Introduction

Ovarian cancer is the most aggressive gynecologicalmalignancy. The five year survival rate of patients is around 40% and the disease accounts for approximately half of all deaths related to gynecological cancer (***Berrino et al., 2007 andSiegel et al., 2014***).

Epithelial ovarian cancer is the Leading cause of death from gynecologic cancer in USA and is the country's fifth most common cause of cancer mortality inwomen. In 2014, it is estimated that 21, 980 new cases and 14, 270 deaths from thismalignancy will occur in USA, less than 40% of ovarian cancer are cured (***Siegel et al., 2014)***.

The incidence of ovarian cancer is increasing with age, mostly at the sixth and seventh decades ***(Jelvac et al., 2011)***,with median age 63 years old at time of diagnosis. 70% of cases diagnosed at advanced stage (***Fleming et al., 2013)***.

The precise cause of ovarian cancer is unknown, but several risk andcontributing factors have been identified (***Kurman et al., 2010)***.

Reproductive factors as early pregnancy and use of contraceptive pills have shown reduction in risk. Conversely older age at pregnancy and nulliparity confers an increased risk (***Felming et al., 2009)***. Family history plays an important role in the risk of developing ovarian cancer. The risk of ovarian cancer is 1.6% in the general population, while it's 5%when 1 first-degree family member is affected, rising to 7% when 2 relatives are affected (***Paoletti et al., 2013)***.

Ovarian cancer could be part ofsome syndromes as hereditary breast andovarian cancer (HBOC/HOC)which is attributable to a germline mutation in BRCA1 or BRCA2 and hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndromewhich is due to a germline mutation in one of several genes associated with DNA mismatch repair (***Mclemore et al., 2009)***.

Epithelial ovarian cancer presents with a wide variety of vague and non-specific symptoms as pelvic and abdominal pain, increased abdominal size and bloating and difficulty of eating or feeling full (***Goff et al., 2007***).Later stage disease may present bygastrointestinal symptoms such as nausea and vomiting, constipation, and diarrhea, or other digestive disorders (***Ryerson et al., 2007)***.

Epithelial tumors represent the most common histological type (90%) of ovarian tumors. Other types include the following: Sex-cord stromaltumors, Germ cell tumors, primary peritoneal carcinoma, Metastatic tumors ofthe ovary (***Li et al., 2011)***. Based on histopathology, immune-histochemistry, and molecular genetic analysis, at least five maintypes of epithelial ovariancarcinomas are identified as high-grade serous carcinomas (70%), endometrioid carcinomas (10%), clear-cell carcinoms (10%), mucinous carcinomas (3%), and Low-grade serous carcinoma of the ovary (<5%) (***Prat, 2012)***.

Ovarian carcinoma can spread by local extension, lymphatic invasion intraperitoneal implantation, hemato-genous dissemination, and transdiaphragmaticpassage ***(Munjal et al., 2012)***.Intraperitoneal dissemination is the

most common and recognized characteristic of ovarian cancer (***Pannu et al., 2003)***.

Surgery is the mainstay in the treatment of epithelial ovarian cancer, and anextensive surgical staging is fundamental in the selection of most appropriatepost-surgical therapy (***Zanetta, 1998)***.Over the past three decades, surgical tumor debulking, followed byplatinum-based chemotherapy is the standard treatment for advanced ovarian cancer (***Hennessy, 2009***). More recently, randomized trials have confirmed the benefit of the addition oftaxanes to platinum-containing regimens and the standard of care has become the combination of carboplatin and paclitaxel (***Harries et al., 2001)***.

Although response rates and complete responses in advanced disease are >80% and 40-60%, respectively, after first-line treatment with carboplatin and paclitaxel, most patients will eventually relapse with a median progression-free survival of 18 months (***Rubin, 1999)***.

In this study we will be discussing prognostic factors of advanced ovariancarcinoma asage, performance status, stage, grade, histological subtypes, tumor markers, type of surgery, residual tumor volume, and chemotherapy (timing, types, number of cycles) in the past five years in ourdepartment and its impact on overall survival, progression free survival.

