Ultrasound as a Screening Test for Ovarian Cancer

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Ovarian cancer (OC) is the seventh most common malignancy diagnosed among women, the eighth leading cause of cancer mortality globally, and the most common cause of death among all gynecological cancers. Even though recent advances in technology have allowed for more accurate radiological and laboratory diagnostic tests, approximately 60% of OC cases are diagnosed at an advanced stage. The role of ultrasound (U/S) is well documented in the primary diagnosis of OC and is potentially useful in the detection of OC associated with endometriosis.

Keywords: ovarian cancer (OC) ; ultrasound ; screening test ; biomarkers ; CA-125

1. Introduction

Ovarian cancer (OC) is the seventh most common malignancy in women, the eighth greatest cause of cancer-related deaths globally, and the fifth leading cause concerning women in the USA [1][2]. About 19,880 new cases and 12,810 deaths were attributed to OC in the United States in 2022 [2]. On average, 140,000 women worldwide die each year from ovarian cancer [3][4][5]. It also remains the most common cause of death among all gynecological cancers [6]. Even though recent advances in technology have allowed for more accurate radiological and laboratory diagnostic tests, an advanced-stage diagnosis is made in around 60% of all OC cases. Given the high mortality rate of advanced stages of OC, early diagnosis remains the main prognostic factor [2].

As for the ethnicity demographics, the largest occurrence is among Caucasian women (12 per 100,000), followed by Hispanic (10.3 per 100,000), African American (9.4 per 100,000), and Asian women (9.2 per 100,000). In 2018, the prevalence was 6.6 per 100,000 people, and the death rate was 3.9 per 100,000 [7][8]. Notably, OC mortality is much higher among African populations, which may be attributable to socioeconomic determinants of health. As with other diseases, factors such as poverty and inadequate access to health care may influence the outcome of OC [9].

There are as yet no standardized screening tests for OC, and there is a pressing need for novel diagnostic tools, particularly those that can detect the disease at its initial stages while clinical action is still useful. Due to the fact that it is often diagnosed at an advanced stage, recurrence rates are rather high. Despite progress, OC remains the most lethal form of female gynecologic cancer [6]. With an average age of 63 at diagnosis and over 70% of patients presenting with advanced disease, the five-year survival rate is less than 50% [2][10][11][12]. In recent decades there has been a moderate change in the 5-year survival rate, which depends mainly on the disease stage during diagnosis, reaching a percentage of 70–80% in early-diagnosed cases but dramatically decreasing to 20–25% in cases where the disease has been diagnosed at advanced stages [2][12]. Recurrence rates remain high, ranging between 25% and 80% depending on the stage of the disease at diagnosis, despite promising findings from new targeted therapy regimens.

OC can be divided into two subgroups based on its pattern of inheritance. The majority of women with OC have the sporadic variety; however, there is a subset of ovarian cancer that may occur in a familial way. In this particular subset, a substantial family history of ovarian or breast cancer is the most significant risk factor. In general, a hereditary predisposition is responsible at least for 10% of all epithelial OCs, and, more specifically, mutations in the BRCA genes are responsible for 90% of these cases. In these high-risk patients, annual screening with serum CA-125 and transvaginal ultrasound surveillance is indicated. Since the efficacy of these screening approaches is still unclear, prophylactic ovarian surgery is an essential option for patients with confirmed BRCA1 or BRCA2 mutations or a strong family history of breast and/or ovarian cancer. This operation has been shown to lower the likelihood of developing ovarian cancer by 96% and the risk of breast cancer by 53% in individuals who have the BRCA1 or BRCA2 mutation [13].

CA-125 (cancer antigen 125) was established almost forty years ago and has since become the most extensively used and significant biomarker for ovarian cancer. CA-125 is an epitope of MUC16: a 3–5 million Da mucin. On the one hand, its usefulness in OC for the follow-up evaluation of chemotherapeutic effectiveness and prognosis is unquestionable; on the other hand, it is insufficiently trustworthy in early-stage ovarian cancer diagnosis or as a screening tool for the general population [14][15][16][17]. There have been several follow-up strategies proposed; however, according to NCCN guidelines, it has been suggested that follow-up strategies have to be adapted to the tumor's characteristics and the patient's needs [18].

