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## Clinical and Histopathological Features of Ovarian Cancer in Iraq, Baghdad Between 2014-2020

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### Abstract

Ovarian cancer is a heterogeneous disease with disparities in clinical performance and consequences. It is a cluster of numerous subtypes with diverse biological topographies that cause alterations in response to treatments, relapse rates and endurance. This study was designed to investigate the epidemiology of the diagnosed cases of ovarian cancer from 2014 to 2020 in Baghdad. A total of 51 cases of different ovarian cancer samples were collected from Al-Elwea Maternity Hospital and Medical City Teaching Hospital, Baghdad. Clinical information, including patients' age, tumor size and location, pathological grade and stage. Results revealed a high incidence of OC in patients at age of <55 years with 59% rate. The most common type was epithelial serous ovarian cancer by 52.9% overall, with high frequency at right ovary by 63.3%. The dominant tumor size was 5cm in malignant cases. While the most frequent tumor stage was IC with rate of 29.6%, and Grade 3 was the foremost one by 40.7%. Conclusion: The most common type of cancer is epithelial serous ovarian cancer that occurs in patients younger than 55 years and is present at early stage of disease (IC) with high tumor grade (poor differentiation) at the time of diagnosis.

**Keywords:** Ovarian tumors, Adenocarcinoma, Risk factors, Epidemiology, Prevalence.

## الخصائص السريرية و النسجية المرضية لسرطان المبيض في العراق ، بغداد بين 2014-2020

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### الخلاصة

سرطان المبيض هو مرض متباين الخواص ومتفاوت في الأداء السريري والنتائج. يضم المرض العديد من الأنواع الفرعية ذات السمات المظهرية المتنوعة التي تسبب تغيرات في الاستجابة للعلاجات ومعدلات الانتكاس والقدرة على التحمل. تم تصميم هذه الدراسة لتحري وبائية الحالات المشخصة لسرطان المبيض للفترة بين 2014-2020 في بغداد. تم جمع 51 حالة من عينات سرطان المبيض المختلفة من مستشفى العلوية للولادة ومستشفى مدينة الطب التعليمي ، بغداد. كما تم جمع المعلومات السريرية بما في ذلك عمر المريض وحجم الورم وموقعه ودرجته المرضية ومرحلته. أظهرت النتائج وجود نسبة عالية من سرطان المبيض في

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المرضى بعمر اقل من 55 سنة وبنسبة 59%. كان النوع الأكثر شيوعاً هو سرطان المبيض المصلي الظهاري بنسبة 52.9% إجمالاً ، مع ارتفاع معدل حدوثه في المبيض الأيمن بنسبة 63.3%. كان حجم الورم السائد 5 سم في الحالات الخبيثة. في حين كانت أكثر مراحل الورم انتشاراً هي المرحلة IC بنسبة 29.6% ، وكانت الدرجة الثالثة هي الأولى بنسبة 40.7%. الخلاصة: أكثر أنواع السرطانات شيوعاً هو سرطان المبيض المصلي الظهاري الذي يصيب المرضى الذين تقل أعمارهم عن 55 عاماً ويظهر في مرحلة مبكرة من المرض (IC) مع درجة ورم عالية (تمايز ضعيف) في وقت التشخيص.

## Introduction:

Ovarian cancer (OC) is ranked as the fifth leading cause of death among women [1]. According to Iraqi cancer registry 2016, OC is among the ten types of cancers in Iraq, where it ranks 7th with an incidence of 3.98% [2]. Cancer starts when the cells of body begin to grow increasingly out of control. Vast majority of OC patients are diagnosed at late stages because of the fast progression of metastasis and difficulty in diagnosis at early stage [3]. OC can be classified into three groups termed after the type of cells that cancer initiated from into the following: epithelial ovarian carcinoma (EOC), stromal cell ovarian carcinoma and germ cell ovarian carcinoma [4]. It must be pointed out that greater than 90% of cancerous (malignant) tumors are epithelial tumors [5]. The present standard of care for patients with recurrent EOC is palliative chemotherapy, endocrine therapy and cytoreductive surgery, when appropriate, with radiation therapy confined for the management of symptomatic metastases. Even though this treatment paradigm yields a prolonged survival rate in number of patients with recurrent EOC, it is not curative [6]. Depending on the information provided by Iraqi cancer registry 2016, there were 571 cases of OC among females for 3.98% of all diagnosed cancer cases. OC ranks as the 7th among top ten cancers in Iraqi women. Trend incidence rate of new cases of OC between 2011 – 2016 showed that the highest rate of diagnosed cases in the year 2012 for 4.64 per 100,000 female population, and highest incidence of disease in women age for year 2016 occurred at age between (60 – 64) for about 79 cases. In Baghdad 2016, there were 156 cases accounting for 4.75% total cancer cases [2]. OC has a much less survival rate than other cancers as people are unaware that its symptoms and risk factors are easily camouflaged either as normal menstrual problems or as abdominal ailments/diseases. In that sense, ovarian cancer is mostly detected at advanced stages that could be untreatable, resulting in unfavorable prognosis [7]. Furthermore, mutations in BRCA1 and BRCA2 genes lead to increase the risk of developing OC, around 55% for women having mutations in BRCA1 and 25% for women having mutations in BRCA2 [8]. In this study, we investigated the epidemiology of ovarian tumors in malignant and benign epithelial ovarian tumors among Iraqi women patients, and its correlation with clinicopathological features (age, tumor site & size, pathological stage, and grade).