Aim of the Work

The aim of the study is to evaluate prognostic factors in advanced ovarian carcinoma in Oncology department in Ain Shams University the past five years and its impact on overallsurvival, progression free survival.

Epidemiology

Epithelial ovarian cancer (EOC) is the Leading cause of death from gynecologic cancer in USA and is the country's fifth most common cause of cancer mortality in women. In 2015, it is estimated that 21, 290 new cases and 14, 180 deaths from thismalignancy will occur in USA, less than 40% of ovarian cancer are cured***(Siegel et al., 2015)***.

Worldwide in 2008, approximately 225, 000 women were diagnosed with ovarian cancer and 140, 000 died from this disease ***(Jemal et al., 2011)***.

The 4th most common cancer among Females in Egypt, by 4.5% of all cancers in females***(Ibrahim et al., 2014)***.

According to a cancer pathology registry which included all cases presented to the department of pathology, at NCI, Cairo, during the years 2003-2004, surface epithelial carcinomas is forming 73.3% of ovarian cancer ***(Alfered, 2008)***.

The average age at diagnosis of ovarian cancer in the US is 63 years old. The lifetime risk of developing ovarian cancer in the US is 1.3 percent***(Cancer of the Ovary - SEER Stat Fact Sheets, 2015)***.

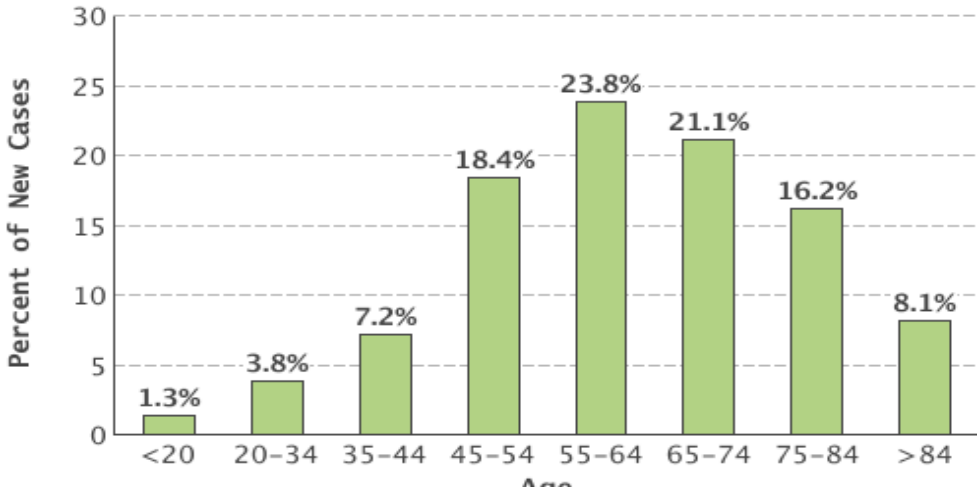

Figure (1): shows incidence of ovarian cancer:

(Cancer of the Ovary - SEER Stat Fact Sheets, 2015)

Seven thousand one hundred sixteen women in the UK were diagnosed with ovarian cancer (2% of all cancer) in 2011.There were 4, 271 deaths from ovarian cancer in the UK (3% of cancer deaths) in 2012. Thirty five percent of adult ovarian cancer patients diagnosed in 2010-2011 in England and Wales are predicted to survive ten or more years. Twenty one percentage of ovarian cancer cases each year in the UK are linked to major lifestyle and other risk factors***(Ovarian cancer statistics|Cancer Research UK, 2015).***

In a report done in Gharbia, Egypt, over the three years 2000-2002, 225 ovarian cancer cases are registered with an average of 75 cases per year. They represented 2.2% of all incident cancer accounting for 4.4 % of all newly diagnosed female cancers.Ovarian cancer is ranked third in females. Mean age at diagnosis was 47.2 years ranging 8-90 with a median of 49 years. Eighty percent was epithelial ovarian cancer, of which papillary serous cystadenocarcinoma was

the most common by 28.7%.The majority of cases presented with metastatic disease (61.6%) (***Ibrahim et al., 2007)***.

