RESEARCH
www.commprac.com
ISSN 1462 2815

ABDOMINAL COMPUTED TOMOGRAPHY WITH SERUM CEA AND CA-125 MARKERS IN OVARIAN TUMORS

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DOI: 10.5281/zenodo.13347726

Abstract

Most studies on the cystic component of ovarian tumors have been aimed at determining tumor biomarkers, with CA-125 and CEA being the most commonly studied tumor markers. The CEA content in the cystic component of the tumor is increased in mucinous type ovarian tumors although it can be increased in both cystadenoma and cystadenocarcinoma. The CEA value was found to be highest in tumor cystic fluid, followed by ascites fluid, then lowest in blood. 46 Different things were found in the tumor marker CA-125, where higher concentrations of this biomarker were found in serous type ovarian tumors compared to mucinous types, although several other studies have shown that the opposite is true. Another study also reported that there was no difference in the concentration of the tumor marker CA-125 in benign or malignant ovarian tumors. 46 Attenuation value (Hounsfield Unit) of soft tissue on Abdominal Computed Tomography. The attenuation value of x-ray beams on CT (computed tomography) is very dependent on the thickness and anatomical composition of the soft tissue that affects it.

Keywords: Ovarian Tumors, CT Scan, CA-125, CEA.

INTRODUCTION

The ovaries are one of the organs of the female reproductive system. This pair of endocrine glands is located intraperitoneally in the right and left lower quadrants of the abdomen. Adult female ovaries are oval-shaped, resembling almonds, measuring around 2.5 – 5.0 cm long and 1.5 – 3.0 cm wide and around 1.0 – 2.0 cm thick. The normal volume of the ovaries before menarche is around 3.0 mL, around 9.8 mL in menstruating women and around 5.8 mL in menopausal women.[1]

Ovarian tumors, especially malignant ones, are the seventh leading cause of death in women from cancer after breast, lung, colorectal, cervical, gastric, liver and pancreas. It is estimated that 4.4% of the 4.2 million cancer deaths are caused by ovarian cancer. Around 239,000 new cases are reported with a death rate of around 152,000 every year.[2]

The incidence of ovarian tumors varies in various countries, where Asian countries are lower than Western countries. There is a wide geographic distribution of ovarian tumors with the highest incidence being in Northern Europe (13.3 per 100,000 population/year) and the lowest being in North Africa (2.6 per 100,000 population/year). In China the incidence of ovarian cancer is 3.2 per 100,000 population/year. Although the incidence rate in China is lower, with a large population

with an estimated new case of around 52,000 and a death rate of 22,500 in 2015. For comparison, new cases in the United States were 21,290 new cases with a death rate of 14,180 in the same year. In 2018, there were 184,799 deaths due to ovarian cancer, which is around 4.4% of all cancer deaths in women. Based on Globoccan 2018, the highest mortality rate in Asian countries is in India, while the mortality rate in Europe and North America has decreased in recent years, especially in young patients. It is reported that around two-thirds of deaths from ovarian cancer are related to high grade serous type carcinoma.[3]

The National Cancer Institute (NCI) in the United States in 2007 reported that 47.8% of ovarian cancer occurred in those aged 20-60 years and the incidence was increasing in women over 65 years of age. Epithelial ovarian tumors occur more frequently in the 4th to 6th decades, while sex-cord stromal ovarian tumors and germ cell tumors occur more frequently at younger ages.[4]

In general, the position of the ovaries is greatly influenced by the size of the uterus, the size of the ovaries themselves, the degree of filling of the urinary bladder, distension of the rectosigmoid colon and the presence or absence of a mass in the pelvic cavity. However, due to the presence of a mesovarium that holds the ovary posteriorly from the broad ligament, the normal ovary is generally located in the posterior compartment of the pelvic cavity and above the uterine fundus and is not between the urinary bladder and the uterus.[5]

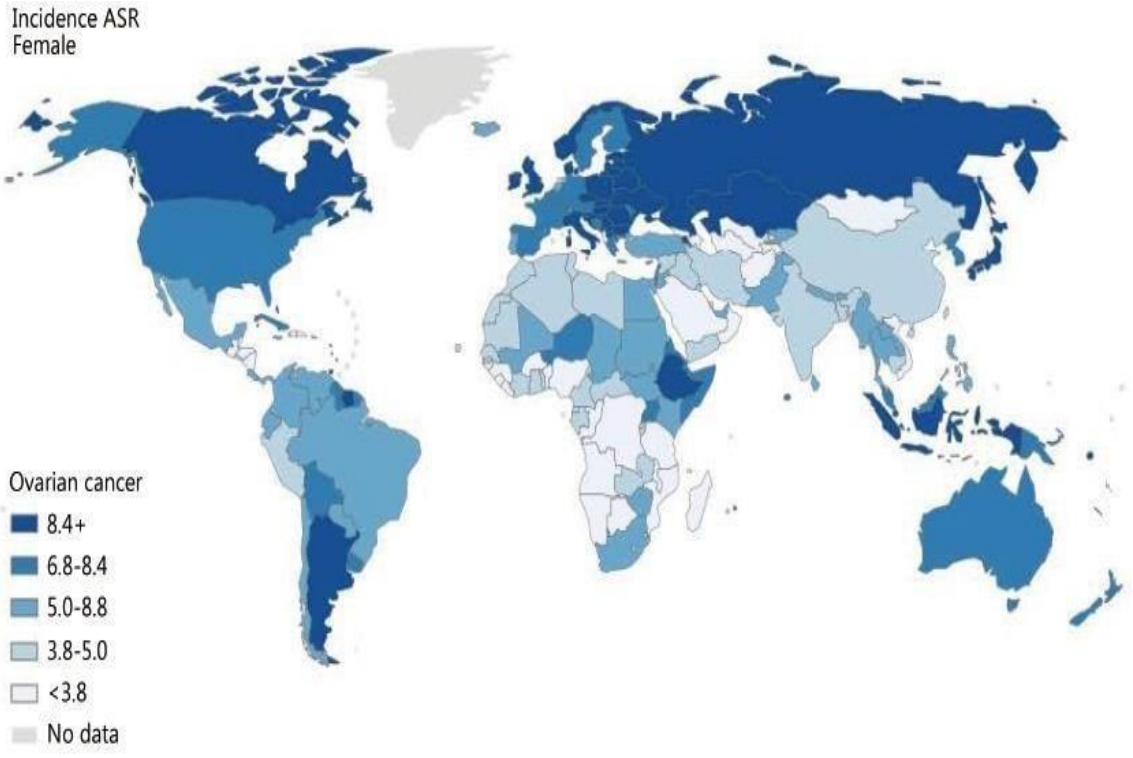


Figure 1: The incidence of ovarian malignancies shows a geographical distribution with wide variations with a high incidence in European and North American countries.[5]

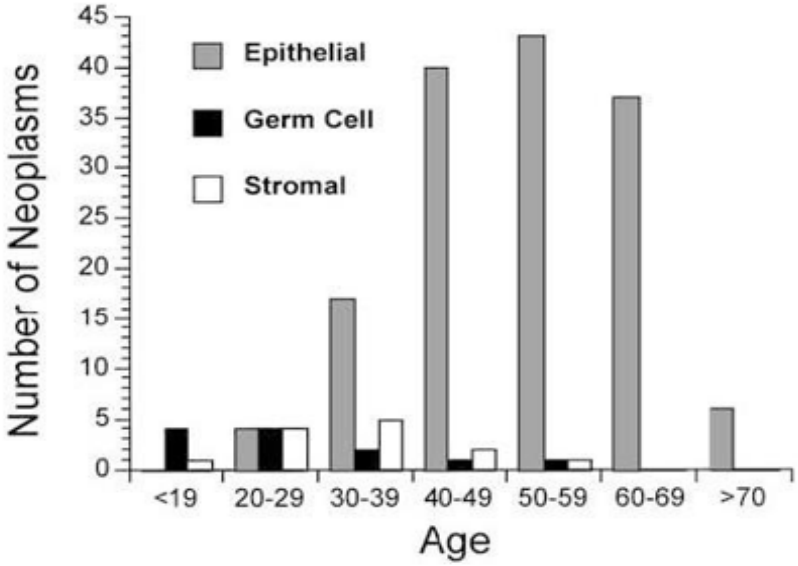


Figure 2: Distribution of ovarian tumors based on age shows that epithelial tumors are more common in the 4th to 6th decade of age while germinal ovarian and sex cord-stromal tumors are at a younger age.[6]

In Indonesia, the highest incidence occurs in the 45-54 year age group. Fransisca and Kartika in their research at RSCM in 2016 reported that the incidence of ovarian cancer was higher in those of reproductive age (< 55 years), nulliparous and more often found in advanced stages (stages III and IV). Ramayuda et al, in their research at RSUD Dr. Soetomo Surabaya reported that around 46.6% of ovarian tumors were found in the age range 41 – 60 years with 81.4% being malignant tumors.[7]

