

Distinguishing Benign and Malignant Ovarian Tumors Preoperatively

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Introduction

Ovarian cancer ranks as the fifth leading cause of cancer-related mortality among women globally. In 2020, there were approximately 314,000 reported cases of new ovarian cancer patients, resulting in an estimated 207,000 deaths.¹ The highest incidence rates were observed in non-Hispanic white women, with 12.0 cases per 100,000 individuals, followed by Hispanics (10.3 per 100,000), non-Hispanic blacks (9.4 per 100,000), and Asian/Pacific Islander women (9.2 per 100,000). Disparities in access to healthcare services and treatment modalities contribute to varied mortality patterns, with the highest rates recorded among African populations. In Indonesia, ovarian cancer ranks as the third most prevalent cancer, comprising 7.84% of total cancers diagnosed in women.¹ The heightened mortality rate observed in ovarian cancer can be ascribed to several factors including asymptomatic tumor growth, delayed manifestation of symptoms, and inadequate screening methods, ultimately resulting in diagnoses at advanced stages. Consequently, ovarian cancer is frequently described as a “silent killer”.² To address diagnostic delays and reduce mortality rates associated with ovarian cancer, early detection and differentiation between benign and malignant ovarian tumors are crucial. This requires a comprehensive assessment comprising patient history, physical examination, and supporting investigation.

Diagnosis

Distinguishing Through Patient History and Physical Examination

Approximately 60% of women diagnosed with ovarian cancer are already at the metastatic stage, as early stages typically present no symptoms. Late-stage ovarian cancer often manifests symptoms, albeit nonspecific ones. Around 72% of ovarian cancer patients endure symptoms such as back pain, fatigue, abdominal pain/bloating, constipation, or urinary disturbances persisting for three months or longer before diagnosis; 35% report symptoms persisting for six months or more.³

This variation in symptom distribution across different stages was validated by a case-control study utilizing an index comprising six symptoms, revealing that the presence of any of these symptoms (pelvic pain, abdominal pain, increase in abdominal size, bloating, difficulty eating, or rapid fullness) for 12 or more days per month over the previous 12 months exhibited low sensitivity (56.7%) for early-stage disease but higher sensitivity (79.5%) for late-stage disease. Specificity was 90% for women aged 50 years and older and 86.7% for those younger than 50 years. The diminished sensitivity observed in early-stage patients suggests a propensity for asymptomatic presentation in this cohort.⁴ Another investigation examining symptoms in ovarian cancer patients relative to their histopathological results identified six symptoms significantly associated with benign tumors: flatulence, nausea-vomiting, decreased appetite, bloating, menstrual disorders, and weight loss.³

In addition to the nonspecific symptoms mentioned above, ovarian cancer can manifest

with paraneoplastic syndromes including subacute cerebellar degeneration, seborrheic keratosis, or recurrent and migratory spontaneous venous thrombosis (known as Trousseau syndrome). Advanced stages may present with symptoms indicative of regional spread or metastasis, such as intestinal or ureteral obstruction, or dyspnea. Ovarian cancer of the sex cord stromal subtype can elicit hormonal manifestations such as precocious puberty, abnormal uterine bleeding, and virilization. Due to the distinctiveness and early onset of symptoms, approximately 70% of tumors of this subtype can be diagnosed at stage I.⁵

Distinguishing Through Supporting Modalities

Women presenting with suspected ovarian cancer, either clinically or due to the identification of a pelvic mass, should undergo a series of diagnostic imaging procedures including transvaginal ultrasonography (USG), abdominal ultrasonography, CT, MRI, and/or PET scans. These imaging modalities enable the assessment of ovarian morphology and vascularity, differentiation between cystic and solid masses, and detection of ascites.

