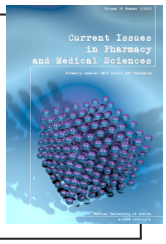
DOI: 10.2478/cipms-2024-0031 Curr. Issues Pharm. Med. Sci., Vol. 37, No. 3, Pages 190-194

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/



Molecular alterations in mucinous ovarian tumors – a review

Weronika Kawecka[1*], Michal Bielak[2], Karolina Urbanska[3]

[1] Stefan Wyszynski Regional Specialist Hospital in Lublin, Poland
[2] Students' Scientific Association, Department of Paediatric Neurology, Medical University of Lublin, Poland
[3] Students' Research Group at the Chair and Department of General and Paediatric Ophthalmology, Medical University of Lublin, Poland

ARTICLE INFO

Received 18 January 2024
Accepted 08 June 2024

Keywords:
mucinous ovarian tumors,
molecular alterations,
targeted therapy,
ovarian metastasis.

ABSTRACT

Mucinous ovarian tumors (MOTs) include primary and secondary neoplasms, the latter of which contribute for 80% of all cases. The most common site of origin for secondary MOTs is the gastrointestinal tract. Proper differentiation between primary and metastatic lesions is essential for effective treatment. Currently, definitive diagnosis is made based on post-operative histopathological examination with the use of immunohistochemical markers. However, the final diagnosis presents a challenge because of the histopathological similarity between mucinous metastases and primary ovarian lesions. Generally, treatment consists of cytoreductive surgery and adjuvant chemotherapy, even though malignant tumors are found to be chemo-resistant. Prognosis depends on the type of the tumor, presence of metastases and patient's general condition. Further research on the genetic background of MOTs is necessary for the better understanding of their origin and more effective treatment. This review aims to summarize recent advances in the field of the molecular features of MOTs and their implications for the diagnostic pathways and potential adjuvant therapy options. The analysis of molecular alterations might not only be an important prognostic factor, but also a useful diagnostic tool in distinguishing between primary mucinous tumors and extra-ovarian metastases or other subtypes of epithelial ovarian neoplasms. Moreover, the examination of genetic mutations seems to increase the efficiency of targeted therapy. However, more research evaluating such therapies in pre-clinical models is needed to improve the results of the diagnostics and treatment of MOTs.

INTRODUCTION

Mucinous ovarian tumors (MOTs) are a heterogenous group of diseases that include primary tumors (PMOTs) and metastases from extra-ovarian sites, the latter of which are much more common [1]. Accurate diagnosis and treatment are challenging because of the histopathological similarity between PMOTs and mucinous metastases, especially those of gastrointestinal origin [2-4]. Deepened research on the genetics of MOTs is crucial to improve the management of the disease. Molecular alterations were once believed to be mainly prognostic factors, but current studies highlight their implications for differential diagnosis and targeted therapy [1,2,5-8]. The aim of this study is to summarize the current state of knowledge about the most common mutations in MOTs, the differences between primary and metastatic tumors, and possible therapeutic pathways in adjuvant treatment.

* **Corresponding author**
e-mail: wkawecka@szpital.lublin.pl

Histological classification and epidemiology

Primary mucinous ovarian tumors (PMOTs) are one of the histological subtypes of epithelial ovarian neoplasms (EONs) and account for 3-15% of all primary malignancies of the ovary [1,2,9-11]. They are divided into benign (mucinous cystadenoma and mucinous adenofibroma), borderline (mucinous borderline tumor), and malignant (mucinous carcinoma) type [2,12]. PMOTs may also exhibit intestinal-type morphology or, rarely, endocervical-type morphology, and therefore be mistaken for metastases from diverse extra-ovarian sites, such as the colon, stomach, pancreas and uterus [1,2,13]. 80% of all PMOTs are benign lesions, while the incidence of mucinous carcinoma (MOC) is estimated at 3% [12,14-16]. Borderline ovarian tumors account for 10-15% of all epithelial ovarian tumors; approximately 80% being of mucinous origin [12,17,18]. MOCs, on the other hand, are divided into expansile and infiltrative subtype, both of which may co-occur. However, the expansile MOC is more common [12,19-21].