During 2010-2011 in England and Wales, five-year survival is highest in the youngest women and decreases with increasing age. Five-year net survival ranges from 87% in 15-39 year-olds to 17% in 80-99 year-olds for patients diagnosed with ovarian cancer in England during 2007-2011. In UKOne-Year Relative Survival (%) by Stage, from 2006 to 2010 Stage I 97.7, Stage II 86.0, Stage III 63.7, Stage IV 40.9, All Stages 69.8, Stage Not Known 21.5 (***Ovarian cancer statistics | Cancer Research UK, 2015)***.

Risk factors & Etiology:

The precise cause of ovarian cancer is unknown, but several risk and contributing factors have been identified ***(Kurman and Shih, 2010)***.

The 'incessant ovulation' theory has for many years been the most accepted hypothesis of EOC carcinogenesis. It proposes that ovulation traumatizes the ovarian surface epithelium such that, with time, there is an increasing chance of error occurring during cell replication. Women with a high number of lifetime ovulations are therefore at increased risk of EOC (***Harley et al., 2014)***.

This was supported by the observation that women with periodic suppression of ovulation as nulliparous womenand those with early menarche and late menopause, had an increased risk of EOC. Conversely, women with suppression of ovulation had a lower risk of EOC: for example, multiparous women and users of the combined oral contraceptive pill***(Salehi et al., 2008)***.

Other theories include the ‘gonadotrophin hypothesis’, which suggests that excessive gonadotrophin exposure increases estrogenic stimulation of the ovarian surface epithelium. Gonadotrophin levels increase with advancing age, especially after menopause, which is consistent with the age-specific rates of EOC.Furthermore, one case-control study failed to demonstrate a relationship between serum levels of luteinizing hormone and the risk of ovarian cancer***(Akhmedkhanov et al., 2001)***.

Alternatively, the ‘hormonal hypothesis’ proposes that excess androgen stimulation of the ovarian surface epithelium leads to an increased risk of cancer, while progesterone stimulation of ovarian surface epithelium is protective.All of these theories are based on epidemiological and circumstantial evidence with little or no direct experimental or pathological evidence (***Harley et al., 2014)***.

It is well accepted that most ovarian clear cell and endometrioid carcinomas arise from endometriosis. This was best illustrated in a meta-analysis of 13 case-control studies that included almost 8000 women with EOC and found a statistically significant association between a self-reported history of endometriosis and an increased risk of clear celland endometrioidEOC, but not high-grade serous or mucinous EOC (***Pearce et al., 2012)***.

Studies have consistently shown that prolonged use of oral contraceptives (OC) reduces the risk of ovarian cancer. An analysis of 45 epidemiological studies from 21 countries found that, compared with women who had never used OC, any use of OC was associated with a statistically significant reduction in risk of developing ovarian cancer.Larger

reductions in ovarian cancer risk occurred with increasing duration of OC use [relative risk (RR) decreased by approximately 20 percent for each five years of use; by 15 years, the risk of ovarian cancer was reduced by 50 percent]. Importantly, the protective effect persisted for 30 years after cessation of OC, although the effect attenuated over time (for women with five years of OC use, the risk reduction in ovarian cancer within 10 years compared with 20 to 29 years after discontinuing OC was 29 versus 15 percent)***(Beral et al., 2008)***.

Late age at menopause (after age 52) appears to be associated with an increased EOC risk. As an example, European Prospective Investigation into Cancer and Nutrition(EPIC) found a statistically significant increase in the risk of EOC in women who became menopausal at >52 years old compared with ≤45 years old (RR 1.46, 95% CI 1.06-1.99) (***Tsilidis et al., 2011)***.