Ultrasonography

Primary screening utilizing ultrasonography or multimodal approaches combining CA 125 values has been investigated in numerous studies.⁶ The findings reveal that transvaginal ultrasound alone yields a high false positive rate and is highly dependent on operator skill. Specifically, the study results indicate a lower survival rate among patients with positive CA 125 but negative ultrasound results (42% compared to 67% in those with positive ultrasound results), underscoring the inadequacy of ultrasound in detecting malignant ovarian tumors.^{6,7}

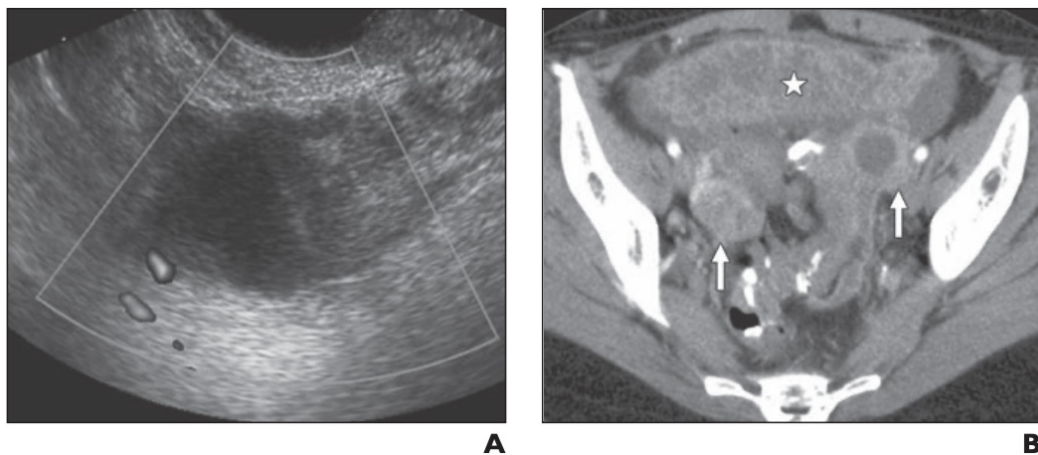


Figure 1 Imaging of a 42-year-old patient who experienced the growth of a malignant ovarian tumor.⁷

- A) The transvaginal ultrasound examination identified a 2.4 cm cystic lesion on the left ovary, with the right ovary appearing normal and no evidence of ascites.
- B) Subsequent CT examination conducted 7 weeks later revealed the presence of solid and

cystic nodules in both the right and left ovaries, along with the detection of ascites.

CT, MRI, and PET

Follow-up assessments utilizing CT, MRI, and PET scans can serve as evaluation tools after the initial ultrasound examination. When assessing suspicious adnexal masses, MRI surpasses ultrasound or CT due to its ability to detect small nodules, exhibit high specificity (84 – 89%), and decrease false positive findings for malignancy, thereby mitigating the need for extensive surgery.^{7,8} Nonetheless, the high cost associated with MRI precludes its use as a primary detection tool, and it is only employed if initial evaluation employing ultrasound and CA 125 levels leaves uncertainty regarding the nature of the mass.⁷

CT and PET exhibit a broad spectrum of sensitivity and specificity outcomes, ranging from 58% to 100% and 67% to 92%, respectively. Due to their limited spatial resolution and challenges in detecting small tumors, PET and CT examinations are not recommended for routine screening of malignant ovarian tumors. However, CT is advocated for staging malignant ovarian tumors, boasting an accuracy rate of up to 94% and facilitating the detection of chemotherapy response.⁷

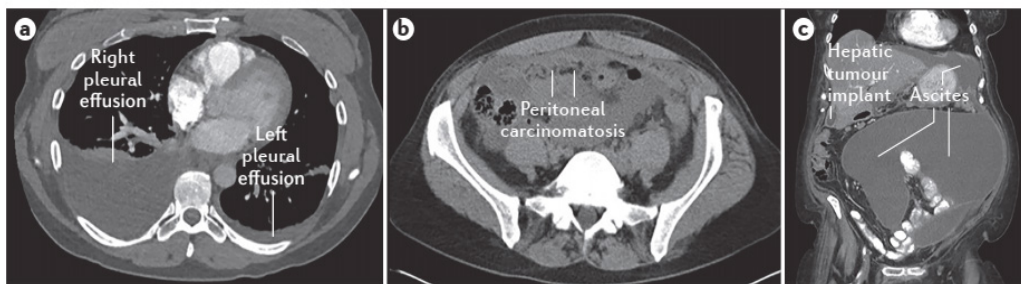


Figure 2 CT Scan atient with ovarian cancer stage IV.

a) pleural effusion bilateral, b) peritoneal carcinoma, c) High volume ascites and peritoneal liver implant.⁷