According to research, 80% of all MOC are metastases: 45% from the gastrointestinal tract, 2-20% from the pancreas, 18% from cervix and endometrium, and 8-15% from the breast [3,15,22-24]. The average age of patients with ovarian metastases is 55 years [24]. Because of the histopathological similarity between PMOTs and gastrointestinal/appendiceal tumors, some authors suggest a modified classification, which includes low-grade or high-grade mucinous neoplasm and mucinous adenocarcinoma, intestinal type [12,25]. The differentiation between PMOTs and metastases is mainly based on histopathological examination with the use of immunohistochemical (IHC) markers [9]. Histologically, mucinous carcinomas are categorized into cystic and colloid type, based on intracellular or extracellular mucin localization. A large amount (>50%) of intracellular mucin in at least 90% of tumor cells is characteristic of ovarian and pancreatic cystic mucinous carcinomas, whereas colloid carcinomas deriving from the gastrointestinal tract, lung, breast or skin contain abundant extracellular mucin, accounting for at least 50% of tumor volume [15,26]. The investigation of IHC markers is a complementary procedure for the histopathological examination, although the levels of markers overlap in primary and secondary mucinous ovarian tumors [3,4]. The typical IHC profile for MOC is CK7(+), CK20 and CDX2(+/-), PAX8(+/-), and SATB2(-). The positivity of PAX8 strongly suggests ovarian origin [15,27-31]. The characteristic histopathological features of PMOTs are shown in Table 1.

Table 1. Abbreviated classification of primary mucinous neoplasms of the ovary [2,12,15,16,20,21,25,32–34]

Feature	Benign	Borderline	Carcinoma
Histological subtypes	Mucinous cystadenoma Mucinous adenofibroma With focal epithelial proliferation	With microinvasion With microinvasive carcinoma With mural nodule	With expansile invasion With infiltrative expansion With mural nodules
Age	50 years old	45 years old	<40 years old
Histopathological characteristics	Cysts and gland lined by a single layer of gastrointestinal or Müllerian-type mucinous epithelium Possibility of uncommon incidence of goblet cells, neuroendocrine or Paneth cells	Multiloculated Variably-sized cysts with at least 10% of the total tumor area demonstrating epithelial stratification with small papillae or tufts	Expansile growth: architecturally complex and confluent, well-formed glands with round, convex outer outlines, absent or minimal stroma, which does not surround individual glands entirely Infiltrative growth: glands with irregular contours, possibility of stromal desmoplasia

Molecular relation between benign, borderline and malignant ovarian mucinous tumors

The most frequent molecular alterations in all PMOTs are K*RAS* mutation and *CDKN2A* inactivation [1,2,6,7]. It is indicated that, in most cases, mucinous carcinomas develop from mucinous borderline tumors, and sporadically from mature cystic teratomas or Brenner tumors with gastrointestinal type cells [6,9,35,36]. Recent studies are not unanimous in determining the particular changes in molecular features between benign, borderline and malignant mucinous tumors [8]. Some sources suggest that benign tumors exhibit either *KRAS* mutation or *CDKN2A* inactivation, while borderline tumors are more likely to have both, with additional copy number variations. In MOC, copy number alterations (especially amplification of 9p13.3) and *TP53* mutations are even more likely to appear [6,35,36]. One study has revealed that the prevalence of *KRAS*, *BRAF* and/or *CDKN2A* mutations in mucinous borderline tumors and MOCs totals 95% and 91%, respectively [1]. It is believed that the frequency of TP53 pathogenic variants and whole genomic copy number variations are key drivers of malignancy [1,37]. Other studies suggest that the increased number of *KRAS* mutations is the strongest predictor of unequivocal malignancy in ovarian mucinous neoplasms [2,38]. Moreover, the less common *BRAF* mutations also seem to appear more frequently in carcinomas than in benign or borderline mucinous tumors [39]. A recent study reveals that *HER2* overexpression or amplification is observed more often in MOC than in borderline mucinous tumors (35,3% and 5,3%, respectively), and this correlation might play a role in differential diagnosis [8]. On the other hand, the absence of *KRAS* or *HER2* mutations in mucinous carcinomas might suggest that they originated from less frequent precursors, such as like mature cystic teratomas [40].