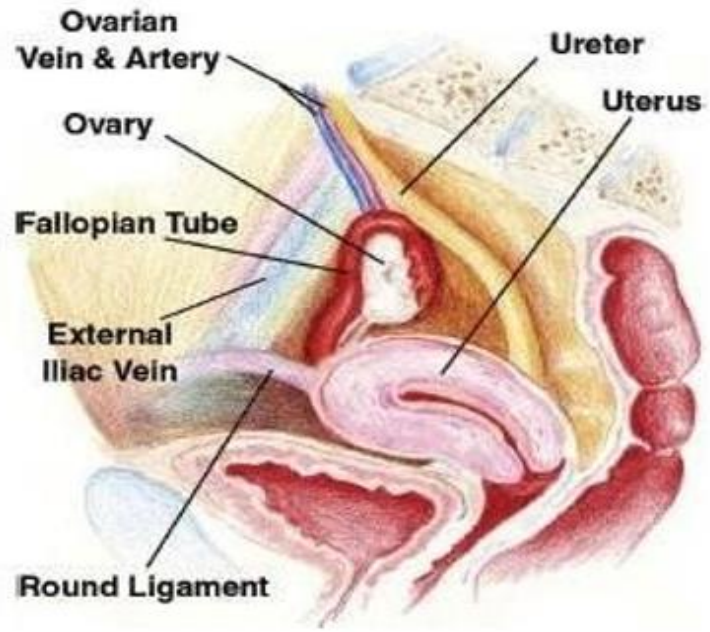


Figure 3: Illustration of the ovarian fossa on the posterolateral wall of the pelvic cavity. In the posterior part of this fossa there is the ureter, while on the superior side there is the external iliac vein.[6]

The ovaries are connected to the fallopian tubes in the ovarian fossa or also known as the fossa of Waldeyer. Each ovary is attached to the intraperitoneal pelvic cavity via three main supporting structures, namely: the mesovarium at the back of the broad ligament; utero-ovarian ligament (ovarian ligament) which holds the ovary to the uterus; and the ovarian suspensory ligament which holds the ovary against the lateral wall of the pelvic cavity. The ovaries are connected to the lateral side of the uterus via the round ligament. The medial umbilical ligament is located on the anterior side of the ovary while on the posterior side there are the ureters and internal iliac arteries. On the superior side of the ovary there is the infundibulu.[8]

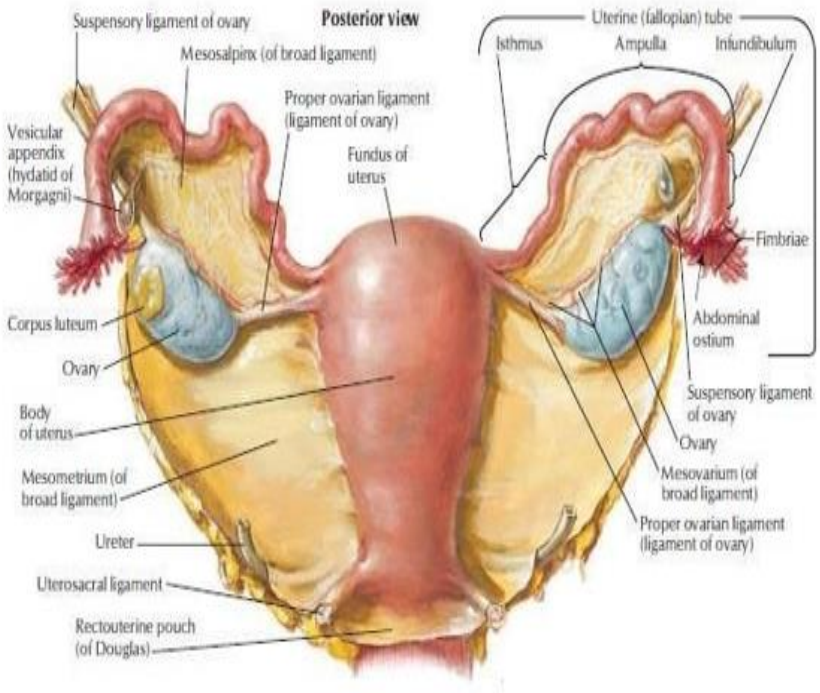


Figure 4: Illustration from the posterior side showing the broad ligament and attachment of the ovary to the fallopian tube which is separated from the ovary. The ovarian suspensory ligament extends from the superilateral part of the broad ligament to the lateral wall of the pelvic cavity. On the medial side there is the utero-ovarian ligament or propria ovarian ligament which is between the two layers of peritoneum from the broad ligament. [6]

The ovaries get their blood supply through the ovarian arteries and uterine arteries. The ovarian artery is a branch of the abdominal aorta below the renal artery at the level of the L2 vertebral body. This artery runs along the ovarian suspensory ligament and then towards the mesovarium. The ovarian artery then anastomoses with the uterine artery in the broad ligament. The ovarian vein originates from the ovary and also runs within the suspensory ligament providing drainage of the parametrium, cervix, mesosalpinx and pampiniform plexus. The left ovarian vein will empty into the left renal vein while the right ovarian vein will empty directly into the inferior vena cava.[9]

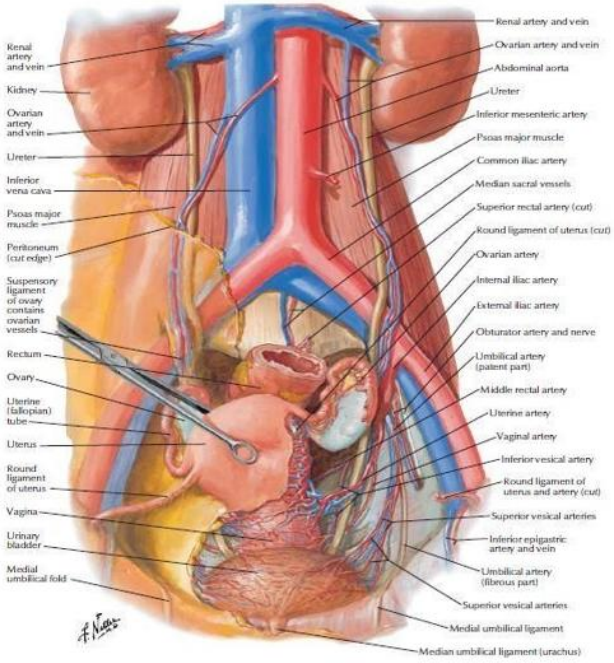


Figure 5: Illustration of vascularization of the ovaries. It appears that the uterine artery is branched by the internal iliac artery while the right ovarian vein empties into the vena cava while the left ovarian vein empties into the left renal vein.[10]

Lymphatic drainage runs along the ovarian vascular pathway to the para-aortic lymph nodes at the level of the L2 vertebral body in the branching area of the renal artery and aorta. The researchers discovered two lymphatic pathways in the ovaries. The first is via a lateral pathway to the hypogastric lymph node which will also drain to the para-aortic lymph node, while the second is via a pathway near the round ligament which leads to the external iliac and inguinal lymph nodes. These two pathways are clinically important because they are metastatic pathways for ovarian malignancies. There are two sources of innervation from the ovaries, the first is through the ovarian plexus. The ovarian plexus originates from the renal plexus which also innervates the uterine fundus. The ovarian plexus runs within the suspensory ligament. The second is sympathetic innervation via the superior ovarian nerve, this pathway is in the ovarian ligament. Parasymatic innervation of the ovaries originates from the uterine plexus which is a branch of the pelvic splanchnic nerves.[10]

The ovaries play a fundamental role as they produce germ cells, ova and reproductive hormones in adult women. The ovaries are covered by one layer of cells on the surface or outer layer which is a cuboidal epithelium called the germinal epithelium. In the layer below the epithelium there is supporting tissue composed of collagen called the tunica albuginea. The next layer is the ovarian follicular zone called the cortex. In this cortex there are a large number of follicles that are developing in different phases and will differentiate and mature. The innermost layer is the medulla which is composed of loose cellular connective tissue and blood vessels. In this layer there are also blood vessels that enter through the hillus.[11] An ovarian follicle consists of an oocyte surrounded by one or more layers of follicular cells. Follicles are divided into three phases of development, namely primordial follicles, developing follicles and de

Graafian follicles or mature follicles. Primordial follicles are most commonly found before birth. Consists of a primary oocyte with a nucleus and large nuclei surrounded by a layer of flattened follicular cells called granulosa cells. While the follicle develops, the ovarian stroma surrounding the follicle will differentiate into theca interna and theca externa. Theca interna is richly vascular while the theca interna is composed of connective tissue. Granulosa cells and theca cells produce estrogen and progesterone. In the ovaries, follicle maturation also occurs during the proliferation phase. The dominant follicular nerve matures accompanied by a surge of LH (luteinizing hormone), the oocyte will be released into the ovarian tube and then go to the uterus.[12]

Physiologically, the ovaries have two functions. The first function is as an endocrine organ that produces hormones. Estrogen, testosterone, inhibin and progesterone are produced in response to the presence of GnRH (Gonadotropin-Releasing Hormone). GnRH is secreted by the hypothalamus which triggers the anterior pituitary to produce FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone) so that the hypothalamus - pituitary - ovarian axis occurs in this process. FSH causes the granulosa cells of the ovarian cortex to produce and mature follicles, while LH influences theca cells which will produce androgen hormones and precursors of the hormone estradiol. This estradiol will then become estrogen which will cause the development of sexual characteristics and puberty. The average number of follicles is below 25, where during menstruation the follicles enlarge leaving the dominant follicle while the rest will experience degeneration.[13]

In general, in normal humans without the influence of contraceptive hormones, the ovarian cycle lasts around 24 – 32 days which is divided into two phases, namely the follicular growth phase or follicular phase and then followed by the ovulatory phase or luteal phase. The follicular phase is dominated by follicular growth triggered by estrogen and lasts approximately 10 – 14 days. Gonadotropin synthesis and secretion from the anterior pituitary is regulated in a pulsatile manner by GnRH. FSH and LH secretion is then modulated by GnRH and through a feedback mechanism, estradiol will suppress FSH and LH secretion directly through the hypothalamus or indirectly through the GnRH receptor in the pituitary. The luteal phase lasts approximately 12 – 15 days and is characterized by the dominance of the corpus luteum – progesterone derivatives. Even though estrogen and androgen are still produced, high progesterone levels will trigger negative feedback to the hypothalamus and pituitary so that FSH and LH production is reduced. Systemic progesterone will induce endometrial gland secretion in preparation for blastocyst implantation in the uterus. At the end of the luteal phase, if there is no embryo / fetus, the corpus luteum will experience regression, followed by a decrease in estrogen and progesterone levels and will again provide negative feedback and allow FSH and LH to increase again for the next phase.[14]