## Materials and Method:

### *Samples Preparation and Staining:*

A total of 51 cases of different ovarian tissues in the form of paraffin embedded tissue blocks and patients' data were collected from archive files between the years 2014 - 2020 from the Department of Pathology of Al-Elwea Maternity Hospital, and teaching laboratories of Medical City Teaching Hospital, Baghdad, Iraq. Tissue samples from Iraqi patients with EOC involved 27 cases of malignant tumors, 12 borderline tumors, 12 benign tumors and 10 cases of ovarian tissue without significant pathology as a control. Clinical information including patient age, side of tumor, pathological grade and stage were likewise collected from the patient's data reports. One section from each paraffin embedded tissue block was cut by a microtome cutter (Leica, RM2255) with thickness between 4-5  $\mu$ m. Then, these sections were placed on a positive charged slide (Pathnsitu, USA), and heated at 60-70°C overnight

before staining. Sections were then stained with Hematoxylin and Eosin (H&E) and were later examined by a pathologist.

#### Statistical analysis

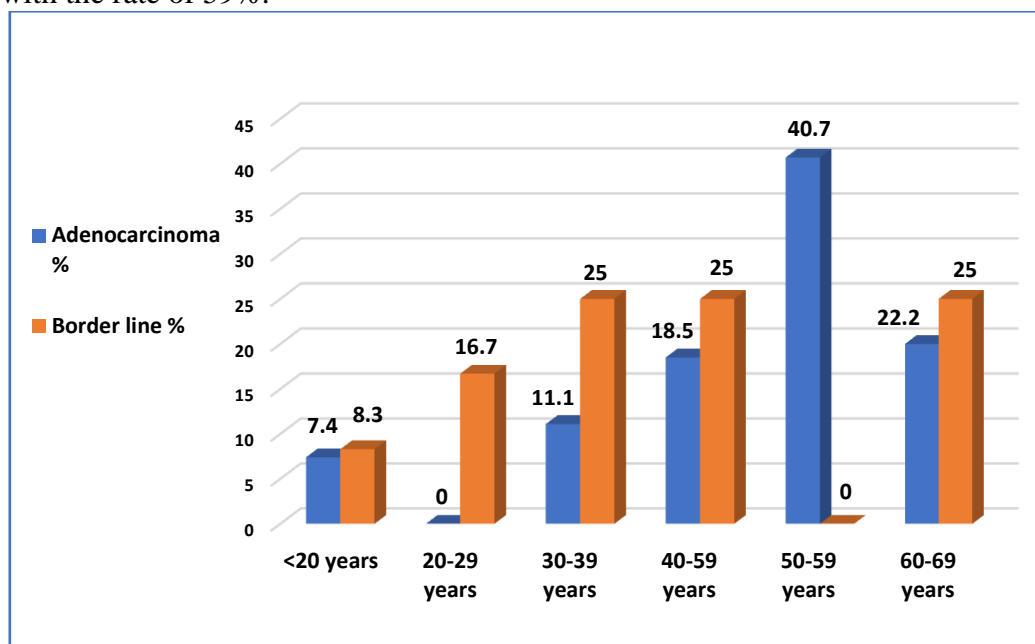
Analysis of data was carried out using available statistical package of SPSS-26 (Statistical Packages for Social Sciences- version 26). Data was presented in simple measures of frequency, percentage, mean, standard deviation and range (minimum-maximum values). The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test ( $\chi^2$ -test), with application of Yate's correction or Fisher Exact test wherever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05 ( $P \leq 0.05$ ).