Laboratorium

If ovarian cancer is suspected, a comprehensive diagnostic approach should include obtaining a complete blood count, blood chemistry analysis including liver function and calcium tests to assess for paraneoplastic syndromes, as well as serum biomarker assessments such as CA 125, and Human Epididymis 4, among others.^{6,7} Simple laboratory tests aimed at identifying markers of the inflammatory response, such as white blood cell counts, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR), have shown promise in differentiating various types of malignant tumors.⁸ Several studies in ovarian tumors have reported a significant increase in these parameters compared to benign or borderline tumors.^{8,9} However, further research is needed to fully elucidate the predictive potential of these values, as there is considerable heterogeneity among studies and variations in the numerical values of each ratio.⁹

Ovarian Cancer Biomarker

The lack of specific symptoms in early-stage ovarian cancer contributes to over 70% of patients being diagnosed at an advanced stage, resulting in persistently high mortality rates. The prognosis for ovarian cancer can only be enhanced through advancements in diagnostic technology. Consequently, tumor biomarkers hold promise in ameliorating the morbidity and mortality associated with ovarian cancer.⁴

Cancer Antigen 125 (CA 125)

Cancer Antigen 125 (CA 125), also referred to as mucin 16 or MUC16, represents a widely utilized biomarker, although its diagnostic efficacy depends on the disease risk and stage of cancer detection. MUC16, a substantial membrane glycoprotein, belongs to the membrane-associated mucin (MAM) family. Expressed across various human cell surfaces, MUC16 plays a pivotal role in safeguarding cell layers against external threats. Structurally, MUC16 comprises three domains: the amino terminal, tandem repeat, and carboxyl terminal domain. Upon release into the bloodstream, the extracellular portion of MUC16 serves as a diagnostic biomarker for cancer diagnosis and patient monitoring. Initially identified as CA 125 by Bast et al., MUC16 serves as a Mullerian duct differentiation antigen that exhibits overexpression in ovarian cancer.¹⁰

Under physiological circumstances, CA 125 expression is confined to cell membrane and cannot be passed through infiltrate the bloodstream due to the impermeability of cell junction. Pathological disruptions of this barrier result in CA 125 entering the bloodstream, consequently elevating serum CA 125 levels. In cases of ovarian cancer, CA 125 is expressed during the metaplastic conversion of ovarian epithelium to Mullerian-type endothelium or neoplastic transformation. Following transformation, tumor cells infiltrate and disrupt the surrounding tissue architecture, gaining access to the bloodstream. Conversely, in benign ovarian cysts, although CA 125 may permeate into the cyst fluid, it is unable to penetrate the bloodstream.¹⁰

CA 125 accuracy in detecting early-stage ovarium cancer is notably restricted, with only 50% of early-stage patients exhibiting elevated CA 125 levels, resulting in a low sensitivity (50-62%) of this biomarker in early-stage ovarian cancer. Various studies have demonstrated disparities in CA 125 levels between advanced-stage cancer patients and healthy individuals. Additionally, CA 125 levels may remain within normal ranges in patients with early-stage cancer. Consequently, CA 125 screening may delay diagnosis and worsen the patient prognosis.¹¹

Furthermore, the specificity of CA 125 is relatively low (73-77%) with over 60% patients with elevated CA 125 levels are not diagnosed with ovarian cancer. Elevated CA 125 levels may occur in physiological condition such as pregnancy and during the menstrual cycle. Additionally, other cancers including breast, pancreatic, uterine, liver, and colon cancer may also have an increase CA 125 levels. Benign conditions such as pelvic inflammation, adenomyosis, uterine myoma, and endometriosis are also associated with elevated serum CA 125 levels.¹¹ CA 125 serves as a marker capable of distinguishing between benign and malignant tumors and may provide enhanced diagnostic accuracy when used in conjunction with other tumor markers such as glutaminase.¹²

Human Epididymis 4 (HE4)

Human Epididymis 4 (HE4) represents a novel biomarker for ovarian cancer. HE4 is a glycoprotein belonging to the four-disulfide whey acid core protein family, alternatively known as WFDC2, and is part of the larger whey acid protein (WAP) family. The primary gene responsible for encoding the WAP protein is predominantly located on chromosome 20q12-13.1.¹³ This protein, found in whey, is termed WAP and comprises approximately 50 amino acids, although its precise biological function remains incompletely elucidated. HE4, characterized by the presence of two WAP domains, was initially identified in the epididymis and is thought to potentially participate in sperm maturation.¹⁴