Based upon the persistent ovulation hypothesis of EOC pathogenesis, either early menarche or late menopause would increase the total number of ovulations in a woman's lifetime. A one-year increase in menstrual lifespan corresponded to a 2% higher risk***(Gates et al., 2010; Tsilidis et al., 2011)***.

Compared with nulliparous women, women who had children had a 29% lower risk of ovarian cancer, with a progressive reduction in risk with each additional pregnancy. Compared with women with one full-term pregnancy, women with four or more full-term pregnancies had a 23% lower risk, which corresponded to an 8% lower risk per full-term pregnancy. Compared with nulliparous women, women

with four or more full-term pregnancies had a 38% lower risk. Age at first full-term pregnancy, ever having had an incomplete pregnancy and breastfeeding were not associated with risk***(Hinkula et al., 2006; Tsilidis et al., 2011)***.

Women with a history of tubal ligation had a reduction in ovarian cancer risk (RR 0.69, 95% CI 0.64-0.75) in a meta-analysis of 13 case-control studies.Data were not provided regarding the tubal ligation techniques used. In addition, it was found that tubal ligation lowered the rate of ovarian cancer among BRCA1 and BRCA2 carriers by 50–60% ***(Cibula et al., 2010).***

Recent studies have linked mutation in ARID1A with endometrioid and clear cell carcinomas arising in endometriosis, although this gene does not appear linked to serous neoplasms ***(Wiegand et al., 2010)***.

The definitive confirmation of the association betweenendometriosis and epithelial clear cell and endometrioidovarian cancer is adjusted according to the results of the molecular studies that show the presence of mutations in the ARIDIA gene in 46% of clear cell and 30% of endometrioid epithelial ovarian cancer in the zones contiguous to the ovarian epithelial cancer with endometriosis. The molecular bases of this connection with low-grade serous epithelial ovarian cancer (characterized by mutations in KRAS, BRAF, and ErbB2) have not been defined and the results of population screening studies on epithelial ovarian cancer have not demonstrated significant benefit due to not being detected in early stages***(Vargas-Hernández 2013)***.

High body mass index (BMI) appears to increase ovarian

cancer risk. A systematic review of 28 studies reported a small, but statistically significant, association between obesity (BMI 30 kg/m 2 or more) and ovarian cancer (OR 1.3, 95% CI 1.1-1.5) ***(Olsen et al., 2007)***.

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Ovarian cancer could be part of some syndromes as hereditary breast and ovarian cancer (HBOC/HOC) which is attributable to a germline mutation in BRCA1 or BRCA2 and hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome which is due to a germline mutation in one of several genes associated with DNA mismatch repair***(McLemore et al., 2009)***.

BRCA1 and BRCA2 are tumor suppressor genes, familial mutations in which account for approximately 5% of breast cancer cases in the USA annually. Germ line mutations in BRCA1 that truncate or inactivate the protein lead to a cumulative risk of breast cancer, by age 70, of up to 80%, whereas the risk of ovarian cancer is 30–40%. For germ line BRCA2 mutations, the breast cancer cumulative risk approaches 50%, whereas for ovarian cancers, it is between 10 and 15%. Like BRCA1 mutations, which almost exclusively result in female breast and ovarian cancers, BRCA2 families also show a marked increase in breast and ovarian cancer. However, unlike BRCA1 families, they exhibit an increased risk of male breast, pancreas and prostate cancers. Tumors of patients from BRCA1 and 2

families typically exhibit a loss of heterozygosity or other somatic alterations of BRCA 1 and 2, respectively, with the wild-type copy being lost. Both BRCA1 and BRCA2 are involved in maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps***(O'Donovan and Livingston, 2010)***.

BRCA1 and BRCA2 are separate genes mapping on two different chromosomes (17q21 and 13q12.3, resp.). They have distinctive primary sequences nevertheless disruption of either BRCA gene leads to similar pathophysiological effects (***Staples and Goodman, 2013)***.