The second function of the ovaries is as a 'home' for egg cells or oocytes. This function develops during intrauterine development and stops when the woman reaches puberty. The ovulation process consists of the rupture of a mature follicle and occurs when a mature egg cell is released due to a surge in the LH hormone in the body. The ovum along with the zona pellucida, the cells that cover it, leave the ovary and enter the uterine tube. After ovulation, granulosa cells and cells from the theca interna that reside in the ovary form a temporary endocrine gland called the corpus luteum that secretes estrogen and progesterone.[15]

1. Ovarian Tumors

Ovarian tumors are tumors, both benign and malignant, that develop from the ovaries or ovaries. This tumor can originate from one of three ovarian components, namely: epithelium, germ cells and ovarian stroma including sex chords, including secondary tumors or metastases to the ovaries. 8 Most ovarian tumors can be classified into 3 main groups, namely: (1) Surface epithelial-stromal tumor or more commonly called epithelial tumor; (2) Sex cord-stromal tumors and (3) Germ-cell tumors. There are several subtypes from each category with a combination of several types and subtypes have also been found several times and are classified as mixed ovarian tumors. 9, 10 Epithelial tumors histologically resemble mesothelioma because they originate from epithelial tissue that can grow anywhere in the abdominal cavity or pelvic cavity (originating from the primitive coelomic epithelium). 60% of ovarian tumors are epithelial tumors. And 90% of malignant ovarian tumors are tumors of this type.[16]

Sex cord-stromal tumors include tumors originating from mesenchymal cells and tumors originating from mesonephric tissue. Included in this category are thecoma and fibroma as well as several tumors originating from granulosa cells. Meanwhile, germ-cell tumors are tumors that are identical to testicular germ-cells, namely tumors that originate from cells that form the gonad or cells that get out of line during yolk sac migration that grow outside the gonad.[17]

In 2014, the World Health Organization (WHO) revised the classification of epithelial ovarian tumors, namely: (1) Serous; (2) Mucinous; (3) Endometrioid; (4) Clear Cell; (5) Seromucinous: (6) Brenner; and (7) Undifferentiated. An abridged version of the WHO classification proposed by IARC (International Agency for Research on Cancer) is used for comparative studies.[18]

Table 1: Classification of ovarian tumors based on IARC which is a summary of the WHO classification.[18]

IARC Histologic Groups of Ovarian Tumors[a]

Histologic type	WHO ICD-O morphology code
1. Carcinoma	8010–8570,[b] 9014–9015, 9110
1.1 Serous carcinoma[c]	8441–8462, 9014
1.2 Mucinous carcinoma[c]	8470–8490, 9015
1.3 Endometrioid carcinoma	8380–8381, 8560, 8570
1.4 Clear cell carcinoma	8310–8313, 9110
1.5 Adenocarcinoma NOS	8140–8190, 8211–8231, 8260, 8440
1.6 Other specified carcinomas	
1.7 Unspecified carcinoma	8010–8034
2. Sex cord-stromal tumors	8590–8671
3. Germ cell tumors	8240–8245, 9060–9102
4. Other specified cancers (including malignant Brenner tumor, müllerian mixed tumor, and carcinosarcoma)	
5. Unspecified cancer	8000–8004

IARC: International Agency for Research on Cancer; WHO: World Health Organization; ICD-O: International Classification of Diseases for Oncology; NOS: not otherwise specified.

[a] Source: Parkin DM, Shanmugaratnam K, Sobin L, Ferlay J, Whelan SL. Histological groups for comparative studies, volume 31. IARC technical report. Lyon: International Agency for Research on Cancer, 1998.[15]

[b] Excludes 8240–8245.

[c] Includes tumors of borderline malignancy (low malignant potential). Unlike borderline tumors of other types, borderline tumors of serous and mucinous types are included with carcinomas by ICD-O. This approach remains to be validated fully.

2. Serous Type and Mucinous Type Ovarian Tumors

Epithelial ovarian tumors represent 60% of all ovarian tumors. 85% of all malignant ovarian tumors are epithelial tumors. Epithelial tumors are rarely found in pre-pubertal age with prevalence increasing with age with peak prevalence in the fifth and seventh decades. Subtypes of ovarian tumors include serous, mucinous, endometrioid, clear cell and Brenner tumors.[19]

Epithelial ovarian tumors have the main picture of cystic lesions, can be unilocular, multilocular and for malignant ones there is usually a solid component with varying proportions. The two most common types of epithelial ovarian tumors are serous type and mucinous type ovarian tumors. In relation to the pathological features, disease course and prognosis, serous and mucinous ovarian tumors have different features although differentiating them is not always easy.[20]

In most cases, epithelial tumors tend to give a cystic and solid appearance morphologically and are difficult to differentiate imaging using MRI, CT Scan or Ultrasonography (USG). However, there are several features that can be used to differentiate serous type tumors from mucinous types. An ovarian tumor with a unilocular or multilocular appearance with homogeneous attenuation of the CT or MRI signal, regular and thin walls without any endo or exocystic features can be considered a serous type ovarian tumor (serous cyst-adenoma). An ovarian tumor with multilocular cystic manifestations with thin and regular walls/septa with varying attenuation of CT or MRI signals can be considered a benign mucinous tumor (mucinous cyst-adenoma).[21]

Mucinous cyst-adenoma tends to be larger in size than serous cyst-adenoma. Approximately 60% of all serous type ovarian tumors are benign, 15% of them have low malignant potential and the remaining 25% are malignant. On the other hand, 80% of all mucinous ovarian tumors are benign, 10 – 15% of them have low malignant potential, and 5% – 10% are malignant. Psammoma bodies (calcifications) are found histologically in malignant serous type ovarian tumors. Peritoneal carcinomatosis and bilateral tumors are more common in serous tumors than mucinous.[22]

Genetic Risk Factors

Genetic factors are the most important risk factors for ovarian tumors. Genetic predisposition is found in 10-15% of cases. A previous history of breast cancer or a family history of breast, uterine and ovarian cancer increases the risk of ovarian tumors significantly.13 Mutations in the BRCA1 and BRCA2 genes are associated with ovarian and breast cancer. These two genes were first discovered in 1994 and 1995, where BRCA1 is an oncosuppressor gene on chromosome 17q21, while BRCA2 is located on chromosome 13q. Mutations in the BRCA1 gene are associated with a 50% increased risk of ovarian cancer while BRCA2 gene mutations are 20%. Salpingo-oophorectomy in individuals with positive BRCA mutation carriers significantly reduces the risk for ovarian cancer by up to 75%.[23]

Demographic Risk Factors (Age)

Epithelial type malignant ovarian tumors occur more often in postmenopausal age, especially those aged > 65 years. The average age at diagnosis is 50 – 79 years. The relationship between age and the outcome of ovarian malignancy is still unclear, although many researchers show that younger patients have better outcomes, while other researchers say that age does not affect patient outcomes. In general, it is said

that older patients usually present with more advanced disease and have a lower survival rate.[24]

Reproductive Risk Factors

Many studies show that women with early menarche (age < 12 years) and late menopause (age > 50 years) have a higher risk of ovarian tumors due to a greater number of ovulatory cycles. Women with early menarche have a 1.1 to 1.5 times higher risk, while women with late menopause have a 1.4-1.6 higher risk of suffering from ovarian tumors.

On the contrary, pregnancy and breastfeeding are protective factors against ovarian tumors. Several studies have shown a reduced risk of ovarian malignancy, both mucinous and non-mucinous, in women who have given birth at term. Pregnancy is also reported to reduce the risk of aggressive or advanced types of ovarian tumors.[25]

Gynecologic Risk Factors

The role of pelvic inflammatory disease (PID) in the incidence of ovarian cancer is still unclear. Several studies have shown that inflammation of the pelvis contributes to the onset of ovarian cancer. The hypothesis is that inflammation in the ovaries will trigger the release of cancer cells in the tissue around the ovaries. Chlamydia trachomatis infection which results in recurrent PID is associated with the incidence of ovarian cancer. The relationship between endometriosis and ovarian cancer has been shown in several studies, this is because endometriosis has the potential for malignant transformation with a higher risk for endometrioid and clear cell ovarian tumor types.

Compared with other types of ovarian tumors, endometriosis-related ovarian tumors are usually detected at a younger age and at an earlier stage. Melin et al in their study stated that although endometriosis increases the risk of ovarian cancer, hysterectomy may have a protective effect against ovarian cancer before or when a diagnosis of endometriosis is made. Stewart et al. in a cohort study stated that nulliparous women with endometriosis had a 3 times higher risk of developing ovarian cancer. They stated that although hysterectomy has a protective effect against ovarian cancer, unilateral oophorectomy/salpingo-oophorectomy without hysterectomy increases the risk of ovarian cancer by 4 times.[26]

Hormonal Risk Factors

Many studies indicate that oral contraceptive use is associated with a reduced risk for all histologic types of ovarian cancer. A case-control study in Canada showed that the use of hormonal contraceptive pills was associated with a reduced risk of epithelial type ovarian cancer except the mucinous type. On the other hand, an increased risk of ovarian tumors was found in women who received hormone replacement therapy, where researchers believe that the use of estrogen for therapy for more than 10 years will increase the risk of ovarian cancer.[27]

Lifestyle Risk Factors

Nutrition and dietary patterns also influence the risk factors for ovarian tumors. Consumption of saturated fat is associated with an increased risk, while consumption of fish and vegetables is said to have a protective effect against ovarian tumors due to their calcium and vitamin D content.[28]

Obesity, especially the central type, and lack of physical activity are said to increase the risk factors for ovarian tumors and reduce the survival rate of this disease. This risk factor increases even more in those who are obese but have never received post-menopausal estrogen therapy. 13 Several studies show that alcohol does not increase the risk of ovarian cancer, but in a case-control study it was stated that consumption of caffeine and coffee can increase the risk of ovarian cancer in those who have not yet reached menopause.