Generally, the most common molecular alterations in MOC include *KRAS* (40-76%) or *HER2* amplification (15-35%), *CDKN2A* (33-76%) and *TP53* (52-75%) mutations, as well as copy number alterations, which are much more prevalent in MOC than in their non-carcinomatous counterparts. One such example of copy number alteration is amplification of 9p13, which is usually seen in tumors with both *KRAS* and *TP53* mutations. Among the genes less frequently altered in MOC are *RNF43*, *BRAF* (0-9%), *PIK3CA* (6%) and *ARID1A* (8-12%) [1,2,6,8,12,15,27,39,41,42]. There is still limited data available to compare molecular features between infiltrative and expansile MOC. One study suggests that *HER2* overexpression or amplification is more common in expansile MOC than in infiltrative MOC, but the difference is not statistically significant [8].

Differences between mucinous ovarian neoplasms and other tumor types

MOTs show different molecular mutations than other subtypes of EONs. Epithelial ovarian cancer (EOC) is histologically divided into serous (high-grade (71% of all EOCs) and low-grade (4,1%)), endometroid (8,3%), clear-cell (9,5%), and mucinous EOC [43]. However, there is another dualistic classification, which divides EOC into type I (low-grade) carcinoma and type II (high-grade) carcinoma [7]. Type I EOCs account for 25% of the total and include low-grade serous EOC, low-grade endometroid EOC, mucinous EOC, and clear-cell EOC, meanwhile type II account for 75% of all EOC and include high-grade serous EOC, high-grade endometroid EOC, undifferentiated carcinoma and carcinosarcoma [7]. Generally, in type II EOCs, *TP53* mutation is the most frequent (>95%), followed by *BRCA1* or BRCA2 mutation, which is found in 30-50% of all type II EOCs [5-7,44]. The most common mutations in low-grade serous EOC are *BRAF* (8-38%) and *KRAS*

(19-25%), while other genes, such as *NRAS* (8%), *EIFAX* (15%) or *USP9X* (11%), are less often involved [5-7,45]. Mutations most characteristic of clear-cell carcinoma include *ARID1A* (40-75%), *PIK3CA* (40-50%), *PPP2R1A* (10-20%), *KRAS* (5-20%) and *TERT* (15%); *HER2* amplification, on the other hand, appears in 15% of all cases [5,6,46-49]. In turn, endometroid carcinomas usually exhibit mutations in genes *CTNNB1* (30-50%), *PIK3CA* (15-45%), *ARID1A* (30-40%), *PTEN* (20-45%), *KRAS* (10-40%) and *TP53* (10-25%) [5,6,50,51]. In borderline endometroid tumors, the incidence of *CTNNB1* mutations is exceptionally high and amounts to 90% [6]. The most frequent mutations in histological subtypes of MOCs are listed in Table 2.

Table 2. Comparison of the most common molecular alterations in the most significant subtypes of epithelial ovarian carcinomas [5-7]

Subtype of EOC	Endometroid EOC	Clear-cell EOC	Mucinous EOC	Low-grade serous EOC	High-grade serous EOC
The most common mutations	*CTNNB1, PIK3CA, ARID1A, PTEN, KRAS, TP53* genes	*PIK3CA, ARID1A, KRAS, PPP2R1A, TERT* promoter genes	*KRAS, TP53, RNF43, ARID1A, BRAF, PIK3CA, CDKN2A* genes	*KRAS, BRAF, NRAS, USP9X, EIF1AX* genes	*TP53, BRCA1, BRCA2* genes