The role of ultrasound (U/S) is also well documented in the primary diagnosis of OC and is potentially useful in the detection of OC associated with endometriosis. On the other hand, there is still controversy regarding the use of ultrasound in the follow-up of surgically treated OC. Over the last decade, technological developments have led to a major improvement in U/S imaging quality. The main advantages of U/S are the non-invasive exam procedure, the cost-effectiveness of this technique, which is widely available. Additionally, this technique is a valuable method for monitoring patients with fertility-sparing surgery and a sufficient guide for the biopsy of suspicious lesions in the pelvic area [19].

2. Ultrasound as a Potential Screening Test

One of the most important challenges regarding OC screening is the requirement for effective screening strategies that have a positive predictive value of 10% [20]. In order to achieve this rate of positive predictive values, the screening tool must have a sensitivity of at least 75% and a specificity of 99.6% [21]. Timing is also of great importance in the development of an efficient screening strategy. In this case, OC has no particular time frame for the development of invasive disease nor a particular time frame for the interval stage between stage I and stage III carcinomas [22].

Currently, available biomarkers can be evaluated with samples derived from clinically diagnosed patients and a small number of patients with early-stage or high-grade carcinomas. This is the reason why it is often necessary to make speculations based on cases of advanced disease and not cases of early-stage disease. The difficulty in evaluating the diagnostic ability of screening tests is also evident. The ability of screening tests is correlated to the impact of ovarian cancer mortality rates: a rating that can be confirmed through prospective, randomized, controlled trials. Consequently, very large cohorts are needed in order to evaluate the ability of a certain exam [23].

The ultrasound screening modality allows the detailed imaging of the ovaries as well as the identification of possible morphologic changes that may be recognized as signals for the development of malignancy [24][25][26][27][28]. In order to provide a clear diagnosis, healthcare professionals require certain data, such as the presence of an abnormality in ovarian lesions, the size of the ovaries, blood flow, or the presence of abdominal/pelvic fluid around the ovarian mass, which is evidence that increases the possibility of a tumor being malignant. All of the aforementioned data have been estimated as possible diagnostic factors that could provide the early detection of ovarian cancer. Additionally, any persistent abnormalities that are repeatedly depicted during scanning, between a timeframe of 4 to 6 weeks after the initial screening examination, may reduce the possibility of a false positive result [29][30].

The interpretation of ultrasound images is of great importance since most ovarian masses depicted through an ultrasound examination are benign [26][27]. Consequently, interpretation should be conducted with a strategy that decreases the possibilities of observer variation and thus reduces the frequency of false-positive results. In order to evade these possible pitfalls, a number of screening protocols have been proposed and are utilized in ultrasound examinations. The majority of these protocols are based on morphologic index-based criteria. More specifically, these criteria include findings that can be obtained through a transvaginal ultrasound, such as a cyst wall structure, septation, papillary projections, echogenicity, and ovarian volume, in order to successfully detect the malignancy [31].

2.1. Ultrasonographic Assessment of Ovarian Masses

Even though the morphological criteria are similar among the screening protocols, no standardized index is universally accepted, and the systems vary mainly on the type and number of factors that they include. Sassone et al. proposed a widely used index that is based on four different morphological characteristics of an ovarian cyst's architecture (wall structure, cyst wall thickness, echogenicity, and septae) [31]. (**Table 1**) A score over nine has high rates of sensitivity and specificity when diagnosing malignancy (100% and 83%, respectively) [32]. Another proposed morphologic index is based on three structural characteristics (septae, ovarian volume, and cyst wall) with lower rates of sensitivity and specificity (89% and 70% correspondingly) [33].

Table 1. Sassone scale for morphologic ovarian characteristics.

Value	Inner Wall Structure	Wall Thickness	Echogenicity	Septa
1	Smooth	Thin ≤ 3 mm	Sonolucent	None
2	Irregularities ≤ 3 mm	Thick > 3 mm	Low echogenicity	Thin ≤ 3 mm
3	Papillaries > 3 mm	Not applicable, mostly solid	Low echogenicity with echogenic core	Thick > 3 mm
4	Not applicable, mostly solid	-	Mixed echogenicity	-
5	-	-	High echogenicity	-

Many clinical trials that focus on the efficiency of ultrasound screening techniques in the diagnosis of OC have been published since the 1980s. These studies have shown that ultrasound is a promising technique; however, a significant variation among the interpretations of the obtained images has been evident [34][35].

