

## Review Article

# Three-dimensional color power Doppler as an imaging technique in cancer

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**Abstract:** Ultrasound analysis plays an important role in the assessment of morphology of different forms of cancerous lesions. However, owing to the large number of false positive results, the accuracy of the technique has been largely restrictive in nature. Pulsed Doppler spectral analysis and color Doppler imaging enable the evaluation of blood vessel distribution, tumor blood flow, and quantitative measurement of blood flow velocity in different forms of cancer. Unfortunately, no consensus could be found regarding the exact cut off values and the Doppler parameters most predictive of malignancy. Tumor vascular features could be efficiently evaluated with three-dimensional power Doppler ultrasound. Three-dimensional power Doppler imaging in patients showing 'positive' results with available standard tests, in combination with color Doppler, represents a novel procedure for accurate early detection of different cancer types. Combined evaluations of neovascularity and morphology by three dimensional color power Doppler possess the potential of differentiating between benign and malignant tumors and may facilitate early detection. In this review, we assess the potential of three dimensional color power Doppler in the evaluation and diagnosis of different types of cancers.

**Keywords:** Cancer imaging, power Doppler, three dimensional, color Doppler, ultrasound

## Introduction

Accurate early diagnosis of cancer is the hallmark for its successful treatment. As such, diagnostic modalities should be put into application based on their sensitivity and specificity and the extent of distinguishing ability between benign and malignant tumors depending on small available changes. In recent times, the development and upgradation of fast processors has made 3D image rendering and ultra-rapid calculation possible. With these newer systems, the visualization of various anatomical structures in minute details and in different modes becomes a reality. Also, color Doppler and 3D power Doppler helps in the examination of vascular anatomy, visualization of low flow small vessels and spatial course of the vessels. Thus, by combining 3D technology with color and power Doppler, it is possible to study the differences between benign and malignant tumors.

The ability to discriminate between malignant and benign tumors has been improved enor-

mously with the introduction of sonography [1]. Although this technique has showed good potential in the precise diagnosis of some benign lesions [2, 3], it comes at the expense of considerably high false-positive rates [4]. Pulsed and color Doppler imaging that allows tumor vascularization assessment was brought into clinical practice for decreasing the rate of false positives in the evaluation of complex tumor masses. Notwithstanding the initial encouraging velocimetric results with this technique [5], available literature shows conflicting results [6, 7]; thereby making this method poorly reproducible and unpractical. Another approach has been proposed that relies on the sonographic assessment of morphology and distribution of vessels using power or color Doppler sonography [8]. This method has been found to be quite useful in distinguishing malignant and benign tumors since there is a high malignancy probability in central vessel distribution containing complex masses as compared to the peripheral blood flow containing or non-vessel containing complex masses that are usually considered benign [8]. Contrary to this observation, central

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vessel distribution can also be presented by some benign tumors as well.

The technique of three dimensional color power Doppler (3D-CPD) imaging is a result of combination of the technologies of three dimensional ultrasound and color power Doppler, through which the organs of interest along with their vascular distribution can be visualized in three dimensions [9, 10]. This form of Doppler technology which is based on evaluation of blood flow and anatomical structures of blood vessels, allows acquisition of 100 to 250 images in 15 to 20 seconds since it can undergo multiple scanning at the target site at an interval of 0.3 to 1.0 mm; within 3 minutes, the 3D reconstruction can be completed. Both systemic as well as 3D pictures of the lesions or organs with their precise quantity, distribution and branching of blood vessels is demonstrated by 3D-CPD, thus it can be extremely helpful in diagnosis of different types of cancer and become an ideal replacement for a conventional mode of clinical examination of tumor blood supply [11, 12]. Moreover, the nature of different lesions can be specifically determined by 3D-CPD, since it can accurately map the differences in flow of blood inside or outside of tumors. The vascular distribution patterns within the tumors are more accurately described with 3D-CPD, and hence it can assist in the classification of tumor vascularity [13, 14].

In this review, we discuss about the potential of 3D-CPD in the early and precise diagnosis of different types of cancer. Presently, there is no other review available that deals with this important topic and hence it can be a useful source of information regarding three dimensional color power Doppler as a diagnostic modality in the field of cancer.