The molecular findings might be helpful in differentiating between PMOTs and metastatic mucinous tumors involving the ovary. For instance, *APC* inactivating mutations are more frequent in colorectal metastases than in primary *MOCs* (71% vs 4%, respectively) [52]. Another study shows that *TP53* and *KRAS* mutations are more common in primary MOCs than gastric metastases, meanwhile *APC*, *PIK3CA* and *FBXW7* are more common in colorectal (CRC) metastases than in primary MOCs [11,15,26,41]. In contrast, the prevalence of KRAS mutations in MOCs and mucinous CRC metastases is similar (33-46% vs 31-48%, respectively), while BRAF mutations in MOCs (0-9%) are significantly lower than in mucinous CRC metastases (15-27%). Moreover, *HER2* amplification appears in 18-35% of all MOCs, as compared to <1% in mucinous CRC metastases and only 2% in non-mucinous CRC metastases [11,15,26]. Furthermore, metastases derived from HPV-associated endocervical adenocarcinoma do not typically include *TP53* mutations, unlike MOC. Although the *TP53*, *KRAS*, and *CDKN2A* alterations overlap in gastric-type endocervical adenocarcinoma and MOC, the presence of *STK11* mutations is more indicative of the first one [53,54].

Molecular alterations in targeted therapy and prognosis

The management of PMOTs depends on the histopathological subtype and the size of the tumor. Generally, in the case of benign mucinous tumors, complete surgical resection is sufficient and recurrence is not observed [2]. 90% of all mucinous borderline tumors are diagnosed in stage I and only 10% are associated with extra-ovarian spread. In young patients, resection of primary borderline tumor with fertility preservation is recommended and relapse is uncommon. Postoperative therapy is dedicated to patients with serous borderline tumors and invasive implants [17]. In early-stage MOC, staging procedure including peritoneal washing for cytology, hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and multiple peritoneal biopsies, is the gold standard. In advanced MOC, cytoreductive surgery with complete removal of all measurable disease is recommended [11,15,22,34,55]. The advanced stage of the disease requires platinum-based chemotherapy, although MOC has lower response than other types of EOC and is suspected to be platinum-resistant [7,11,23,37].

The rarity of advanced-stage MOC and its chemoresistance make proper management exceptionally difficult. Targeted therapy puts a new light on the treatment of the disease, although the available data is limited [15,56]. Amplification of *ERBB2* (26,7%) and *BRAF* mutation (9%) have been proven to be good targets for such therapy. Genetic alterations that are currently being examined as potential targets in clinical trials include: *KRAS*/*NRAS* mutations (66%), TP53 missense mutation (49%), *RNF43* mutation (11%), ARID1A mutation (10%) and *PIK3CA*/*PTEN* mutation (9%) [56,57]. In non-mucinous type EOC, poly-adenosine diphosphate-ribose polymerase inhibitors (PARPIs) turned out to be a milestone. However, they have no role in the treatment of MOCs as these tumors are not associated with BRCA mutations or homologous recombinant deficiency [15]. Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is found to improve progression-free survival (PFS) in EOC in the primary setting and in the platinum-sensitive and platinum-resistant recurrence settings. Moreover, the adjuvant therapy with bevacizumab has been demonstrated to increase overall survival in sub-optimally cytoreduced EOC and in metastatic colorectal carcinoma [58-63]. Cetuximab, EGFR monoclonal antibody, seems to be efficient in *KRAS* wild-type cases of CRC metastases and ovarian cancer. However, the results of cetuximab both as a single therapy or in combination with standard chemotherapy in ovarian cancer without specification of *KRAS* status were disappointing [15,64-66]. Limited studies suggest that anti-HER2 therapy with trastuzumab in MOC with *HER2* amplification might be sufficient, although more data is needed [6,15,56,67]. Moreover, PLK1 inhibitors, dual RAS/RAF inhibitors and MEK inhibitors are suggested to be efficient in treatment of MOC, although there are currently no published studies evaluating such therapies in pre-clinical models [56].

Benign mucinous ovarian tumors, borderline mucinous ovarian tumors, and early-stage MOC have an excellent prognosis (>90% of 5-year OS), however, survival in metastatic disease ranges between 12 and 30 months (15,37,68). Moreover, infiltrative MOC has a significantly poorer PFS than expansile MOC (65,6% *vs* 94,7%), while the difference in OS was similar (90% *vs* 88.9%, respectively) (16). It is clearly evident that high copy number aberration burden is associated with poorer prognosis in MOC [1,6].