Disease-associated mutations are scattered across the entire length of the BRCA1 and BRCA2 genes and usually result in a truncated protein. Deleterious missense mutations occur frequently in exons-encoding domains that interact with BRCA1-binding proteins, such as BARD1, BRIP1, and PALB2, which (along with RAD51C, RAD51D, and possibly RAP80 and FAM175A) are also breast and/or ovarian cancer susceptibility genes***(Foulkes and Shuen, 2013)***.

Colorectal cancer is the hallmark disease for Lynch syndrome; endometrial cancer is the second most common malignancy in affected women (occurring in up to 70 percent), but ovarian cancer is also increased in frequency. The lifetime risk of ovarian cancer in women with Lynch syndrome is 3 to 14 percent compared with 1.5 percent in the general population ***(Barrow et al., 2009)***.

Ovarian cancer risk in women with Lynch syndrome is 6–8%, and Lynch-syndrome associated ovarian cancers

exhibit a variety of histopathological subtypes ***(Lu and Daniels, 2013)***.

Lynch syndrome, caused by a germline pathogenic variant in a mismatch repair gene and associated with tumors exhibiting microsatellite instability (MSI), is characterized by an increased risk for colon cancer and cancers of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin. In individuals with Lynch syndrome the following life time risks for cancer are seen: 52%-82% for colorectal cancer (mean age at diagnosis 44-61 years); 25%-60% for endometrial cancer in women (mean age at diagnosis 48-62 years); 6% to 13% for gastric cancer (mean age at diagnosis 56 years); and 4%-12% for ovarian cancer (mean age at diagnosis 42.5 years; approximately 30% are diagnosed before age 40 years) ***(Kohlmann and Gruber, 2014)***.

The risk for other Lynch syndrome-related cancers is lower, though substantially increased over general population rates. The diagnosis of Lynch syndrome can be made on the basis of family history in those families meeting the Amsterdam criteria who have tumor microsatellite instability (MSI) or on the basis of molecular genetic testing in an individual or family with a germline pathogenic variant in one of four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). MLH1 and MSH2 germline pathogenic variants account for approximately 90% of pathogenic variants in families with Lynch syndrome; MSH6 pathogenic variants in about 7%-10%; and PMS2 pathogenic variants in fewer than 5%. Germline deletions in EPCAM (not a mismatch repair gene) inactivate MSH2 in about 1% of

individuals with Lynch syndrome ***(Kohlmann and Gruber, 2014)***.

In a series of 80 women with Lynch-associated ovarian cancer, synchronous and metachronous cancers included: endometrial cancer in 21 patients, colorectal cancer in 28 patients and either gastric, small bowel, or urinary tract cancer in six patients ***(Watson et al., 2001)***.

Diagnosis

Although the diagnosis of ovarian cancer is made at the time of surgery or by biopsy, benign diseases of the female genital tract such as functional cysts, endometriosis, and uterinemyomas must be differentiated from ovarian cancer; thereforepatients who present with an adnexal mass must undergo afull evaluation, including history and physical examination.Pelvic ultrasonography and determination of CA 125 level arealso used to assist in evaluating the malignant potential of the adnexal mass (***Vicus et al., 2012)***.

The presentation of ovarian cancer is typically subtle, requiring a high index of suspicion, and delaying diagnosis. Although no symptoms are pathognomonic, persistent (>2 weeks) abdominal or pelvic pain, bloating, change in bowel habit, urinary, and constitutional symptoms are typical of peritoneal involvement by advanced disease and early stage, surgically curable, ovarian cancer is generally asymptomatic. Unfortunately, most symptomatic women do not have a prompt diagnosis and indeed it is common for these women to be assigned erroneous diagnoses of irritable bowel syndrome, hiatus hernia, diverticulosis, or endometriosis***(Penson, 2007)***.

Pelvic examination remains an essential part of the examination of women complaining of abdominal symptoms; including an abdominal, pelvic, and rectovaginal examination as well as palpation of groin and supraclavicular lymph nodes. Findings suggestive of epithelial ovarian cancer include: adnexal mass, abdominal ascites, a mass in the mid to left upper abdomen, which may represent an