Although many researchers believe that smoking does not change the risk of ovarian cancer in women before and after menopause, Jordan et al. stated that smoking 1 pack a day for more than 20 years increases the risk of mucinous, borderline and malignant types of ovarian cancer more than double. 13, 19

Table 2: Risk factors for ovarian tumors

Factors		Protective	Predisposing	Controversial
Demographic	Age		✓	
Reproductive	Menstrual-related factors		✓	
	Age of menarche and menopause			✓
	Parity	✓		
	Pregnancy characteristics			✓
	Higher age of childbirth	✓		
Gynecologic	Pelvic inflammatory disease			✓
	Endometriosis		✓	
Hormonal	Contraceptive methods	✓		
	Hormone Replacement Therapy (HRT)			✓
	Infertility treatments			✓
Genetic	Family history		✓	
	BRCA mutations		✓	
	Lynch syndrome		✓	
Lifestyle	Nutrition and Diet			✓
	Obesity and physical activity			✓
	Alcohol, caffeine and cigarettes			✓
Other	Lactation	✓		
	Lower socioeconomic status		✓	

Until now, the pathogenesis of ovarian tumors is still not completely clear. One of the big problems in uncovering its pathogenesis is the fact that the origin of the cells and their biological and histological properties are heterogeneous. [28]

The Relentless Theory of Ovulation and Fallopian Tubes

Initially, ovarian tumors were believed to originate from the epithelial cells on the surface of the ovary. During ovulation, trauma occurs to these epithelial cells which then quickly recover. In a woman's life cycle, ovulation occurs repeatedly resulting in repeated trauma to the ovarian epithelium. This repetitive trauma causes damage to DNA. Cells with DNA damage are susceptible to characteristic changes. With trauma the ovarian epithelial cells are 'facilitated' or invaginated into the ovarian stroma. These epithelial cells then form cortical inclusion cysts within the stroma.

Ovarian hormones then trigger the proliferation of cells which then transform into tumor cells. Previously, experts believed that ovarian tumors originated from the ovarian cells themselves.

Therefore, only a few try to look for cancer precursor lesions in other places. It is reported that epithelial dysplasia is found with a high incidence in the fallopian tubes (50%) of women with BRCA1 and BRCA2 gene mutations. This epithelial dysplasia is similar to a high-grade serous type of ovarian cancer called tubal intraepithelial carcinoma (TIC).

Other studies show the similarity of the histological characteristics of ovarian cancer with high grade serous peritoneal cancer regardless of BRCA status. Examination of the contralateral ovary in patients with ovarian cancer shows normal histological features or morphological changes that do not resemble the characteristics of high grade serous cancer. Based on these studies, it can be concluded that the fallopian tubes are the location of ovarian cancer precursor lesions which ultimately spread to nearby ovaries.[29]

Two Path Theory

This theory was developed by Kurman and Shih in 2004 which integrates clinical, histological and genetic findings of ovarian tumors. In this theory, ovarian cancer is divided into two types, called Type I and Type II. Type I ovarian cancer consists of five subtypes, namely: low grade serous, mucinous, endometrioid, clear cell and transitional type. While Type II consists of three subtypes, namely: serous high grade, undifferentiated and carcinosarcoma.

In Type I ovarian cancer, the precursor lesions are believed to originate from the ovaries, which grow slowly and tend to be benign and genetically more stable. This tumor can undergo a series of morphological changes and become ovarian cancer after passing through the intermediate (borderline) phase.

The pathogenesis of Type I ovarian cancer is through the traditional route where inclusion cysts occur on the ovarian surface epithelium which proliferate due to environmental stimulation which ultimately transform into cancer cells. The most common genetic changes in Type I ovarian cancer are KRAS AND BRAF mutations, both of which can activate the MAPK oncogenic pathway.[30]

In contrast to Type I ovarian cancer, the precursor lesions in Type II ovarian cancer are believed to originate outside the ovaries, one of which originates from the fallopian tubes. In type II ovarian cancer grows more aggressively, is genetically unstable and is usually only diagnosed when the tumor is at an advanced stage.

The majority of Type II ovarian cancers show mutations in the TP53 gene (50-80%), HER2/neu gene (10-20%) and AKT gene (12-18%). Nearly half of Type II ovarian cancer cases are associated with BRCA ½ gene mutations. Cancer precursors of this type can originate from the fallopian tubes where a combination of TP53 mutations and environmental stressors such as pro-inflammatory cytokines and free radicals cause secretory cells in the epithelium in the tubes to undergo neoplastic changes.

Many studies show that TP53 gene mutation is associated with low parity, therefore ovulation is still considered a risk factor for TP53 gene mutation. In general, this theory can explain the pathogenesis of ovarian cancer compared to other theories. However, it is still little understood about cancers that develop from outside the ovaries.[31]

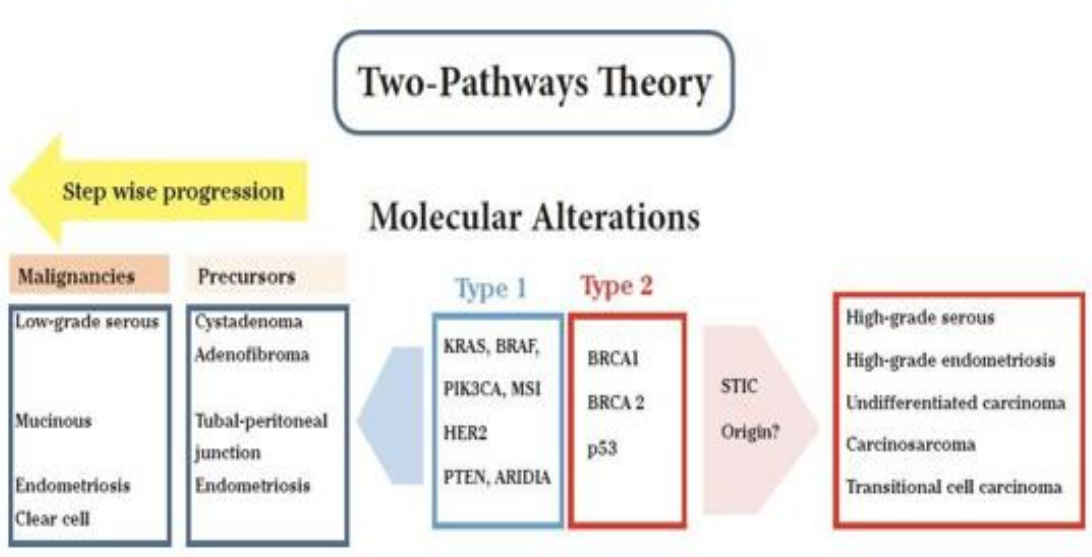


Figure 5: Two pathway theory in the pathogenesis of ovarian cancer with two genetic change pathways[31]

Clinical Manifestations

About 60% of women with ovarian cancer have metastasized when the diagnosis is first made. This is because this malignancy is asymptomatic in the early stages. The clinical manifestations of advanced ovarian cancer are also often non-specific so they are not recognized as symptoms of malignancy and are therefore called the "silent killer".

The reported that there are at least 10 symptoms that can be found in patients with ovarian tumors which include: (1) Abdominal Pain; (2) Gastrointestinal Symptoms such as diarrhea, constipation or flatulence; (3) Urinary Tract Symptoms both dysuria and urgency; (4) Abdominal Distended; (5) Persistent Fatigue; (6) Back Pain; (7) Abnormal Vaginal Bleeding; (8) Palpable abdominal mass; (9) Weight loss and swelling of both legs; (10) Nausea and Vomiting. Jelovac et al. reported a symptoms index, namely 6 of these symptoms that occurred more than 12 times a month during the last year, had a sensitivity of 56.7% for early stage tumors and around 76.5% for advanced stage tumors. In this study, it was also stated that these symptoms had a specificity of around 90% in women aged > 50 years and around 86.7% in women aged < 50 years.[32]

Muhabat et al in their research reported that the most frequently found clinical symptom was abdominal mass, namely around 44%, followed by urinary tract symptoms and nausea and vomiting, while Goff et al in their study of 1709 patients with ovarian tumors who came to primary care reported that symptoms the most common are gastrointestinal symptoms (51%), back pain (45%), fatigue (34%) and abdominal pain (22%) 24, 25 Clinical manifestations also vary depending on the histologic type of the tumor itself.

The real differences are in the symptoms of abdominal enlargement, abnormal vaginal bleeding and gastrointestinal complaints. Complaints of abdominal enlargement were 2.6 times more common in the serous type than in the mucinous type. Women with endometrioid ovarian cancer are three times more likely to experience abnormal vaginal bleeding.

Patients with serous type of ovarian cancer complain of gastrointestinal symptoms more often than other types. The majority of patients with serous type ovarian cancer are diagnosed at an advanced stage and have a shorter duration of symptoms than other types. In contrast, patients with mucinous ovarian cancer are generally diagnosed at an early stage with a longer duration of symptoms.[33]

Diagnosis and Staging

Early stage ovarian cancer often shows non-specific symptoms, while in the late stage it generally shows symptoms of abdominal abnormalities. Anamnesis in patients with suspected ovarian tumors includes anamnesis of the main complaint and previous history and family history of tumors.