### Technical background

**Equipment:** An integrated 3D power Doppler feature is present in the few commercially available 3D systems; the different ultrasound systems can also be adapted with external workstations that offer post-processing offline evaluation and analysis.

**Advantages of 3D rendering with power Doppler:** Both color and power Doppler are used in the visualization of vessels and can also be used for 3D visualization. The various advan-

tages of color power Doppler [15-17] that make it feasible for the 3D mode are:

**Better edge definition:** In displaying flow, color power Doppler shows better edge definition. Since, owing to the lower signal amplitude, colored samples extending partially beyond the edges are presented in a different color, the problem is eliminated with 3D-CPD.

**Flow detection sensitivity:** Instead of frequency, Doppler signal amplitude is analyzed in 3D-CPD that in turn increases sensitivity by nearly five times as compared to low flows and small vessels [16].

**Orthogonal to beam flow detection:** Flow directed at right angles to the beam can be detected with 3D-CPD. Negative and positive components of flow amplitude are added up, generating powerful signal.

**Improvement in noise differentiation:** Noise signals are encoded by 3D-CPD in a uniform color. Therefore, the gain can be turned up all the way; thereby the entire image is filled with noise, while it is still possible to distinguish the vascular signal.

### Principle

The use of a 3D imaging system involves the consideration of two main aspects:

**Data acquisition:** The information gets stored in a volume of interest during the course of volume data acquisition. A pre-defined number of 2D slice sequences form the content of the acquired volume. The spatial arrangement of the structures in 2D images with respect to each other is assessed by the system thereby allowing a 3D rendering. In order to obtain a good quality 3D-color Power Doppler image it is necessary to know how the vessels could be best visualized using this technique. In this regard, the optimization of filter, insonation angle, pulse repetition frequency (PRF), and persistence are needed to be considered. The setting of filter and vessels should be done as high as possible so as to visualize only the vessels of interest. This is because orientation may be complicated within the 3D volume with superimposed vessels. During off-line reconstruction, interfering noise signals within the region of interest (ROI) can be removed. How-

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ever, for obtaining an optimal rendering, it is essential to have a good quality original volume.

**Image rendering and display:** In image rendering, the parameters of interest are used to create a 3D representation. Usually, the 'planar geometric projection' principle is used, i.e., 3D data represented by the 2D image. The third dimension virtual impression is given by on-line image rotation and by different posterior and anterior structure shadowing. Different post-processing features like changing the transparency of color, threshold and brightness as well as various color maps can be used. Furthermore, the examiner can decide whether to gather the information of surrounding structures as well besides viewing the vessels. This is called glass-body rendering. The examiner can progressively switch between transparent and surface mode.

### Ovarian cancer

There are reports that suggest for the ability of pulsed and color Doppler ultrasound in the detection of ovarian cancer at Stage I [18-20]. In a related study, ovarian cancer in some of the patients with normal size ovaries was detected solely by the presence of abnormal pattern of blood flow [18]. It was suggested that a high suspicion index for abnormal neovascularization should be generated with any color flow yielded from post-menopausal ovary. Pulsed Doppler analysis is indicated in such circumstances. Abnormal blood flow detection formed the basis of diagnosis for 3 among 17 Stage I cancers in a related study [19]. However, flow was not demonstrated by two of the stage I tumors in the same study, although they were larger than 15 cm. This goes on to suggest that the pulsed and color Doppler equipment could not depict small sized blood vessels which might have been the case with these tumors. Besides, blood flow features showed significant overlap between malignant and benign ovarian lesions as reported by a number of publications [18, 21].

Three-dimensional power Doppler is another technique for morphological analysis of blood vessels in the diagnosis of ovarian tumors [21]. The vascular and morphologic characteristics of ovarian tumors can be better defined by three-dimensional power Doppler imaging [22].

Specificity of ovarian cancer detection was significantly improved with three-dimensional power Doppler as compared to 2D gray-scale ultrasound or 3D ultrasound. In a retrospective analysis of 43 suspected stage I ovarian cancer patients, the detection rate was found to be 97% for 3D ultrasound power Doppler while that for 3D ultrasound the detection rate was 74% [23]. In asymptomatic women, three-dimensional ultrasound power Doppler showed improvement in the early detection of ovarian cancer [24].