#### Results and Discussion:

This study included fifty-one cases of ovarian tumor tissue samples of Iraqi female patients. Twenty-seven cases of them had adenocarcinoma mostly of serous type, while twelve were borderline, in addition to twelve cases with benign adenomas. Also, ten cases with no significant pathology were collected for comparison purposes in this study.

#### Age:

Patients age ranged from 14-75yrs., with the mean age of malignant adenocarcinoma group was  $49.4 \pm 12.8$ , while the mean age of borderline group was  $42.8 \pm 16.1$  and that of benign adenoma group was  $34.3 \pm 13.9$ . Furthermore, the peak age of ovarian cancer incidence in adenocarcinoma group was within the 50-59 years age category. It comprised 40.7% of total (Figure 1). A comparison between age groups  $\geq 55$  and  $>55$  years within ovarian cancer group (malignant & borderline) showed a high frequency of malignancies among age group  $<55$  years with the rate of 59%.



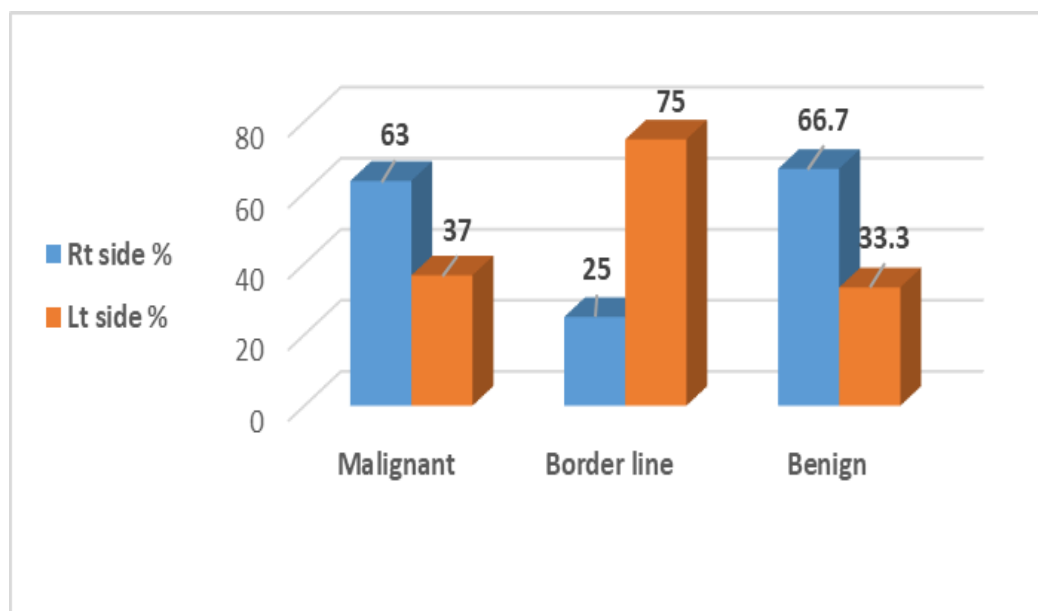
**Figure 1-** Distribution of malignant & borderline cases according to age groups

Results from this study revealed that the incidence of OC (malignant and borderline) was higher within the  $<55$  years age group, with the rate 59%, which is close to the finding of Jumaah, 2019, who reported that OC incidence increased after the age of 50 comprising over than 85% of total [9]. As well as another study showed that the highest ratio of OC among patients aged between 50-60yrs in Iraqi provinces rates was distributed as following: Kirkuk: 34%, Sulaimaniyah: 28.8% and Dhi-Qar: 26.1% [10]. According to Harper et al. 2018, age is the most powerful risk factor for OC incidence among women. The median age of diagnosis is 63 years and for mortality it is 70 years. In comparison between younger and older aged

patients, differences in survival rates between older and younger aged patients were observed. Epidemiological data explained the differences in survival as older patients often receive less radical treatment, hence contributing to this disparity. A point of view is that once OC cells adhere to mesothelial cells, they next invade the collagen-rich matrix below. Aged patients have an increase in matrix metalloproteinase MMP activity and lower rates of collagen synthesis, resulting in a less dense matrix that facilitates invasion. Moreover, aged collagen accumulates crosslinks that make the tissue stiffer and more aligned, which allow OC cells to adhere more readily. Furthermore, the accumulation of adipocytes increases, providing energy for the OC metastases. Meanwhile aged adipose tissue has a chronic inflammation response resulting in immune stimulation and secretion of MMPs and growth factors that contribute in OC invasion & proliferation [11].