A complete physical examination is also carried out along with a rectovaginal examination by emptying the bladder to evaluate the pelvic mass. A physical examination is also carried out to evaluate signs of endocrine abnormalities, pleural effusion, signs of metastasis including examination of the inguinal glands and masses in the umbilical region. 26 Complete blood count, liver function and tumor marker CA 125 should be performed at any suspicion of ovarian tumor. CA 125 is elevated in about 80% of cases of epithelial ovarian tumors, but only about 50% in the early stages.

Moreover, CA 125 can also be elevated in benign conditions such as endometriosis and fibroids. The specificity and positive predictive value of CA 125 were higher in postmenopausal than premenopausal patients. Other serum biomarkers that can be checked are Carcinoembryonic Antigen (CEA) and Human Epydidymal Protein 4 (HE4), a glycoprotein that is expressed in one third of ovarian cancers. HE4 is primarily used for evaluating progression and monitoring disease recurrence.[34]

The first imaging modality used in evaluating ovarian masses is ultrasonography or ultrasound. The International Ovarian Tumor Analysis (IOTA) and Ovarian-Adnexal Reporting and Data System (O-RADS) can be used to characterize and stratify risk and ovarian masses.

If the lesion is benign, follow-up can be carried out and there is no need for further evaluation. If the ultrasound results indicate malignancy, further evaluation with CT of the abdomen with contrast and pelvis and CT of the thorax is recommended for disease staging and pre-treatment planning.[31]

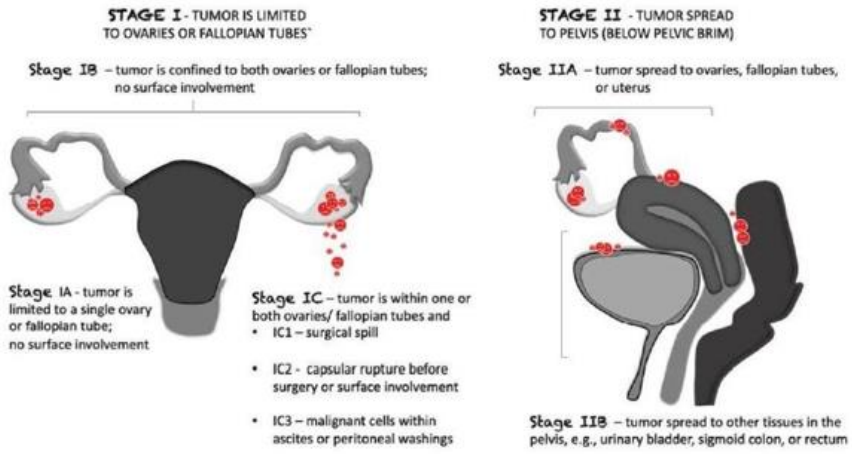
Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) Scans are not included in routine preoperative or staging examinations but can be used for more accurate evaluation in advanced stages.

Laparoscopic surgery is still the mainstay in diagnosis and staging. FIGO 2014 Staging is the currently recommended system. There are no changes to the latest FIGO staging system in 2021. FIGO classification and Union of International Cancer Control (UICC) TNM staging are shown in table 3. [35]

Table 3: FIGO staging for ovarian tumors[35]

UICC stage	FIGO Stage	Stage description
T1N0M0	I	The tumor is limited to the ovary (or ovaries) or fallopian tube(s).
T1aN0M0	IA	The tumor is limited to one ovary with an intact capsule or one fallopian tube. There is no tumor on the surface of the ovary or fallopian tube. No cancer cells are found in the ascitic fluid or peritoneal washings.
T1bN0M0	IB	The tumor is limited to both ovaries or fallopian tubes but not on their outer surfaces. No cancer cells are found in the ascitic fluid or peritoneal washings.
T1cN0M0	IC	The cancer is in one or both ovaries or fallopian tubes and any of the following are present: IC1: rupture and spillage of tumor during surgery IC2: capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: tumor cells in the ascites or peritoneal washings
T2N0M0	II	Involvement of 1 or both ovaries or fallopian tubes with extension to pelvis (below pelvic brim) or primary peritoneal cancer.
T2aN0M0	IIA	Extension/implants on the uterus and/or the fallopian tubes and/ or the ovaries.
T2bN0M0	IIB	Involvement of other intraperitoneal pelvic structures
T1-3N0-1M0	III	Involvement of 1 or both ovaries or fallopian tubes, or peritoneal cancer with spread to the peritoneum outside the pelvis confirmed by cytology or histology and/or metastasis to the retroperitoneal lymph nodes
T1-2 N1M0	IIIA1	Positive retroperitoneal lymph nodes (cytologically or histologically proven) IIIA1(i) Metastasis up to 10 mm in greatest dimension IIIA1(ii) Metastasis more than 10 mm in greatest dimension
T3a2N0-1M0	IIIA2	Microscopic involvement of extra pelvic peritoneum with or without positive retroperitoneal lymph nodes
T3bN0-1M0	IIIB	Macroscopic deposits in the extra pelvic peritoneum, with largest deposit less than 2 cm in size with or without retroperitoneal lymph nodes
T3cN0-1M0	IIIC	Macroscopic deposits in the extra pelvic peritoneum with largest deposit more than 2 cm in size (includes extension of tumor to capsule of the liver and spleen without parenchymal involvement of either organ)
Any T Any N M1	IVA	Pleural effusion with positive cytology
Any T Any N M1	IVB	Parenchymal metastases to solid organs and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO staging shows stage I tumors that are limited to the ovaries or fallopian tubes. IA is limited to 1 ovary with an intact capsule, IB tumor affects both ovaries or fallopian tubes and at stage IC the tumor affects one or both ovaries/tubes accompanied by surgical spill or rupture of the capsule. 28, 29 In stage II the tumor has spread to organs in the pelvic cavity, where IIA the tumor has spread to the tubes or uterus and IIB if the tumor has spread to the urinary bladder, sigmoid colon or rectum. In stage III the tumor spreads to the extra-pelvic with or without retroperitoneal lymph node involvement, where IIIA1 if retroperitoneal lymph node involvement is found, IIIA2 if there is evidence of microscopic extra-pelvic peritoneal implantation and IIIB if there is macroscopic extra-pelvic peritoneal implantation < 2 cm. Patients enter stage IIIC if a macroscopic extra-pelvic peritoneal implantation measuring > 2 cm is found. Stage IV indicates distant metastases, with IVA in the pleura and IVB in the liver.[36]



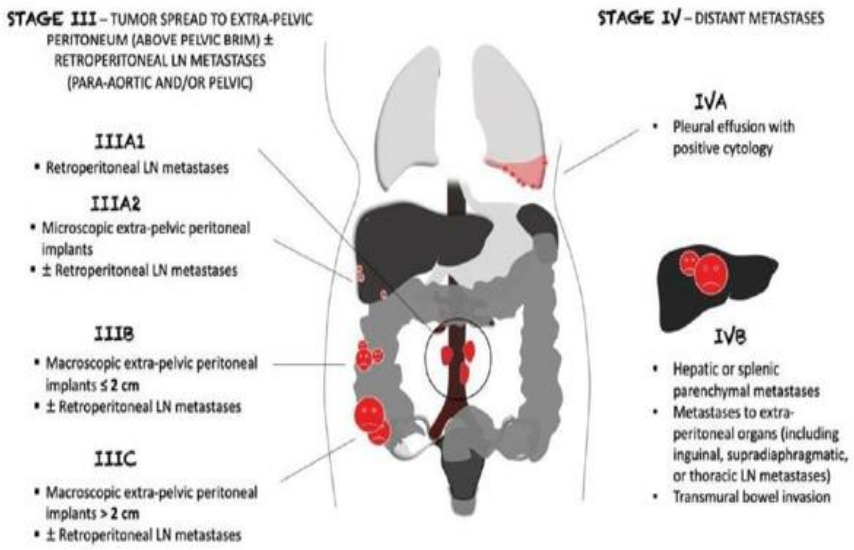


Figure 6: Illustration of FIGO staging.[36]

The Role of CT scan In Ovarian Tumors

Ultrasonography (USG) is the first and most frequently used modality in the evaluation of patients with ovarian tumors. This is because ultrasound has several advantages, namely that it is relatively cheap, easy to access and has quite high sensitivity, namely around 85 – 100%. However, in some cases it is difficult to predict whether the lesion is malignant or benign due to the relatively low specificity of ultrasound. Magnetic Resonance Imaging (MRI) is imaging that can provide additional information about the characteristics of ovarian lesions, while CT scans are usually used in staging and evaluating lesions before surgery. The advantage of CT scanning with the latest technology is its ability to detect metastatic deposits and tumor expansion. Apart from that, another advantage is that there is multiplanar reconstruction and the shorter acquisition time compared to MRI allows for a more detailed evaluation of the lesion. 2, 10, 30 Ramayuda et al. from Dr. Soetomo Hospital Surabaya in his research revealed that CT Scan had a sensitivity of 93.3% and a specificity of 64.3% in the diagnosis of ovarian tumors.[37]

The CT scan appearance of ovarian malignancy has been studied in quite a lot of literature. Several imaging features (lesion size, multilocularity, septa thickness, solid component, calcification, contrast enhancement, papillary projection and feeding artery) are routinely evaluated and can provide clues about the malignancy of the ovarian lesion. Although additional findings (lymphadenopathy, ascites, involvement of the peritoneum or other abdominal organs) can raise suspicion that the lesion is at an advanced stage, some benign lesions can suggest malignancy on CT scan. Several characteristics of CT Scan findings on ovarian masses include: lesion consistency, wall enhancement, loculation, septation, mass size, presence or absence of ascites and presence or absence of peritoneal nodules or omental cake. Lesion consistency is a strong predictor of the malignant status of an ovarian mass. Completely cystic lesions without septations and solid components are reported to have a 95.8% chance of being benign. On the other hand, 55.9% of lesions with a mixture of solid and cystic were malignant. Most cases of ovarian malignancy are of the epithelial type where CT scan findings show predominantly cystic lesions.[38]