Routine implementation of 3D power Doppler in the screening of ovarian cancer faces some pitfalls and obstacles. A successful subjective scoring system was obtained in a screening trial that depended solely on descriptive and qualitative 3D power Doppler for the evaluation of ovarian tumor microcirculation anatomy [23]. The accuracy of ovarian cancer screening has been improved by the application of 3D imaging modalities such as 3D power Doppler imaging and 3D ultrasound in patients showing 'positive' results on standard available tests followed by color Doppler has improved the accuracy of ovarian cancer screening [23]. Therefore, 3D color power Doppler can be a useful technique among the future diagnostic modalities in the specific and early detection of ovarian cancer.

### Cervical cancer

The local recurrence of cervical cancer has been assessed with computed tomography (CT), magnetic resonance imaging (MRI), and 2-fluoro-2-deoxyglucose positron emission tomography (PET) [25, 26]. However, routine surveillance with these technologies is not possible due to their low rates of detection. In addition, there are other disadvantages such as use of intravenous and/or oral contrast, radiation load, considerable length of time required to carry out the examination and so on. Color Doppler with 2D ultrasound has been found to have a possible role in the diagnosis of cervical cancer-related clinico-pathological prognostic factors [27, 28]. Also, power Doppler or color Doppler with 3D ultrasound (3D-PDU) [29] has been used to investigate intra-tumoral vascularization, measure tumor volume and find the relationship between clinico-pathological factors in gynecological cancer [30-34]. It has well

documented that 2D ultrasound is not as effective as transvaginal 3D ultrasound in accurate measurement of tumor volume in cervical cancer [25]. Also, with 3D power Doppler, different vascular distributions in cervical cancer tissues could be observed; besides finding a positive correlation between flow index and tumor volume [35]. However, exclusive utilization of transvaginal 3D power Doppler ultrasound in the evaluation of cervical cancer has been reported by only a few groups [31, 32]. Power Doppler is less susceptible to aliasing, less angle dependent and is amplitude base as compared to conventional color Doppler [29]. Therefore, low velocity flow as occurs within the tumor vessels could be sensitively detected with power Doppler. Thus, combining 3D power Doppler and color Doppler, i.e., 3D-CPD should have the potential to improve both sensitivity as well as accuracy for comprehensively assessing vascularization and tumor volume in cervical cancer. Only a few case reports have been found in relation to cervical cancer assessment with 3D power Doppler ultrasound [31, 32].

### Endometrial cancer

Both in asymptomatic and symptomatic women endometrial polyps are often diagnosed [36]. The pathogenesis and etiology of endometrial polyps are yet to be fully elucidated, but it is generally agreed that they can result in endometrial cancer as well as hyperplastic endometrial changes [37]. Conventional transvaginal sonography can be used for the detection of endometrial polyps, while the diagnosis can be refined with the use of hysteroscopy or gel and/or saline contrast sonography, the results can be confirmed by histological examination [38-40]. Hysteroscopic resection is carries a risk of postoperative morbidity and complications and considered to be relatively safe [41, 42]. So the detection of malignancy and atypia in these intrauterine lesions require a sensitive and simple method [43]. Color flow Doppler seems to be useful in the evaluation of tissue vascularization as well as in the malignant endometrial change prediction as suggested by previous studies [43, 44]. Similarly, atypical endometrial polyps can be predicted by low blood flow resistance [45]. The accuracy and quality of Doppler examination can be significantly enhanced by using color Doppler imaging in combination

with intravenous contrast [46]. 3D-PD angiography provides an objective by means of indices such as flow index (FI), vascularization index (VI), and vascularization flow index (VFI) thereby tumor vascularization can be assessed more comprehensively as compared to other conventional methods. Detection of pathological changes in endometrial vascularization and small changes in endometrial blood flow could be easily done by using these indices [47]. Thus, assessment of blood flow by 3D-CPD may be useful in the differentiation between malignant and benign endometrial polyps.