This biomarker demonstrates weak expression in epithelial tissues of the respiratory and reproductive organs but exhibits overexpression in ovarian tumors, particularly in endometrioid ovarian cancer. Furthermore, it appears that HE4 is not as strongly expressed in clear cell ovarian carcinoma as in other epithelial ovarian cancers. Yanaranop et al. reported that HE4 examination exhibited superior performance in distinguishing non-cancer patients from those with type II epithelial ovarian cancer, as well as in distinguishing between type I and type II epithelial ovarian cancer cases.¹⁵ These findings align with those of a recent Italian multicenter study involving 387 patients, which indicated that HE4 may be more reliable than CA 125 in diagnosing epithelial ovarian cancer. However, despite its relatively high specificity, the sensitivity of HE4 remains comparatively low, at approximately around 67%.¹¹ Another study reported that CA 125 demonstrated better sensitivity than HE4 in diagnosing advanced ovarian cancer (90.8% vs. 56.9%), whereas HE4 exhibited superior specificity (96.9% vs. 67.1%).¹⁶

HE4 levels are typically measured with a lower threshold of 70 pmol/L for premenopausal patients and 140 pmol/L for menopausal patients. However, a critical review of the literature underscores the necessity to consider variations in screening methodologies for HE4 measurement in all meta-analyses, emphasizing the need for cautious interpretation of results. Unlike CA 125 levels, which tend to increase in endometriomas, HE4 levels generally remain stable. Notably, HE4 levels in patients with endometriomas are comparable to those in patients with other benign ovarian cysts (53.0 pmol/L vs. 52.8 pmol/L). This observation can be attributed to the lack of HE4 gene overexpression in endometriotic lesions.¹⁷

Variations in HE4 levels can be influenced by various patient characteristics. Bolstad et al. observed modifications in HE4 levels according to Body Mass Index (BMI), whereas Ferraro et al. did not find significant differences in HE4 levels among 103 patients based on BMI. This discrepancy may be attributed to the inclusion of both men and women in Ferraro et al.'s study, potentially introducing bias. Overall, serum HE4 levels do not appear to be significantly affected by BMI, unlike CA 125.²⁰ However, smoking emerges as a notable factor influencing variations in serum HE4 levels, with levels increasing by 20% to 30% in smokers compared to non-smokers. Hence, caution should be exercised when interpreting HE4 levels in smokers to avoid false positive results.^{18,19} In contrast to CA 125, contraceptive use contributes to variations in HE4 levels. Ferraro et al. reported significantly lower HE4 levels in patients using oral contraceptives compared to those using other contraceptive methods.¹⁸ Therefore, careful consideration of the contraceptive method in the patient's clinical history is essential to avoid misinterpretation of HE4 levels.¹⁷

Extracellular Matrix

Over recent decades, the quest for specific biomarkers has primarily targeted tumor cells themselves, with a particular emphasis on proteins, notably glycols. However, for tumor cells to invade and metastasize, they must navigate through various obstacles within the surrounding microenvironment, including the extracellular matrix (ECM).¹⁹ The tumor microenvironment encompasses diverse cell types such as fibroblasts, immune cells, and endothelial cells, along with non-cellular components including extracellular matrix components, remodeling enzymes, tissue inhibitors of metalloproteinases, lysyl oxidases, and growth factors.^{19, 20}

The extracellular matrix (ECM) represents a complex structural network surrounding cells, crucial for maintaining cellular architecture. Additionally, ECM facilitates cellular interactions with surface receptors, growth factors, and cytokines, thereby mediating diverse cellular activities and intercellular communication processes.²⁰ Comprising constituents such as collagen, laminin, fibronectin, vitronectin, proteoglycans, and gelatin, the ECM assumes a fundamental role in tumor invasion mechanisms.^{19, 20}

The ECM plays important role in normal cell function, as it can impede or even combat cancer development by maintaining malignant tumors in situ. Each component of the ECM collaborates to regulate cell behavior and execute tissue functions both biochemically and biomechanically. Signals originating from cells are secreted into the ECM, thereby stimulating intracellular signaling pathways while concurrently activating mechanosensory pathways. These collective signals orchestrate cell adhesion, proliferation, polarity, migration, differentiation, and apoptosis. Moreover, the ECM undergoes dynamic remodeling and tightly regulates tissue development, wound healing, and tissue homeostasis. However, aberrant ECM dynamics serve as a hallmark of cancer or can facilitate tumor development.¹²