CONCLUSIONS

Molecular features in mucinous ovarian tumors are believed to help understand the origin and taxonomy of these rare neoplasms. They are not only prognostic factors, but also useful diagnostic tools in differentiating between PMOTs and other subtypes of EONs and mucinous metastases involving the ovary. Because surgical

management and adjuvant chemotherapy might be insufficient in the advanced disease, the possibilities within targeted therapies associated with molecular aberrations should be intensively investigated.

ORCID iDs

Weronika Kawecka https://orcid.org/0000-0001-7367-5859
Michał Bielak https://orcid.org/0000-0002-0899-8069
Karolina Urbańska https://orcid.org/0000-0002-8432-7232

REFERENCES

1. Cheasley D, Wakefield MJ, Ryland GL, Allan PE, Alsop K, Amarasinghe KC, et al. The molecular origin and taxonomy of mucinous ovarian carcinoma. *Nat Commun*. 2019;10(1).
2. Mills AM, Shanes ED. Mucinous ovarian tumors. *Surg Pathol Clin*. 2019;12:565-85.
3. Kubeček O, Laco J, Špaček J, Petera J, Kopecký J, Kubečková A, et al. The pathogenesis, diagnosis, and management of metastatic tumors to the ovary: a comprehensive review. *Clin Exp Metastasis*. 2017; 34:295-307.
4. Dundr P, Singh N, Nožičková B, Němejcová K, Bártů M, Stružinská I. Primary mucinous ovarian tumors vs. ovarian metastases from gastrointestinal tract, pancreas and biliary tree: a review of current problematics. *Diagn Pathol*. 2021;16(1):20.
5. Hollis RL. Molecular characteristics and clinical behaviour of epithelial ovarian cancers. *Cancer Lett*. 2023;555:216057.
6. Ordulu Z, Watkins J, Ritterhouse LL. Molecular pathology of ovarian epithelial neoplasms: predictive, prognostic, and emerging biomarkers. *Surg Pathol Clin*. 2021;14:415-28.
7. Dion L, Carton I, Jaillard S, Timoh KN, Henno S, Sardain H, et al. The landscape and therapeutic implications of molecular profiles in epithelial ovarian cancer. *J Clin Med*. 2020;9:1-12.
8. Dundr P, Bártů M, Bosse T, Bui QH, Cibula D, Drozenová J, et al. Primary mucinous tumors of the ovary: An interobserver reproducibility and detailed molecular study reveals significant overlap between diagnostic categories. *Mod Pathol*. 2023;36(1): 100040.
9. Mehra P, Aditi S, Prasad KM, Bariar NK. Histomorphological analysis of ovarian neoplasms according to the 2020 WHO classification of ovarian tumors: A distribution pattern in a tertiary care center. *Cureus*. 2023;15(4).
10. Köbel M, Kang EY. The evolution of ovarian carcinoma subclassification. *Cancers*. 2022;14:416.
11. Xu W, Rush J, Rickett K, Coward JIG. Mucinous ovarian cancer: A therapeutic review. *Crit Rev Oncol Hematol*. 2016;102:26-36.
12. Talia KL, Parra-Herran C, McCluggage WG. Ovarian mucinous and seromucinous neoplasms: problematic aspects and modern diagnostic approach. *Histopathology*. 2022;80:255-78.
13. Ledermann JA, Luvero D, Shafer A, O'Connor D, Mangili G, Friedlander M, et al. Gynecologic cancer intergroup (GCIG) Consensus review for mucinous ovarian carcinoma. *Int J Gynecol Cancer*. 2014;24:14-9.
14. Hart WRMD. Mucinous tumors of the ovary: A review. *Int J Gynecol Pathol*. 2005;24(1):4-25.
15. Babaier A, Ghatage P. Mucinous cancer of the ovary: Overview and current status. *Diagnostics*. 2020;10(1):52.
16. Nistor S, El-Tawab S, Wong F, Zouridis A, Roux R, Manek S, et al. The clinicopathological characteristics and survival outcomes of primary expansile vs. infiltrative mucinous ovarian adenocarcinoma: a retrospective study sharing the experience of a tertiary centre. *Transl Cancer Res*. 2023;12(10):2682-92.
17. Gershenson DM. Management of borderline ovarian tumours. *Best Pract Res Clin Obstet Gynaecol*. 2017;41:49-59.
18. Song T, Lee YY, Choi CH, Kim TJ, Lee JW, Bae DS, et al. Histologic distribution of borderline ovarian tumors worldwide: A systematic review. *J Gynecol Oncol*. 2012;24(1):44-51.
