eds): Blaustein's Pathology of the Female Genital Tract (6th Ed). 2011; 393-452.

10. Sivridis E, Giatromanolaki A. The pathogenesis of endometrial carcinomas at menopause: facts and figures. J Clin Pathol. 2011; 64: 553-560.

11. Tashiro H, Lax SF, Gaudin PB, Isacson C, Cho KR, Hedrick L. Microsatellite instability is uncommon in uterine serous carcinoma. Am J Pathol. 1997; 150: 75-79.

12. Cirisano FD, Robboy SJ, Dodge RK, Bentley RC, Krigman HR, Synan IS, et al. The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecologic oncology. 2000; 77: 55-65.

13. Hamilton CA, Cheung MK, Osann K, Balzer B, Berman ML, Husain A, et al. The effect of adjuvant chemotherapy versus whole abdominopelvic radiation on the survival of patients with advanced stage uterine papillary serous carcinoma. Gynecol Oncol. 2006; 103: 679-683.

14. Boruta DM, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC, et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer. 2004; 101: 2214-2221.

15. Fader AN, Starks D, Gehrig PA, Secord AA, Frasure HE, O'Malley DM, et al. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). Gynecologic oncology 2009; 115: 244-248.

16. Tropé C, Kristensen GB, Abeler VM. Clear-cell and papillary serous cancer: treatment options. Best Pract Res Clin Obstet Gynaecol. 2001; 15: 433-446.

17. Soslow RA, Pirog E, Isacson C. Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis. Am J Surg Pathol. 2000; 24: 726-732.

18. Slomovitz BM, Burke TW, Eifel PJ, Ramondetta LM, Silva EG, Jhingran A, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol. 2003; 91: 463-469.

19. Wheeler DT, Bell KA, Kurman RJ, Sherman ME. Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. Am J Surg Pathol. 2000; 24: 797-806.

20. Hui P, Kelly M, O'Malley DM, Tavassoli F, Schwartz PE. Minimal uterine serous carcinoma: a clinicopathological study of 40 cases. Modern pathology: an official journal of the United States and Canadian Academy of Pathology. 2005; 18: 75-82.

21. Semaan A, Mert I, Munkarah AR, Bandyopadhyay S, Mahdi HS, Winer IS, et al. Clinical and pathologic characteristics of serous carcinoma confined to the endometrium: a multi-institutional study. International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists. 2013; 32: 181-187.

22. Silva EG, Jenkins R. Serous carcinoma in endometrial polyps. Mod Pathol. 1990; 3: 120-128.

23. Goff BA, Kato D, Schmidt RA, Ek M, Ferry JA, Muntz HG, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecologic oncology 1994; 54: 264-268.

24. Spiegel GW. Endometrial carcinoma in situ in postmenopausal women. Am J Surg Pathol. 1995; 19: 417-432.

25. Sherman ME, Bur ME, Kurman RJ. p53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. Human pathology. 1995; 26: 1268-1274.

26. Baergen RN, Warren CD, Isacson C, Ellenson LH. Early uterine serous

⦿SciMedCentral

carcinoma: clonal origin of extrauterine disease. International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists 2001; 20: 214-219.

27. Kupryjanczyk J, Thor AD, Beauchamp R, Poremba C, Scully RE, Yandell DW. Ovarian, peritoneal, and endometrial serous carcinoma: clonal origin of multifocal disease. Modern pathology: an official journal of the United States and Canadian Academy of Pathology. 1996; 9: 166-173.

28. Snyder MJ, Bentley R, Robboy SJ. Transtubal spread of serous adenocarcinoma of the endometrium: an underrecognized mechanism of metastasis. International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists. 2006; 25: 155-160.

29. Stewart CJ, Doherty DA, Havlat M, Koay MH, Leung YC, Naran A, et al. Transtubal spread of endometrial carcinoma: correlation of intra-luminal tumour cells with tumour grade, peritoneal fluid cytology, and extra-uterine metastasis. Pathology. 2013, 45:382-7.

30. Muto MG, Welch WR, Mok SC, Bandera CA, Fishbaugh PM, Tsao SW, et al. Evidence for a multifocal origin of papillary serous carcinoma of the peritoneum. Cancer Res. 1995; 55: 490-492.

31. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983; 15: 10-17.

32. Caduff RF, Johnston CM, Frank TS. Mutations of the Ki-ras oncogene in carcinoma of the endometrium. Am J Pathol. 1995; 146: 182-188.

33. Caduff RF, Johnston CM, Svoboda-Newman SM, Poy EL, Merajver SD, Frank TS. Clinical and pathological significance of microsatellite instability in sporadic endometrial carcinoma. Am J Pathol. 1996; 148: 1671-1678.

34. Enomoto T, Inoue M, Perantoni AO, Terakawa N, Tanizawa O, Rice JM. K-ras activation in neoplasms of the human female reproductive tract. Cancer Res. 1990; 50: 6139-6145.

35. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. Journal of the National Cancer Institute. 2000; 92: 924-930.

36. Schlosshauer PW, Ellenson LH, Soslow RA. Beta-catenin and E-cadherin expression patterns in high-grade endometrial carcinoma are associated with histological subtype. Modern pathology: an official journal of the United States and Canadian Academy of Pathology. Inc 2002; 15: 1032-1037.

37. Palacios J, Catasus L, Moreno-Bueno G, Matias-Guiu X, Prat J, Gamallo C. Beta- and gamma-catenin expression in endometrial carcinoma. Relationship with clinicopathological features and microsatellite instability. Virchows Archiv : an international journal of pathology. 2001; 438: 464-469.

38. Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. Nature. 1997; 386: 623-627.

39. Nordstrom B, Strang P, Lindgren A, Bergstrom R, Tribukait B. Endometrial carcinoma: the prognostic impact of papillary serous carcinoma (UPSC) in relation to nuclear grade, DNA ploidy and p53 expression. Anticancer research. 1996; 16: 899-904.

40. Harris CC. 1995 Deichmann Lecture--p53 tumor suppressor gene: at the crossroads of molecular carcinogenesis, molecular epidemiology and cancer risk assessment. Toxicology letters. 1995; 82-83: 1-7.

41. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer. 2000; 88: 814-824.

42. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. Am J Pathol. 1997; 150: 177-185.

43. Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89: 7491-7495.

44. Zheng W, Liang SX, Yu H, Rutherford T, Chambers SK, Schwartz PE. Endometrial glandular dysplasia: a newly defined precursor lesion of uterine papillary serous carcinoma. Part I: morphologic features. Int j sur path. 2004; 12: 207-223.

45. Liang SX, Chambers SK, Cheng L, Zhang S, Zhou Y, Zheng W. Endometrial glandular dysplasia: a putative precursor lesion of uterine papillary serous carcinoma. Part II: molecular features. International journal of surgical pathology. 2004; 12: 319-331.

46. Jia L, Liu Y, Yi X, Miron A, Crum CP, Kong B, et al. Endometrial glandular dysplasia with frequent p53 gene mutation: a genetic evidence supporting its precancer nature for endometrial serous carcinoma. Clin Cancer Rese.2008; 14: 2263-2269.

47. Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol. 2007; 19: 3-9.

48. Jarboe EA, Pizer ES, Miron A, Monte N, Mutter GL, Crum CP. Evidence for a latent precursor (p53 signature) that may precede serous endometrial intraepithelial carcinoma. Modern pathology: an official journal of the United States and Canadian Academy of Pathology. 2009; 22: 345-350.

49. Hung MC, Lau YK. Basic science of HER-2/neu: a review. Semin Oncol. 1999; 26: 51-59.

50. Busse D, Doughty RS, Arteaga CL. HER-2/neu (erbB-2) and the cell cycle. Semin Oncol. 2000; 27: 3-8.

51. Graus-Porta D, Beerli RR, Daly JM, Hynes NE . ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. EMBO J. 1997; 16: 1647-1655.

52. Reese DM, Slamon DJ. HER-2/neu signal transduction in human breast and ovarian cancer. Stem Cells. 1997; 15: 1-8.

53. Santin AD, Bellone S, Van Stedum S, Bushen W, De Las Casas LE, Korourian S, et al. Determination of HER2/neu status in uterine serous papillary carcinoma: Comparative analysis of immunohistochemistry and fluorescence in situ hybridization. Gynecologic oncology. 2005, 98:24-30.