2.2. SRU Consensus for Adnexal Masses

Another valuable tool is the consensus published by the Society of Radiologists in the Ultrasound. Levine et al. (2019) conducted a study to provide updated guidelines for the management of simple adnexal cysts. The authors reviewed the relevant literature and expert opinions to establish consensus recommendations. This study emphasized the importance of appropriate follow-up and reporting practices for these cysts, aiming to improve patient care and reduce unnecessary interventions.

In their update, Levine et al. (2019) highlighted key recommendations for the management of simple adnexal cysts. These included defining the size thresholds for follow-up, establishing appropriate intervals for imaging surveillance, and determining indications for intervention. The authors also provided guidance on reporting terminology and emphasized the need for clear and concise communication among healthcare providers. This consensus update has served as a valuable resource for radiologists and clinicians involved in the evaluation and management of simple adnexal cysts. By standardizing follow-up protocols and reporting practices, healthcare professionals can ensure optimal patient care while minimizing unnecessary interventions and associated risks. The recommendations put forth are based on current evidence and expert consensus, providing a practical framework for the management of simple adnexal cysts.

In summary, the SRU consensus provides updated guidelines for the follow-up and reporting of simple adnexal cysts. These recommendations aim to improve patient care by establishing standardized practices and promoting clear communication among healthcare providers. This study serves as a valuable resource for radiologists and clinicians involved in the management of these cysts, ensuring optimal patient outcomes and minimizing unnecessary interventions [30].

2.3. Ultrasound Compared to CT/MRI

There has been a comparison between the diagnostic strategies of ultrasound-based models with CT and MRI in the evaluation of ovarian cancer. A study by Kaijser et al., 2013 [36] provided a comprehensive summary of the International Ovarian Tumor Analysis (IOTA) studies, with a specific focus on comparing the diagnostic strategies of ultrasound-based IOTA models with CT and MRI in the evaluation of ovarian cancer. These studies aimed to improve the diagnostic accuracy and management of adnexal masses.

The findings of the IOTA studies demonstrated that ultrasound-based IOTA models had a comparable or even superior diagnostic performance compared to CT and MRI. Ultrasound, as a widely available and cost-effective imaging modality, has the advantage of real-time visualization and can provide valuable information regarding the morphology, vascularity, and internal characteristics of ovarian tumors. The IOTA models, which utilize specific ultrasound features and scoring systems, showed high sensitivity and specificity when distinguishing between benign and malignant ovarian tumors. The authors highlighted that these models could effectively identify malignancies while reducing unnecessary surgical

interventions. Moreover, ultrasound-based IOTA models have the advantage of being non-invasive, allowing for serial examinations and the monitoring of tumor progression over time.

By contrast, CT and MRI are useful adjuncts in certain cases where there is ambiguity or complexity in the ultrasound's findings. These modalities provide additional information, such as detailed anatomical visualization, an assessment of lymph node involvement, and the evaluation of distant metastases. However, they are generally more expensive, less widely accessible, and may require intravenous contrast administration. The study by Kaijser et al. emphasized that the IOTA models, based on ultrasound findings, can serve as the first-line imaging strategy for evaluating adnexal masses. They offer a practical and efficient approach to the initial assessment of ovarian tumors, enabling accurate diagnosis and appropriate management decisions [36].

In conclusion, IOTA studies, as summarized by Kaijser et al., demonstrate that ultrasound-based IOTA models have comparable or superior diagnostic performance to CT and MRI in the evaluation of ovarian tumors. The IOTA models provide a valuable tool for distinguishing between benign and malignant adnexal masses, leading to improved diagnostic accuracy and appropriate patient management. While CT and MRI have their own strengths and can be useful in certain situations, ultrasound-based IOTA models offer a cost-effective, non-invasive, and widely accessible approach for the evaluation of ovarian cancer [36].

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