### Malignant pelvic tumors

When assessed in a two dimensional section [48], solid pelvic tumor masses, are at high risk of being considered malignant [49]. All solid masses are suspected to be malignant using B-mode ultrasonography. However, in the differential diagnosis of adnexal malignancies a high false-positive rate is needed to be taken into consideration. Limited success was achieved with the introduction of pulsed and conventional color Doppler in improving the accuracy of gray scale ultrasound [49]. The characterization of microvasculature of pathological and normal conditions in the benign ovarian masses [29], uterine cervix [27] and normal ovary [50] has been done with the help of 3D power Doppler. Pairleitner et al. [29] described a procedure of selecting ROI within the three dimensional volume so as to improve reproducibility of data obtained with vessel architecture. Within the pre-defined ROI, the whole vascularization is represented by indices generated with specifically designed software. The reproducibility of 3D technology was tested by other authors with the use of manual definition of contours to describe the volume of ROI of a normal ovary. The contours were drawn by generating six planes around a maximum longitudinal section [50]. With the help of a computerized tool, 3D power Doppler inter-observer reliability was examined by Raine-Fenning et al. [51] from 20 patients at different in vitro fertilization stages. The authors confirmed for the reliable use of 3D ultrasound between observers for acquiring power Doppler information from the ovary [51]. Inter- and intra-observer variability was found to be within the acceptable range with the help of a power Doppler signal quantifiable method for the examination of pelvic

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masses [52]. Controversial results have been obtained from several studies that investigated 3D ultrasound examination without or with 3D-power Doppler in the detection of pelvic malignancies [34, 53-55]. Besides, qualitative 3D power Doppler and color score semi-quantitative evaluation of tumor vessels have been contemplated in the diagnosis of pelvic mass malignancies [21, 48]. Thus, there is all the possibility of getting better results by combining the two modalities, color Doppler and 3D power Doppler (i.e., 3D-CPD) in the differential diagnosis of benign pelvic mass malignancies and tumor vascularity.

### Prostate cancer

In order to improve the specificity and sensitivity of prostate cancer detection, power ultrasound, color Doppler, and 3-dimensional (3D) ultrasound have been included in the detection processes by various users. Theoretically, isoechoic cancers can be identified by selective identification of areas of increased blood flow with respect to the surrounding which otherwise remain unidentified on gray scale ultrasound [56]. In addition, benign lesions can be distinguished from cancerous lesions with the help of blood flow characteristics within hypoechoic areas [57].

Owing to differences in reader experience and patient selection, mixed results have been reported with the use of color Doppler. Routine use of color Doppler imaging in 500 biopsy undergoing patients has been reported by Cheng et al [56]. However, it remained unclear what percentage of cancers detected by color Doppler would have been found by systematic biopsy. Color Doppler when compared to gray-scale ultrasound, has been found to improve specificity, however it often comes at the expense of sensitivity. When the two modalities were combined, 97% specificity is achieved. However, sensitivity got reduced from 82% to 18% for color Doppler alone and from 90% for grayscale alone. As such, concomitant systematic biopsy is mandated while using color Doppler so as to maximize sensitivity [58]. Whether the sensitivity of systematic biopsy alone is added by color Doppler is not clear in the literature.

As compared to conventional Doppler, flow detection in smaller blood vessels is facilitated

by power Doppler [59]. As such, a 3-4 fold greater sensitivity is provided by power Doppler for areas of increased flow [60]. A sensitivity of 98% is obtained with power Doppler in a study of 170 men [61]. The performance of power Doppler, TRUS and DRE were compared by the same group in two cohorts from the US and Japan [62]. Power Doppler showed far superior performance with respect to both specificity and sensitivity. The authors further suggested that in men with larger tumor size and smaller prostates relative to the prostate volume, power Doppler was of greater use. It was also concluded that the experience of the operator enhances the test utility to a great extent. The results obtained between power Doppler and TRUS in the evaluation of 282 men undergoing prostate biopsy was evaluated by Sauvain and colleagues [63]. Both specificity and sensitivity was improved with the use of power Doppler as compared to TRUS. It is noteworthy to mention that 41 patients were found to have cancer among 72 patients who had shown negative results with systematic biopsies. Thus, the use of power Doppler added greatly to the repertoire of cancer detection for lesions that remained undetected with systematic biopsy or for isoechoic lesions. The overall accuracy of power Doppler may be improved with the addition of contrast infusion [64].