54. Slomovitz BM, Broaddus RR, Burke TW, Sneige N, Soliman PT, Wu W, et al. Her-2/neu overexpression and amplification in uterine papillary serous carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2004; 22: 3126-3132.

55. Halperin R, Zehavi S, Habler L, Hadas E, Bukovsky I, Schneider D. Comparative immunohistochemical study of endometrioid and serous papillary carcinoma of endometrium. European journal of gynaecological oncology. 2001; 22: 122-126.

56. Mentrikoski MJ, Stoler MH. HER2 immunohistochemistry significantly overestimates HER2 amplification in uterine papillary serous carcinomas. The American journal of surgical pathology 2014; 38: 844-851.

57. Díaz-Montes TP, Ji H, Smith Sehdev AE, Zahurak ML, Kurman RJ, Armstrong DK, et al. Clinical significance of Her-2/neu overexpression in uterine serous carcinoma. Gynecol Oncol. 2006; 100: 139-144.

58. Togami S, Sasajima Y, Oi T, Ishikawa M, Onda T, Ikeda S, et al.

Ali-Fehmi et al. (2015)
Email: rali@med.wayne.edu

SciMedCentral

Clinicopathological and prognostic impact of human epidermal growth factor receptor type 2 (HER2) and hormone receptor expression in uterine papillary serous carcinoma. Cancer science. 2012; 103: 926-932.

59. Santin AD, Bellone S, Van Stedum S, Bushen W, Palmieri M, Siegel ER, et al. Amplification of c-erbB2 oncogene: a major prognostic indicator in uterine serous papillary carcinoma. Cancer 2005; 104: 1391-1397.

60. Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2010; 116: 15-20.

61. Konecny GE, Santos L, Winterhoff B, Hatmal M, Keeney GL, Mariani A, et al. HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. British journal of cancer. 2009; 100: 89-95.

62. Hayes MP, Douglas W, Ellenson LH. Molecular alterations of EGFR and PIK3CA in uterine serous carcinoma. Gynecol Oncol. 2009; 113: 370-373.

63. Moreno-Bueno G, Hardisson D, Sarrio D, Sanchez C, Cassia R, Prat J, et al. Abnormalities of E- and P-cadherin and catenin (beta-, gamma-catenin, and p120ctn) expression in endometrial cancer and endometrial atypical hyperplasia. The Journal of pathology. 2003; 199: 471-478.

64. Kang Y, Massagué J. Epithelial-mesenchymal transitions: twist in development and metastasis. Cell. 2004; 118: 277-279.

65. Sakuragi N, Nishiya M, Ikeda K, Ohkouch T, Furth EE, Hareyama H, et al. Decreased E-cadherin expression in endometrial carcinoma is associated with tumor dedifferentiation and deep myometrial invasion. Gynecologic oncology. 1994; 53: 183-189.

66. Yalta T, Atay L, Atalay F, Caydere M, Gonultas M, Ustun H. E-cadherin expression in endometrial malignancies: comparison between endometrioid and non-endometrioid carcinomas. The Journal of international medical research. 2009; 37: 163-168.

67. Holcomb K, Delatorre R, Pedemonte B, McLeod C, Anderson L, Chambers J. E-cadherin expression in endometrioid, papillary serous, and clear cell carcinoma of the endometrium. Obstet Gynecol. 2002; 100: 1290-1295.

68. Yemelyanova A, Ji H, Shih Ie M, Wang TL, Wu LS, Ronnett BM. Utility of p16 expression for distinction of uterine serous carcinomas from endometrial endometrioid and endocervical adenocarcinomas: immunohistochemical analysis of 201 cases. The American journal of surgical pathology. 2009; 33: 1504-1514.

69. Chiesa-Vottero AG, Malpica A, Deavers MT, Broaddus R, Nuovo GJ, Silva EG. Immunohistochemical overexpression of p16 and p53 in uterine serous carcinoma and ovarian high-grade serous carcinoma. International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists. 2007; 26: 328-333.

70. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497: 67-73.