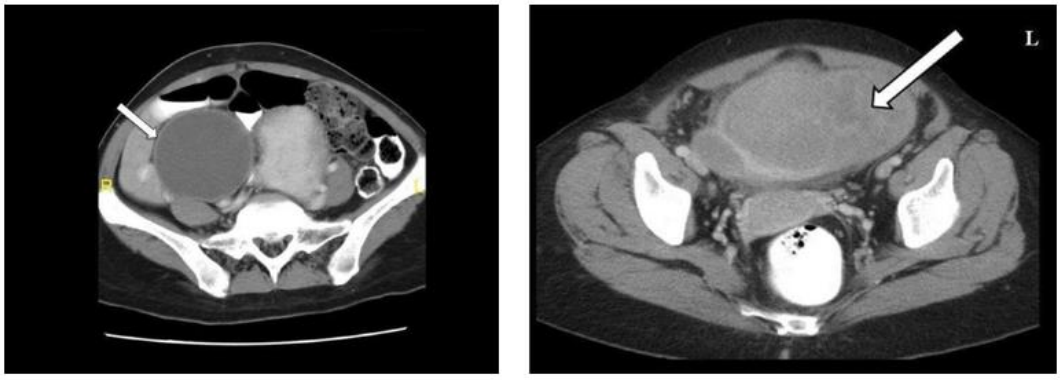


Figure 7: The arrow shows a simple unilocular cyst without septation and a solid component which indicates a benign condition and a CT scan with contrast shows a septated cystic mass without a solid component. No peritoneal nodules or ascites were found. However, histopathological examination showed a borderline seromucinous tumor accompanied by microinvasion.[38]

Wall Reinforcement

There is a strong association between wall enlargement and malignancy of ovarian masses. Lesions whose walls do not have strong contrast are reported to be more often benign lesions, and vice versa. However, low grade serous ovarian carcinoma is reported to be only slightly enlarged on the wall and around 49% of benign cases are moderately or moderately enlarged. Unilocular ovarian tumors are mostly benign conditions, however multiloculation can also be found in benign and malignant conditions with almost the same distribution. Unilocular cystic ovarian tumors of small size (< 5 cm) are more often benign on histopathological appearance and have a low risk of malignant transformation.[39]

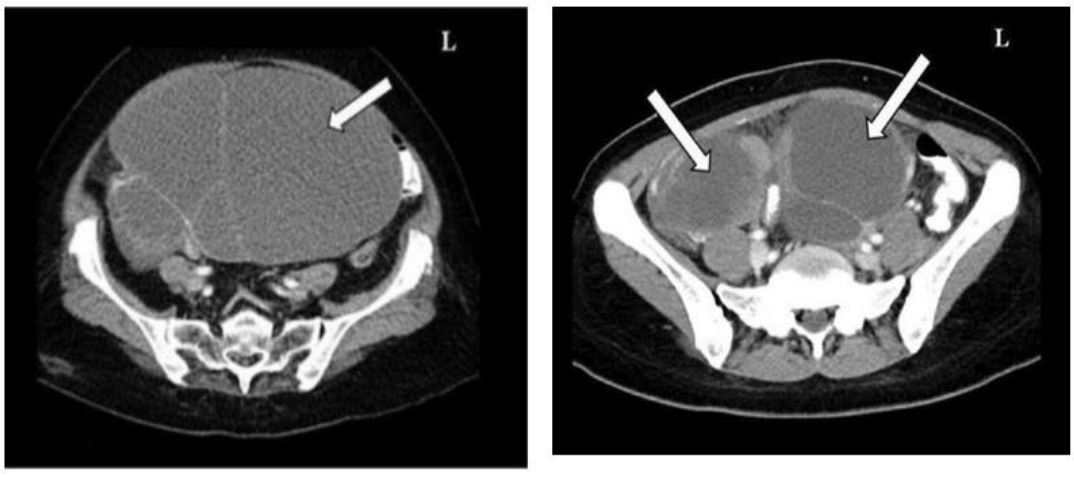


Figure 8: CT scan with contrast shows a septated cystic mass with a solid component accompanied by a nodule in the peritoneum which is suspected of being malignant. Histopathological results confirmed a malignancy. and Figure 14. CT scan with contrast shows a multiloculated cystic lesion accompanied by septation with a solid component. In this case, a metastatic lesion was confirmed.[39]

Peritoneal or Omental Caking Nodules

The presence of findings on a CT scan in the form of nodular, plaque-like or infiltrative type implantation in the peritoneum is a sign of malignancy or metastasis. However, it has been found that in some cases false positives occur where nodules in the peritoneum are a benign condition and endometriosis implantation in the peritoneum is an inflammatory reaction process in the peritoneum.[40]

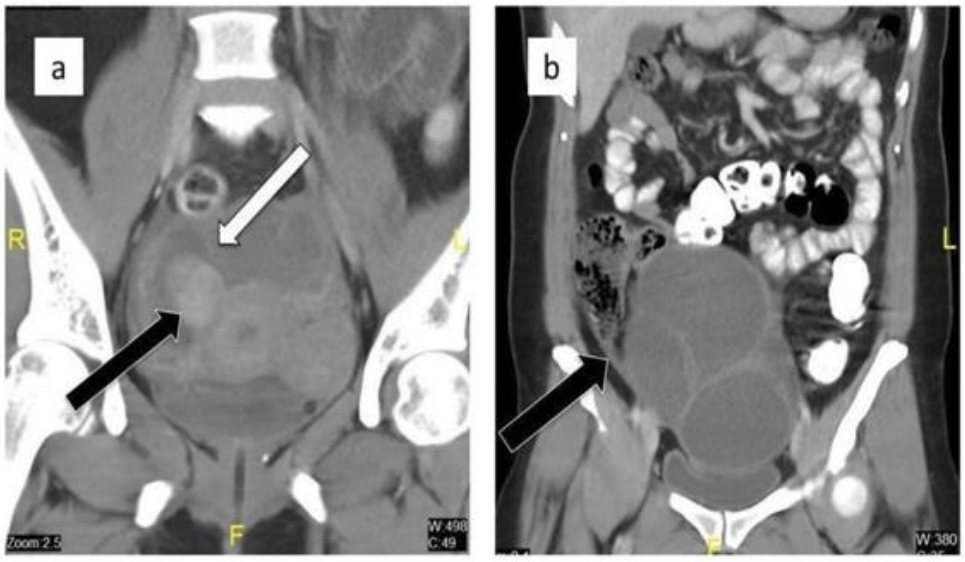


Figure 9. The most frequent mimicking of ovarian carcinoma is endometriosis. Image (a) shows a lesion with a cystic-solid consistency (black arrow), accompanied by septations in it (white arrow) and enlargement of the wall. In image (b) peritoneal nodules are visible showing deposits from endometriosis (black arrows).[40]

Attenuation Value of the Cystic Component of Ovarian Tumors

There is a strong association between ascites and the histopathological appearance of ovarian masses. The presence of ascites further indicates that the lesion is malignant. Benign and malignant lesions actually have the same chance of forming ascites. However, benign lesions generally do not form ascites simultaneously, whereas in malignant cases ascites is usually present in the early stages. In general, the cystic component of ovarian tumors has been widely studied, especially its physical and biochemical composition and its relationship to clinical value. Research on the cystic component of ovarian tumors includes cytological examination, hormonal components, tumor markers and components involved in angiogenesis and tumor invasion.[41]

Cytologic examination of the cystic component is reported to have low diagnostic value. This is because there are few cellular components contained in it. On the other hand, the hormonal components contained in this fluid have been reported mainly in relation to differentiating between neoplastic and functional cysts. Functional cysts are said to have low FSH, LH and high 17β-estradiol hormonal content compared to neoplastic cysts. The composition of cystic fluid in ovarian tumors also contains glycoproteins which are related to the processes of angiogenesis and tumor invasion. Angiogensis is a complex and important process in tumor growth and spread. This process includes the formation of new blood vessels that open pathways for spread

or metastasis. The most important angiogenesis factor in ovarian tumors is VEGF (Vascular Endothelial Growth Factor) which is a glycoprotein. It was reported that the VGEF content in cystic fluid was significantly higher in malignant and borderline ovarian tumors than in benign ovarian tumors.[42]

Other research on the cystic component of ovarian tumors which aims to differentiate benign and malignant cystic ovarian tumors shows that the concentration of gonadotropin hormones (estrogen and progesterone) and steroids is higher in malignant cystic tumors compared to benign ones. The cystic component of ovarian tumors has been widely studied morphologically, but the radiological characteristics of this component are relatively underexplored. On the other hand, the histopathological picture of ovarian tumors shows characteristics related to the composition of the fluid and the cellular type of the lesion. Therefore, it is possible that these characteristics are also reflected in CT scan imaging so that they can provide additional diagnostic information.[1]

The first study reporting the attenuation value of CT scans in ovarian cysts was published in 1997 by Guereiro et al. Although the details of the measurements were not mentioned by the author, the attenuation value showed a correlation with the histopathological picture where the average HU (Hounsfield Unit) value for simple ovarian cysts was 12.4 ± 8 HU, 5.5 ± 5.2 HU for serous cystadenoma and 61 ± 29.7 for cystadenocarcinoma serous.[1]

Song-Mee Cho et al. in their study of 25 patients with mucinous cyst-adenocarcinoma and 47 patients with serous cyst-adenocarcinoma revealed that the CT attenuation value in serous type ovarian tumors was more variable than in the mucinous type, while Boos et al. His research showed that both serous and mucinous tumors had equally varied attenuation values. Another study conducted by Choi et al. However, clear cell carcinoma type ovarian tumors show an average attenuation value of around 24.2 HU (13 – 34 HU). Meanwhile, Lupean et al in their research showed that the non-contrast attenuation value for simple cyst was around 6.56 HU, serous carcinoma around 9.34 HU and serous cyst-adenoma around 23.9 HU. Attenuation higher than 20 HU is caused by necrosis or bleeding components, while attenuation lower than 20 HU is usually serous fluid.[20]

In malignant tumors, bleeding can be caused by the tumor itself, abnormal vascular structures, tumor regression, contrast enhancement or even due to tumor therapy (such as chemotherapy or radiotherapy).

