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Early Detection of Ovarian Cancer with Transvaginal Microbubble Sonography: Current and Potential Applications

Arthur C Fleischer*

Department of Radiology, Obstetrics and Gynecology, Vanderbilt Medical Center, USA

*Corresponding author:** Arthur C Fleischer, Cornelius Vanderbilt Chair Professor, Department of Radiology, Obstetrics and Gynecology, Vanderbilt Medical Center, Nashville, TN 37232, USA, Tel: 615-322-3274; E-mail: arthur.fleischer@vanderbilt.edu

Abstract

Contrast Enhanced microbubble Transvaginal Sonography (CE-TVS) can distinguish benign and malignant ovarian tumors. Initial results from several medical centers around the world have indicated that there are unique enhancement patterns in ovarian neoplasms. Challenges to the implementation of CE-TVS remain since some aggressive ovarian tumors (type 2) that arise in the tubal epithelium and metastasize without producing a clinically detectable mass may be difficult to detect. This is being addressed through the use of labelled microbubbles which can detect rapidly growing tumor vessels. As shown in an avian model, labelled microbubbles can be used to detect neoplastic vessels associated with tumor neoangiogenesis. This has been achieved in vitro by fabrication of microbubbles that have antibody attached to the lipid coat. In this manner, microscopic tumors that arise in the tubal epithelium might be detected in patients. This short communication describes the potential for contrast enhanced sonography to provide a means for early detection of ovarian cancer.

Introduction

Data from a large Japanese screening trial showed that Transvaginal Sonography (TVS) can detect morphologic abnormalities such as papillary excrescences associated with stage 1A ovarian cancers even when CA-125 was negative [1]. The addition of color Doppler sonography has been shown to further improve the detection of early stage ovarian cancer over morphologic assessment [2]. As a means to further improve early detection with morphologic and color Doppler Transvaginal Sonography, contrast enhanced Transvaginal Sonography (CE-TVS) using microbubbles has been proposed as a secondary test to determine which suspicious lesions are indeed malignant [3]. CE-TVS have shown to further improve detection, resulting in sufficiently high accuracy to justify its use as a means for early detection [4]. In fact, the relative accuracy of CE-TVS (sensitivity 97-100%; specificity of 96%) was shown to be better than 2D and 3D color Doppler TVS (sensitivity 100%, specificity 78-82%) [4]. The specifics concerning the relative diagnostic accuracies of these sonographic techniques have been summarized in a recent review [5].

Several recent reports have shown that microbubble (contrast enhanced) Transvaginal Sonography is accurate in the early detection of ovarian cancer [3-8]. Significant differences in enhancement parameters have been documented in benign vs. malignant ovarian masses. CE-TVS, however, cannot distinguish borderline from malignant tumors both of which typically are treated surgically [7].

Type II ovarian cancer that arises from the Fallopian tube epithelium without forming an accompanying mass pose a diagnostic challenge to sonographic detection of ovarian cancer [9,10]. However, recent animal studies and ongoing human trials suggest that labeled microbubbles has potential for the detection of even these difficult to detect lesions [11].

This short commentary will describe the current and potential applications of microbubble sonography in the early detection and enhanced treatment of ovarian cancer. In addition, it will propose direction for future investigation.

Transvaginal Microbubble Sonography

Our initial series demonstrated significant differences in contrast enhancement kinetics in benign vs. early stage ovarian tumors [3,4]. Specifically, wash-out time and area under curve (a reflection of total vascularity) were significantly different in benign vs. malignant ovarian tumors [3,4]. Other studies and a large multi-international one also found significant differences in CE-US of benign and early stage ovarian cancer [6-8].

Some relative limitations of CE-US include added expertise and cost in performing CE-US. These factors are not insurmountable and can be successfully addressed at centers which provide early detection with specialized techniques [12].

One of the major limitations of sonographic imaging for early detection of ovarian cancer is detection of the type II ovarian cancer that arises from tubal epithelium and may not develop morphologically detectable mass before there is intraperitoneal spread [9,10]. However, preliminary studies in an avian model that used labeled microbubbles to VEGF and α3β2 receptors correlated well to histologic evidence of tumor associated neoangiogenesis [9]. Another factor that limits the efficacy of TVS screening involves the relatively low prevalence (compared to endometrial cancer) of ovarian cancer. Pre-selection of patients for further screening might be accomplished by serum screening.

Microbubbles may also have a role in enhancing drug delivery (a.k.a. theranostic application) [13]. In theory, labeled microbubbles could first arrive at a specific neoplastic focus followed by enhanced drug delivery into the tumor's interstitium.

Reasons for Optimism and Further Study

Data for the UK ovarian cancer screening trial which assessed the impact of morphologic Transvaginal Sonographic screening relative to long term outcome revealed encouraging evidence that TVS was associated with a significant (20%) mortality reduction [14]. Other reports of large screening trials in the United States and Japan have also shown a positive effect of TVS relative to long term outcome [12].

Summary

Whether the addition of CE-TVS in screening/early detection programs could further the long-term survival of screened women awaits further investigation. With that said, CE-US is probably best suited as a secondary test after a "liquid biopsy" and/or an initial morphologic assessment of the lesion with standard morphologic TVS identifies women at risk. The basis for optimism concerning the use of CE-TVS for the early detection of ovarian cancer is substantiated and this author encourages further multicenter investigation.

Acknowledgements

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