19. Muyldermans K, Moerman P, Amant F, Leunen K, Neven P, Vergote I. Primary invasive mucinous ovarian carcinoma of the intestinal type: Importance of the expansile versus infiltrative type in predicting recurrence and lymph node metastases. *Eur J Cancer*. 2013;49(7):1600-8.
20. Huin M, Lorenzini J, Arbion F, Carcopino X, Touboul C, Dabi Y, et al. Presentation and prognosis of primary expansile and infiltrative mucinous carcinomas of the ovary. *J Clin Med*. 2022;11(20).
21. Lee KR, Scully RE. Mucinous tumors of the ovary a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with "pseudomyxoma peritonei". *Am J Surg Path*. 2000;24(11):1447-64.
22. Cobb LP, Gershenson DM. Treatment of rare epithelial ovarian tumors. *Hematol Oncol Clin North Am*. 2018;32:1011-24.
23. Shimada M, Kigawa J, Ohishi Y, Yasuda M, Suzuki M, Hiura M, et al. Clinicopathological characteristics of mucinous adenocarcinoma of the ovary. *Gynecol Oncol*. 2009;113(3):331-4.
24. Kondi-Pafiti A, Kairi-Vasilatou E, Iavazzo C, Dastamani C, Bakalianou K, Liapis A, et al. Metastatic neoplasms of the ovaries: A clinicopathological study of 97 cases. *Arch Gynecol Obstet*. 2011;284(5):1283-8.
25. Carr NJFrcp, Cecil TDM, Mohamed FM, Sobin LHM, Sugarbaker PHM, González-Moreno SMP, et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia the results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol*. 2016;40(1):14-26.
26. Kelemen LE, Köbel M. Mucinous carcinomas of the ovary and colorectum: different organ, same dilemma. *Lancet Oncol*. 2011;12(11):1071-80.
27. Bassiouny D, Ismiil N, Dubé V, Han G, Cesari M, Lu FI, et al. Comprehensive clinicopathologic and updated immunohistochemical characterization of primary ovarian mucinous carcinoma. *Int J Surg Pathol*. 2018;26(4):306-17.
28. Hu A, Li H, Zhang L, Ren C, Wang Y, Liu Y, et al. Differentiating primary and extragenital metastatic mucinous ovarian tumours: an algorithm combining PAX8 with tumour size and laterality. *J Clin Pathol*. 2015;68(7):522-8.
29. Stelow EB, Yaziji H. Immunohistochemistry, carcinomas of unknown primary, and incidence rates. *Semin Diagn Pathol*. 2018;35(2):143-52.
30. Li X, Beihua K. PAX8 is a novel marker for differentiating between various types of tumor, particularly ovarian epithelial carcinomas (review). *Oncol Lett*. 2013;5(3):735-8.
31. Aldaoud N, Erashdi M, Alkhatib S, Abdo N, Al-Mohtaseb A, Graboski-Bauer A. The utility of PAX8 and SATB2 immunohistochemical stains in distinguishing ovarian mucinous neoplasms from colonic and appendiceal mucinous neoplasm. *BMC Res Notes*. 2019;12(1).
32. Gouy S, Saidani M, Maulard A, Bach-Hamba S, Bentivegna E, Leary A, et al. Characteristics and prognosis of stage i ovarian mucinous tumors according to expansile or infiltrative type. I*nt J Gynecol Cancer*. 2018;28(3):493-9.
33. Yoshikawa N, Kajiyama H, Mizuno M, Shibata K, Kawai M, Nagasaka T, et al. Clinicopathologic features of epithelial ovarian carcinoma in younger vs. older patients: Analysis in Japanese women. *J Gynecol Oncol*. 2014;25(2):118-23.
34. Brown J, Frumovitz M. Mucinous tumors of the ovary: Current thoughts on diagnosis and management. *Curr Oncol Rep*. 2014;16(6).
35. Mackenzie R, Kommoss S, Winterhoff BJ, Kipp BR, Garcia JJ, Voss J, et al. Targeted deep sequencing of mucinous ovarian tumors reveals multiple overlapping RAS-pathway activating mutations in borderline and cancerous neoplasms. *BMC Cancer*. 2015;15(1).
36. Hunter SM, Gorringe KL, Christie M, Rowley SM, Bowtell DD, Campbell IG. Pre-invasive ovarian mucinous tumors are characterized by CDKN2A and RAS pathway aberrations. *Clin Cancer Res*. 2012;18(19):5267-77.
37. Morice P, Gouy S, Leary A. Mucinous ovarian carcinoma. *N Eng J Med*. 2019;380(13):1256-66.
38. Lee YJ, Lee MY, Ruan A, Chen CK, Liu HP, Wang CJ, et al. Multipoint Kras oncogene mutations potentially indicate mucinous carcinoma on the entire spectrum of mucinous ovarian neoplasms. *Oncotarget*. 2016;7.