Tumor Marker Ca-125 and CEA

There are many tumor markers that have been developed to increase the sensitivity and specificity of preoperative examination of patients with ovarian malignancies. CA-125 and CEA are generally used as predictors for differentiating ovarian tumors benign, borderline and malignant types. In Denmark, CA-125 is routinely used as part of the RMI (Risk Malignancy Index) where ultrasound, menopausal status and serum CA-125 are part of a scoring system that helps predict whether an ovarian tumor is malignant or benign. CA-125 is a monoclonal antibody discovered in 1981 by Bast et al. where immunoassay using CA-125 has a significant correlation with ovarian malignancy. This tumor marker is used either alone or in combination with other tumor markers to detect ovarian tumors. Elevated CA-125 values were found in 82% of patients with ovarian malignancies, 28% of patients with non-ovarian malignancies (including pancreas, breast and colon) and around 6% of patients with benign

gynecological diseases such as endometriosis, leiomyoma and PID (Pelvic Inflammatory Disease).). For epithelial ovarian malignancies, CA-125 levels are related to the histologic subtype and stage of the disease. The CA-125 value is more increased in serous type ovarian tumors compared to mucinous type. It has been reported that CA-125 values increase in 50% of patients with stage I and II ovarian tumors compared to 90% in stage IIIC or stage IV.[25]

Carcinoembryonic antigen (CEA) is a glycoprotein synthesized by fetal tissue and by several types of carcinoma. This tumor marker was first discovered by Freedman and Gold in 1965. They carried out several serological studies using extracts from colon adenocarcinoma tissue. Serological studies show that 70% of patients with non-metastatic primary tumors of the gastrointestinal tract have anti-CEA antibodies in their serum. Subsequent studies showed that this tumor marker was not exclusively found in colon tumor patients, but abnormal values were also found in various other malignancies. An increase in CEA values of more than 5 ng/ml can be found in patients with gastrointestinal carcinoma, breast and some gynecological tumors. Elevated serum CEA is reported to occur in 35% of all patients with ovarian carcinoma and is more common in patients with mucinous type ovarian tumors compared to serous type. Simultaneous examination of the tumor markers CA-125 and CEA provides better diagnostic value in differentiating ovarian tumors from other tumors, especially colorectal tumors. A CA-125 and CEA ratio of more than 25 indicates 100% specificity and 91% sensitivity in differentiating ovarian tumors from colorectal tumors. Ji Hui Choi et al reported that the ratio of CA-125 and CEA was significantly lower in ovarian tumors mucinous type compared with serous type ovarian tumors and other types. In the report, the sensitivity and specificity values of this ratio in detecting mucinous carcinoma versus other types of ovarian carcinoma were 75% and 77.5%.[25]

Cystic Components and Tumor Markers

Most studies on the cystic component of ovarian tumors have been aimed at determining tumor biomarkers, with CA-125 and CEA being the most commonly studied tumor markers. The CEA content in the cystic component of the tumor is increased in mucinous type ovarian tumors although it can be increased in both cystadenoma and cystadenocarcinoma. The CEA value was found to be highest in tumor cystic fluid, followed by ascites fluid, then lowest in blood. Different things were found in the tumor marker CA-125, where higher concentrations of this biomarker were found in serous type ovarian tumors compared to mucinous types, although several other studies have shown that the opposite is true. Another study also reported that there was no difference in the concentration of the tumor marker CA-125 in benign or malignant ovarian tumors. Attenuation value (Hounsfield Unit) of soft tissue on Abdominal Computed Tomography. The attenuation value of x-ray beams on CT (computed tomography) is very dependent on the thickness and anatomical composition of the soft tissue that affects it. In a CT scan, after image reconstruction is formed, each pixel of the CT image has an attenuation value or CT number in Hounsfield Units (HU). The HU scale is the result of calibration with the benchmark that water has a value of 0 HU and air is – 1000 HU, which is the value set on the HU unit scale. Measurement of the Hounsfield value makes it possible to assess tissue characteristics on abdominal CT. The characteristics of cystic lesions, adrenal nodules, hepatic steatosis and the presence of intraperitoneal fluid can be determined by measuring the HU value of the lesion.[28]

CONCLUSION

Ovarian Tumor Biomarkers are CA-125 and CEA are the most frequently studied tumor markers in the context of ovarian tumors. CEA tends to increase in mucinous type ovarian tumors, both cystadenomas and cystadenocarcinomas. The highest CEA levels were found in tumor cystic fluid, followed by ascites fluid, and the lowest in blood. CA-125 concentrations are higher in serous type ovarian tumors than in mucinous types, although there are other studies that show the opposite results. Also, there are reports stating that there is no difference in CA-125 concentration between benign and malignant ovarian tumors. The attenuation value or Hounsfield Unit (HU) on a CT scan varies based on the thickness and anatomical composition of the soft tissue. HU is measured on a scale where water has a value of 0 HU and air -1000 HU. HU measurement allows assessment of tissue characteristics such as cystic lesions, adrenal nodules, hepatic steatosis, and the presence of intraperitoneal fluid.

Reference

1) D. Y. Lee and S. M. Nam, “Association between restrictive pulmonary disease and type 2 diabetes in Koreans: A cross-sectional study,” *World J. Diabetes*, vol. 11, no. 10, pp. 425–434, Oct. 2020, doi: 10.4239/wjd.v11.i10.425.

2) S. Gupta, P. Padhan, S. Subhankar, and P. Singh, “Cardiovascular complications in patients with interstitial lung disease and their correlation with 6-minute walk test and spirometry: A single-center study,” *J. Fam. Med. Prim. Care*, vol. 10, no. 9, p. 3330, 2021, doi: 10.4103/jfmpc.jfmpc_350_21.

3) H. H. Idrus, B. Modding, and S. Basalamah, “Collective Competence as an Enable for Services Integration in Health and Social Care Services [Letter],” *J. Multidiscip. Healthc.*, vol. Volume 15, pp. 2901–2902, Dec. 2022, doi: 10.2147/JMDH.S401005.

4) Y. Mares-Gutiérrez, A. Martínez-González, G. Salinas-Escudero, M. García-Minjares, S. Liu, and Y. N. Flores, “Combining Spirometry and the ARISCAT Respiratory Risk Assessment Can Improve Postoperative Outcomes and Reduce Mortality Risk in Mexico,” *Open Respir. Arch.*, vol. 6, no. 3, p. 100325, Jul. 2024, doi: 10.1016/j.opresp.2024.100325.

5) H.-C. Yeh *et al.*, “Cross-Sectional and Prospective Study of Lung Function in Adults With Type 2 Diabetes,” *Diabetes Care*, vol. 31, no. 4, pp. 741–746, Apr. 2008, doi: 10.2337/dc07-1464.

6) D. K. Jang, H. S. Nam, M. Park, and Y. H. Kim, “Differences in Associated Factors of Sedentary Behavior by Diabetes Mellitus Status: A Nationwide Cross-Sectional Study,” *J. Clin. Med.*, vol. 12, no. 17, p. 5453, Aug. 2023, doi: 10.3390/jcm12175453.

7) H. H. Idrus, - Sunarno, and S. Rijal, “Detection of Antibiotic Resistance Genes in Pseudomonas aeruginosa by Whole Genome Sequencing [Letter],” *Infect. Drug Resist.*, vol. Volume 15, pp. 7125–7126, Dec. 2022, doi: 10.2147/IDR.S399417.

8) H. Idrus, - Fitriana, and S. Adiningsih, “Detection of HIV-1 DNA/RNA in Peripheral Blood, Bone Marrow and Femoral Head of Patients with Osteonecrosis of the Femoral Head [Letter],” *Infect. Drug Resist.*, vol. Volume 17, pp. 683–684, Feb. 2024, doi: 10.2147/IDR.S464127.

9) S. Phatak, J. L. Ingram, P. Goel, S. Rath, and C. Yajnik, “Does hand stiffness reflect internal organ fibrosis in diabetes mellitus?,” *Front. Clin. Diabetes Healthc.*, vol. 4, p. 1198782, Jul. 2023, doi: 10.3389/fcdhc.2023.1198782.

10) H. B. Maan, S. A. Meo, F. Al Rouq, I. M. U. Meo, M. E. Gacuan, and J. M. Alkhalifah, “Effect of Glycated Hemoglobin (HbA1c) and Duration of Disease on Lung Functions in Type 2 Diabetic Patients,” *Int. J. Environ. Res. Public. Health*, vol. 18, no. 13, p. 6970, Jun. 2021, doi: 10.3390/ijerph18136970.