In summary, it seems that the use of a combination of color and power Doppler, i.e., 3D-CPD, particularly in experienced hands, can improve upon the specificity and efficiency in the detection of prostate cancers. Overall, the detection of cancers can be enhanced with the use of such modalities besides sextant biopsy.

### Discussion

Low velocity flow as in tumor vessels could be easily detected by 3D-CPD as it is less susceptible to aliasing, less angle dependent and amplitude-based [65, 66]. Compared to conventional methods, it can improve upon both the sensitivity and accuracy for comprehensively assessing vascularization and tumor volume in cancers. The acquired information from Doppler signals from three dimensional power Doppler ultrasound is assessed by using the signal amplitude and not analyzed by frequency [67]. Therefore, 3D-CPD is much more sensitive than the conventional color Doppler systems

[9]. The technique has become a widely used tool for the clinical diagnosis of various forms of malignant and benign diseases since 3D-CPD can precisely evaluate the perfusion of the lesions or organs by detecting very low blood flow signal [34, 35, 68, 69].

Malignant and benign tumors can be distinguished based on the considerable differences in structure, quantity, and distribution of neo-vascularization [70, 71]. Most malignant tumors are characterized by the presence of structural abnormalities and enriched blood vessels, such as vascular distortion, interruption, enlarged nourishing blood vessels, dense, and arteriovenous fistula. In comparison, the benign tumors are of lower vascular type and have less branching. These differences can form the basis of a reliable pathological mode of differential diagnosis of benign and malignant diseases of the different type as well vascular classification.

In addition, 3D-CPD can provide valuable information when combined with clinical assessment regarding therapy-related changes; besides it can be more efficient in more accurate detection of local disease as compared to serum tumor markers, with fewer false-negative and false-positive. Thus, as a new, adjunctive imaging study 3D-CPD imaging implementation seems both practical and viable in the monitoring of local recurrences and treatment response to radiotherapy. Presently, color Doppler sonography is the major technique that allows direct visualization of intra-tumoral blood flow non-invasively, because the qualitative diagnosis is greatly contributed by the characteristics of the vascular pattern of the tumors [72, 73]. At the end of scanning, the vascular pattern of the intra-tumoral blood flow is known by the expert; however, two-dimensional imaging would not allow their visualization to the same extent. The problem can be solved by using color Doppler sonography at high resolution for three-dimensional viewing of blood flow in organs/tumors.

In conclusion, 3D-CPD is non-invasive, reproducible, short time-consuming, without any side effects. It allows for direct visualization of blood flow both inside and outside of the tumors. However, the limitations of 3D-CPD need to be considered for their successful implementation. Movement of organs or tis-

ues affects 3D-CPD-related interventions. Some of the affecting factors include specific localization of the lesions, inability to control breath rhythm by the patients. The presence of such factors during application of 3D-CPD can lead to generation of signals that could be artifacts. Furthermore, the blood vessels can be correctly shown only when the tumors are deeply localized. The expertise of the performer can be an important factor in determining the end quality of the images. One should acquire images from different angles to more accurately determine the intra- or peri-tumor distribution of blood vessels in case of very large tumors. Nonetheless, 3D-CPD presents itself as a highly efficient technique in the accurate and early detection of different types of cancers since it can display dynamic, complete, and three-dimensional image of tumor blood flow, along with shape, size, and vascular network of tumors [74, 75]. Reports of other types of cancers such as colorectal cancer, hepatic carcinoma and breast cancer being detected by 3D-CPD are also coming up [66, 76] but more detailed studies are necessary in order to suggest the significance of the technique in the detection of other types of cancers other than those mentioned in this review. However, on the basis of the findings and initial indications in the detection of various types of cancers, it can be clearly stated that 3D-CPD shows significant promise to be an important diagnostic modality in the field of cancer.

### Disclosure of conflict of interest

None.

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