#### **Tumor side:**

The distribution of ovarian tumors site in malignant, borderline and benign groups was illustrated in Figure 2. Tumors from right ovary in malignant and benign groups comprised 63% & 66.7% respectively, whereas the highest incidence site of tumor in borderline tumor group was seen in the left side comprising 75% of total cases.

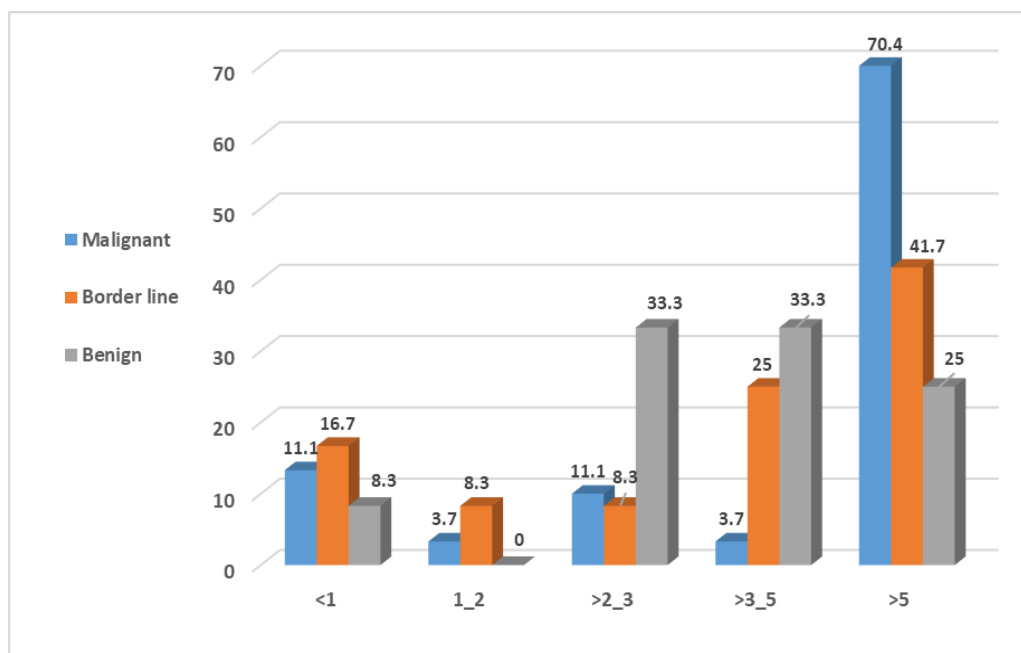


**Figure 2-**Distribution of different ovarian tumors (malignant, border line and benign) according to tumor side

The current study showed a high incidence of borderline ovarian tumors at the left side ovary by 75%, but malignant tumors were with high incidence at the right ovary by 63.3%. A previous study is consistent with our findings and has showed that the right ovary was the most reported for ovarian cancer incidences by rate of 58.82%, while the left side was 41.18% [12]. In another study conducted to determine the cause of ovarian cancer formation in a specific one of the ovaries, it was revealed that this might be due to the differences in lymphatic drainage on left and right side and/or the impact of peritoneal fluid movement [13]. However, ovulation is an important etiologically in EOC, and studies have shown that EOC is more likely to happen significantly in the right ovary by 65% [14].

#### **Tumor size:**

The average tumor size larger than 5cm was perceived in 70.4% of total malignant cases, as well as in 41.7% of overall borderline cases. Whereas in benign tumors, the largest proportions of cases measurements were <2-5cm as shown in Figure 3.



**Figure 3**-Distribution of cases according to size of tumor.

Other finding in this study is that OC is significantly associated with tumor size. The largest tumor size seen in malignant group was >5cm for rate of 70%. Also, borderline tumors exhibited a high percentage of tumor size <5cm for rate 41.7%, while the size of benign tumors rated among tumor sizes (<2-3cm) and (<3-5cm) each of which comprised 33.3%. These results do not match those of Jaffar & Younis, 2013 from Mosul, who concluded that benign tumor size was high within the range 5-10 cm for the rate 63.3%, and malignant tumor group showed the highest level in size range <10cm for rate 60% [15]. Berek & Bast 2003, stated that mucinous tumors inclined to be large with many masses >20 cm in diameter [16]. In addition, a study data suggested that the development of most OCs was characterized by occult development, followed up by explosive growth [17]. However, results from another study showed that previous parity history counteracts aging-associated systemic inflammation, likely by reducing the immunosuppression that typically permits tumor growth and spread [18].