39. Ryland GL, Hunter SM, Doyle MA, Caramia F, Li J, Rowley SM, et al. Mutational landscape of mucinous ovarian carcinoma and its neoplastic precursors. *Genome Med*. 2015;7(1).
40. Bouri S, Simon P, D'Haene N, Catteau X, Noël JC. P53 and PIK3CA mutations in KRAS/HER2 negative ovarian intestinal-type mucinous carcinoma associated with mature teratoma. *Case Rep Obstet Gynecol*. 2020;2020.
41. Mueller JJ, Schlappe BA, Kumar R, Olvera N, Dao F, Abu-Rustum N, et al. Massively parallel sequencing analysis of mucinous ovarian carcinomas: genomic profiling and differential diagnoses. *Gynecol Oncol*. 2018;150(1):127-35.
42. Anglesio MS, Kommoss S, Tolcher MC, Clarke B, Galletta L, Porter H, et al. Molecular characterization of mucinous ovarian tumours supports a stratified treatment approach with HER2 targeting in 19% of carcinomas. *J Pathol*. 2013;229(1):111-20.
43. Bashashati A, Ha G, Tone A, Ding J, Prentice LM, Roth A, et al. Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling. *J Pathol*. 2013;231(1):21-34.
44. Bell D, Berchuck A, Birrer M, Chien J, Cramer DW, Dao F, et al. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011; 74(7353):609-15.
45. Jones S, Wang TL, Kurman RJ, Nakayama K, Velculescu VE, Vogelstein B, et al. Low-grade serous carcinomas of the ovary contain very few point mutations. *J Pathol*. 2012;226(3):413-20.
46. Iida Y, Okamoto A, Hollis RL, Gourley C, Herrington CS. Clear cell carcinoma of the ovary: A clinical and molecular perspective. *Int J Gynecol Cancer*. 2021;31:605-16.
47. Itamochi H, Oishi T, Oumi N, Takeuchi S, Yoshihara K, Mikami M, et al. Whole-genome sequencing revealed novel prognostic biomarkers and promising targets for therapy of ovarian clear cell carcinoma. *Br J Cancer. 2017*;117(5):717-24.
48. Bolton KL, Chen D, de la Fuente RC, Fu Z, Murali R, Köbel M, et al. Molecular subclasses of clear cell ovarian carcinoma and their impact on disease behavior and outcomes. *Clin Cancer Res*. 2022; 28(22):4947-56.
49. Friedlander ML, Russell K, Millis S, Gatalica Z, Bender R, Voss A. Molecular profiling of clear cell ovarian cancers: Identifying potential treatment targets for clinical trials. *Int J Gynecol Cancer*. 2016;26(4):648-54.
50. Cybulska P, Paula ADC, Tseng J, Leitao MM, Bashashati A, Huntsman DG, et al. Molecular profiling and molecular classification of endometrioid ovarian carcinomas. *Gynecol Oncol*. 2019;154(3): 516-23.
51. Pierson WE, Peters PN, Chang MT, Chen L may, Quigley DA, Ashworth A, et al. An integrated molecular profile of endometrioid ovarian cancer. *Gynecol Oncol*. 2020;157(1):55-61.
52. Crobach S, Ruano D, Van Eijk R, Fleuren GJ, Minderhout I, Snowdowne R, et al. Target-enriched next-generation sequencing reveals differences between primary and secondary ovarian tumors in formalin-fixed, paraffin-embedded tissue. *J Mol Diagn*. 2015;17(2): 193-200.