Metabolic dysregulation stands as a hallmark of cancer, characterized by heightened glycolytic activity, fueling cellular energy demands and fostering an environment conducive to malignant growth. Recent studies have revealed that metabolic activity is intricately modulated by various biological properties, including ECM remodeling. This process encompasses dysregulated synthesis, deposition, translational modification, and degradation within the ECM.²¹ Such aberrant ECM remodeling plays a pivotal role in facilitating cancer development, progression, and therapy resistance, while also impacting the adhesive, migratory, invasive, and metastatic capacities of cancer cells.²⁰

For example, one study showed that preserving normal tissue around tumor lesions can prevent tumor cells from invading and metastasizing. Therefore, tumor cells must evolve through proteolytic and glycosidic degradation of normal extracellular matrix, as well as resulting de-novo synthesis of 'tumoral' extracellular matrix, in order to create a more protective environment for tumor cells. A large proportion of intratumoral extracellular matrix has been shown correlating with poor prognosis in various types of cancer, including ovarian cancer.²¹

Several recent studies have shown that tumor biomarkers can also originate from stromal cells. The idea that malignant tumors consist of a group of homogeneous cancer cells is no longer used. Tumors are now better known as complex tissues, where tumor cells interact closely with the surrounding microenvironment. Nowadays, tumor biomarker research has shifted its focus to the tumor microenvironment, namely the extracellular matrix.¹⁹

Glycosaminoglycans

The ECM comprises two primary categories of biomolecules: fibrous proteins, such as collagen, elastin, fibronectin, and laminin; and glycosaminoglycans. Glycosaminoglycans are glycoconjugates predominantly found in connective tissue, existing either in free form or commonly attached to proteins to form proteoglycans. Consisting of polysaccharide chains, glycosaminoglycans serve as critical constituents of the ECM in healthy connective tissue, exerting pivotal roles in homeostasis, regulation of cell growth, angiogenesis, migration, recognition, and the manifestation of aberrant conditions.^{11,22}

Glycosaminoglycans have the capacity to instigate inflammation, which is often observed in a spectrum of inherited and acquired diseases. Dysregulation of glycosaminoglycans expression has been documented in various developmental disorders, including cancer, neuroinflammation, atherosclerosis, and diabetes. In the context of cancer, the role of glycosaminoglycans in disease progression is contingent upon their concentration, spatial distribution, and temporal dynamics. Anomalies in glycosaminoglycan metabolism are intricately linked to the malignancy of cancer; for instance, heightened chondroitin sulfate synthesis activity is observed in several cancer types compared to normal tissue counterparts.^{11,22}

Glycosaminoglycans can trigger inflammation that accompanies various types of inherited and acquired diseases. Modulation of glycosaminoglycan expression has been reported in several developmental diseases such as cancer, neuroinflammation, atherosclerosis, and diabetes. In general, the function of glycosaminoglycans in cancer development depends on the concentration, the extension, and the temporal duration. Irregular glycosaminoglycan metabolism is associated with the malignancy of cancer, for example, the more active chondroitin sulfate synthesis process is found in several types of cancer compared to normal tissue.¹¹

Glycosaminoglycans play a pivotal role in regulating tumor cell proliferation by modulating the activity of growth factors and signaling pathways. Chondroitin sulfate has been implicated in inhibiting PTEN, a tumor suppressor, thereby promoting cell proliferation. Similarly, keratan sulfate (KS) has been identified as a facilitator of proliferation, particularly in lymphoma, astrocytic tumors, and glioblastoma. Additionally, heparan sulfate (HS) has been shown to act as a receptor, triggering the growth of cancer cells.¹⁹

Several studies have indicated the significant involvement of glycosaminoglycans in cancer development, including their contribution to tumor progression, angiogenesis, aggressiveness, drug resistance, and metastasis across various cancer types, including ovarian cancer.^{20,23} Additionally, glycosaminoglycans play a role in the adaptive response to stressors such as hypoxia and acidosis within the tumor microenvironment.

Conclusion

Distinguishing between benign and malignant ovarian tumors requires a combination of comprehensive in taking history as well as appropriate supporting examinations. The results of this research will add insight into new biomarker modalities to be able to differentiate patients with benign and malignant ovarian tumors. Then after, it can help in developing the determination of diagnosis patients with ovarian cancer

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