#### ***Tumour Grade and Stage***

According to tumor grade, the malignant cases were categorized as low grade = 40.7% (11 cases), moderate grade= 18.6% (5 cases) and high grade= 40.7% (11 cases). While the borderline tumors grading were categorized as low grade = 75.0% (9 cases), moderate grade= 8.3% (1 case), and high grade= 16.7% (2 cases) (Table 1).

On the other hand, and according to FIGO staging system, the malignant cases of current study were distributed as follow: IA=25.9% (7 cases), IB=11.1% (3 cases), IC=29.6% (8 cases), II=11.1% (3 case), III=18.6% (5 cases), and IV= 3.7% (1 case). While the staging of borderline group was (IA=41.7% (5 cases), IB=25% (3 cases), IC=8.3 (1 case), II=16.7% (2 cases), III=8.3% (1 case), while no cases were recorded within stage IV (Table 1).

**Table 1** - Percentages of malignant and borderline tumors according to tumor grade and stage.

Parameters		Malignant (n=27)		Borderline malignancy (n=12)	
		No.	%	No.	%
Grade	Low	11	40.7	9	75.0
	Moderate	5	18.6	1	8.3
	High	11	40.7	2	16.7
	P value	0.250			
*Stage	[ IA ]	7	25.9	5	41.7
	[ IB ]	3	11.1	3	25.0
	[ IC ]	8	29.6	1	8.3
	[ II ]	3	11.1	2	16.7
	[ III ]	5	18.6	1	8.3
	[ IV ]	1	3.7	-	-
	P value	0.473			

**Stage 1A:** Cancer is present in one ovary. **Stage 1B:** Cancer is in both ovaries. **Stage 1C** The tissue surrounding the tumor breaks during surgery and cancer may spread to the abdomen and pelvis. **Stage II:** The cancer has spread from one or both ovaries to other areas of the pelvis. However, the cancer has not spread to nearby lymph nodes or distant sites. **Stage III:** The cancer has spread to nearby lymph nodes and/or other parts of the abdomen, but it hasn't spread to distant sites. **Stage IV:** The cancer has spread beyond the abdomen. This is considered a metastatic cancer, which means the cancer has been found in areas outside of the primary cancer area.

In this study, the high tumor grade (40.7%) was presented in malignant cases, but not for borderlines (16.7%). A previous study from Iraq showed that the highest rate of OC was with moderate tumor grade for 35.5% [19]. Also, a study from France showed that the moderate tumor grade was highest seen among patients for the rate 38% [20]. Even though, another study declared that the highest tumor grade was grade 3 for the rate 80% [21]. Besides, a study by Kurman & Shih in 2016, showed that the high-grade serous carcinogenesis is initiated through disruption of DNA repair continued by chromosomal instability, copy number alteration and segregation into molecular subtypes [22]. The HGSOc is the most common and deadliest and is rarely diagnosed at early stages. Also it is disseminated widely within the peritoneal cavity [23]. In contrast to HGSOc, the low grade serous ovarian carcinoma and precursor serous borderline ovarian tumors are characterized by the absence of mutations of p53 [24]. LGSOC seems to be susceptible to metastatic spread, with more limitation to the pelvic area. Lymph node metastases are not rarely detected in LGSOC and are more likely to be presented in the pelvic region [25]. In addition, the low grade serous carcinoma is comparatively chemo-resistant [26]. According to the results of current study, the most frequent tumor stage seen among malignant group was stage IC with rate of 29.6%, while for borderline group was stage IA comprising 41.7%. A study from China corresponded to the results obtained by this study, with high rate of stage I that was seen in borderline and malignant tumors (22.79% & 30.45% respectively) [27]. Whereas another study from Al-Najaf showed the highest percentage of OC was within stage III for the rate 42.86% [28]. Reasons for detecting more samples within stage I in the current study (higher rate was seen in stage IC for malignant and IA for borderline-ovarian cancer) may be due to the attention paid by some patients for the appearance of early symptoms that are often vague and easily ignored such as changes in women's period (irregular bleeding or heavily bleeding), bloating, constipation, back pain, abdominal pain and fatigue (extreme tiredness) [29, 30]. Eventually, the current study illustrated that early stage of cancer was distributed among different age

groups, while it was found mostly in right side ovary of malignant cases and left side ovary for borderline cases, and most frequently the size of early stage ovarian cancer was >5cm.

### Conclusion

In this study, the incidence of OC was higher within the age group >55years, with high incidence in the right ovary. The prevalent tumor size was 5cm in malignant cases. Most malignant cases were detected at early stages of the disease (IA & IC), and a large proportion of malignant cases was with high tumor grade.

**Conflicts of Interest:** Authors have no conflicts of interest to declare.

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