53. Garg S, Nagaria TS, Clarke B, Freedman O, Khan Z, Schwock J, et al. Molecular characterization of gastric-type endocervical adenocarcinoma using next-generation sequencing. *Mod Pathol*. 2019;32(12):1823-33.
54. Hodgson A, Howitt BE, Park KJ, Lindeman N, Nucci MR, Parra-Herran C. Genomic characterization of HPV-related and gastric-type endocervical adenocarcinoma: Correlation with subtype and clinical behavior. *Int J Gynecol Pathol*. 2020;39(6):578-86.
55. Jang JYA, Yanaihara N, Pujade-Lauraine E, Mikami Y, Oda K, Bookman M, et al. Update on rare epithelial ovarian cancers: Based on the rare ovarian tumors young investigator conference. *J Gynecol Oncol*. 2017;28(4):e54.
56. Craig O, Salazar C, Gorringe KL. Options for the treatment of mucinous ovarian carcinoma. *Curr Treat Options Oncol*. 2021;22(12): 114.
57. Gorringe KL, Cheasley D, Wakefield MJ, Ryland GL, Allan PE, Alsop K, et al. Therapeutic options for mucinous ovarian carcinoma. *Gynecol Oncol*. 2020;156(3):552-60.
58. Hurwitz HI, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: Pooled analysis from seven randomized controlled trials. *Oncologist*. 2013;18(9):1004-12.
59. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: A systematic review and meta-analysis, with emphasis on chemotherapy subgroups. *BMC Cancer*. 2012;12:89.
60. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-8.
61. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Eng J Med*. 2011;365(26):2484-96.
62. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. *N Eng J Med*. 2011;365(26):2473-83.
63. Aghajanian C, Blank S V., Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039-45.
64. Schilder RJ, Pathak HB, Lokshin AE, Holloway RW, Alvarez RD, Aghajanian C, et al. Phase II trial of single agent cetuximab in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with the potential for dose escalation to rash. *Gynecol Oncol*. 2009;113(1):21-7.
65. Konner J, Schilder RJ, DeRosa FA, Gerst SR, Tew WP, Sabbatini PJ, et al. A phase II study of cetuximab/paclitaxel/carboplatin for the initial treatment of advanced-stage ovarian, primary peritoneal, or fallopian tube cancer. *Gynecol Oncol*. 2008;110(2):140-5.
66. Sato N, Saga Y, Mizukami H, Wang D, Fujiwara H, Takei Y, et al. Cetuximab inhibits the growth of mucinous ovarian carcinoma tumor cells lacking KRAS gene mutations. *Oncol Rep*. 2012;27(5):1336-40.
67. McAlpine JN, Wiegand KC, Vang R, Ronnett BM, Adamiak A, Köbel M, et al. HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy. *BMC Cancer*. 2009;9:433.
68. Zaino RJ, Brady MF, Lele SM, Michael H, Greer B, Bookman MA. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal. *Cancer*. 2011;117(3):554-62.