11) H. A. Aweto, E. O. Obikeh, and B. A. Tella, “Effects of incentive spirometry on cardiopulmonary parameters, functional capacity and glycemic control in patients with Type 2 diabetes,” *Hong Kong Physiother. J.*, vol. 40, no. 02, pp. 121–132, Dec. 2020, doi: 10.1142/S1013702520500110.

12) M. Sobel *et al.*, “Environmental-level exposure to metals and metal-mixtures associated with spirometry-defined lung disease in American Indian adults: Evidence from the Strong Heart Study,” *Environ. Res.*, vol. 207, p. 112194, May 2022, doi: 10.1016/j.envres.2021.112194.

13) S. M. d’Avila Melo, L. A. D. Oliveira, J. L. F. Wanderley, and R. D. A. Rocha, “Evaluating the extremely elderly at a pulmonary function clinic for the diagnosis of respiratory disease: frequency and technical quality of spirometry,” *J. Bras. Pneumol.*, vol. 45, no. 4, p. e20180232, 2019, doi: 10.1590/1806-3713/e20180232.

14) H. H. Idrus, M. Mustamin, and - Zulfahmidah, “Evaluation of a Multidisciplinary Extracurricular Event Using Kolb’s Experiential Learning Theory: A Qualitative Study [Letter],” *J. Multidiscip. Healthc.*, vol. Volume 16, pp. 39–40, Jan. 2023, doi: 10.2147/JMDH.S402844.

15) H. H. Idrus and - Sunarno, “Evaluation of the Performance of a Multiplex Real-Time PCR Assay for the Identification of Aspergillus, Cryptococcus neoformans, and Pneumocystis jirovecii Simultaneously from Sputum in Multicenter [Letter],” *Infect. Drug Resist.*, vol. Volume 15, pp. 6799–6800, Nov. 2022, doi: 10.2147/IDR.S396184.

16) S. J. Chung *et al.*, “Impact of the severity of restrictive spirometric pattern on nutrition, physical activity, and quality of life: results from a nationally representative database,” *Sci. Rep.*, vol. 10, no. 1, p. 19672, Nov. 2020, doi: 10.1038/s41598-020-76777-w.

17) H. H. Idrus and - Sunarno, “Liquiritin Protects Against Cardiac Fibrosis After Myocardial Fibrosis After Myocardial Infarction by Inhibiting CCL5 Expression and the NF-κB Signaling Pathway [Letter],” *Drug Des. Devel. Ther.*, vol. Volume 17, pp. 331–332, Feb. 2023, doi: 10.2147/DDDT.S405817.

18) K. Kida *et al.*, “Long-term effects of gastrectomy in patients with spirometry-defined COPD and patients at risk of COPD: a case-control study,” *Int. J. Chron. Obstruct. Pulmon. Dis.*, p. 2311, Oct. 2015, doi: 10.2147/COPD.S87135.

19) T.-W. Ho, C.-T. Huang, Y.-J. Tsai, A. S.-Y. Lien, F. Lai, and C.-J. Yu, “Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease,” *Respir. Res.*, vol. 20, no. 1, p. 69, Dec. 2019, doi: 10.1186/s12931-019-1035-9.

20) R.-H. Zhang, J.-B. Zhou, Y.-H. Cai, L.-P. Shu, R. Simó, and A. Lecube, “Non-linear association between diabetes mellitus and pulmonary function: a population-based study,” *Respir. Res.*, vol. 21, no. 1, p. 292, Dec. 2020, doi: 10.1186/s12931-020-01538-2.

21) S. H. Kim, H. S. Kim, H. K. Min, and S. W. Lee, “Obstructive spirometry pattern and the risk of chronic kidney disease: analysis from the community-based prospective Ansan-Ansung cohort in Korea,” *BMJ Open*, vol. 11, no. 3, p. e043432, Mar. 2021, doi: 10.1136/bmjopen-2020-043432.

22) C. A. Vaz Fragoso *et al.*, “Phenotype of Normal Spirometry in an Aging Population,” *Am. J. Respir. Crit. Care Med.*, vol. 192, no. 7, pp. 817–825, Oct. 2015, doi: 10.1164/rccm.201503-0463OC.

23) J. Takala, P. Ilmarinen, L. E. Tuomisto, I. Vähätalo, O. Niemelä, and H. Kankaanranta, “Planned primary health care asthma contacts during 12-year follow-up after Finnish National Asthma Programme: focus on spirometry,” *Npj Prim. Care Respir. Med.*, vol. 30, no. 1, p. 8, Mar. 2020, doi: 10.1038/s41533-020-0166-2.

24) K. Kulbacka-Ortiz *et al.*, “Restricted spirometry and cardiometabolic comorbidities: results from the international population based BOLD study,” *Respir. Res.*, vol. 23, no. 1, p. 34, Feb. 2022, doi: 10.1186/s12931-022-01939-5.

25) A. S. Talpur *et al.*, “Restrictive Pulmonary Disease in Diabetes Mellitus Type II Patients,” *Cureus*, Apr. 2022, doi: 10.7759/cureus.23820.

26) M. Jankowich *et al.*, “Restrictive Spirometry Pattern, Cardiac Structure and Function, and Incident Heart Failure in African Americans. The Jackson Heart Study,” *Ann. Am. Thorac. Soc.*, vol. 15, no. 10, pp. 1186–1196, Oct. 2018, doi: 10.1513/AnnalsATS.201803-184OC.

27) Y. Washio *et al.*, “Risks of Mortality and Airflow Limitation in Japanese Individuals with Preserved Ratio Impaired Spirometry,” *Am. J. Respir. Crit. Care Med.*, vol. 206, no. 5, pp. 563–572, Sep. 2022, doi: 10.1164/rccm.202110-2302OC.

28) A. Sharma, A. Sharma, and R. Chauhan, “Spirometric Lung Functions in Type 2 Diabetes Mellitus: A Hospital-Based Study,” *Cureus*, May 2023, doi: 10.7759/cureus.38919.

29) A. Szylińska *et al.*, “The Relationship between Diabetes Mellitus and Respiratory Function in Patients Eligible for Coronary Artery Bypass Grafting,” *Int. J. Environ. Res. Public. Health*, vol. 15, no. 5, p. 907, May 2018, doi: 10.3390/ijerph15050907.

30) N. V. Chernetska *et al.*, “The Role of MDR1 (C3435T) Gene Polymorphism in Patients with Chronic Obstructive Pulmonary Disease Associated with Type 2 Diabetes Mellitus,” *J. Med. Life*, vol. 13, no. 3, pp. 349–355, Jul. 2020, doi: 10.25122/jml-2020-0139.

31) N. Aamer *et al.*, “A Cross Sectional Study on Impact of Diabetes Mellitus on Lung function Parameters,” *J. Pharm. Res. Int.*, pp. 52–58, Nov. 2021, doi: 10.9734/jpri/2021/v33i49A33301.

32) R. Rani, B. Ebenezer, and M. Venkateswarlu, “A study on pulmonary function parameters in type 2 diabetes mellitus,” *Natl. J. Physiol. Pharm. Pharmacol.*, no. 0, p. 1, 2018, doi: 10.5455/njppp.2019.0414713112018.

33) S.-R. Cha, J. Jang, S.-M. Park, S. M. Ryu, S.-J. Cho, and S.-R. Yang, “Cigarette Smoke-Induced Respiratory Response: Insights into Cellular Processes and Biomarkers,” *Antioxidants*, vol. 12, no. 6, p. 1210, Jun. 2023, doi: 10.3390/antiox12061210.

34) J. Khateeb, E. Fuchs, and M. Khamaisi, “Diabetes and Lung Disease: An Underestimated Relationship,” *Rev. Diabet. Stud.*, vol. 15, no. 1, pp. 1–15, Jul. 2019, doi: 10.1900/RDS.2019.15.1.

35) P. H. Quanjer, D. J. Weiner, J. J. Pretto, D. J. Brazzale, and P. W. Boros, “Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making,” *Eur. Respir. J.*, vol. 43, no. 4, pp. 1051–1058, Apr. 2014, doi: 10.1183/09031936.00128113.

36) A. A. E.-A. I., G. Hamdy, M. Amin, and A. Rashad, “Pulmonary function changes in diabetic lung,” *Egypt. J. Chest Dis. Tuberc.*, vol. 62, no. 3, pp. 513–517, Jul. 2013, doi: 10.1016/j.ejcdt.2013.07.006.

37) G. L. Kinney *et al.*, “Pulmonary Predictors of Incident Diabetes in Smokers,” *Chronic Obstr. Pulm. Dis. J. COPD Found.*, vol. 3, no. 4, pp. 739–747, 2016, doi: 10.15326/jcopdf.3.4.2016.0137.

38) A. Kautzky-Willer, J. Harreiter, and G. Pacini, “Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus,” *Endocr. Rev.*, vol. 37, no. 3, pp. 278–316, Jun. 2016, doi: 10.1210/er.2015-1137.

39) M. R. Miller, “Standardisation of spirometry,” *Eur. Respir. J.*, vol. 26, no. 2, pp. 319–338, Aug. 2005, doi: 10.1183/09031936.05.00034805.

40) D. Pitocco *et al.*, “The Diabetic Lung - A New Target Organ?,” *Rev. Diabet. Stud.*, vol. 9, no. 1, pp. 23–35, 2012, doi: 10.1900/RDS.2012.9.23.

41) C. C. W. Hsia and P. Raskin, “The diabetic lung: Relevance of alveolar microangiopathy for the use of inhaled insulin,” *Am. J. Med.*, vol. 118, no. 3, pp. 205–211, Mar. 2005, doi: 10.1016/j.amjmed.2004.09.019.

42) P. Dalquen, “The Lung in Diabetes mellitus,” *Respiration*, vol. 66, no. 1, pp. 12–13, 1999, doi: 10.1159/000029330.