Breast cancer is one of the most common cancers in women worldwide, with a reported number of 1.7 million being diagnosed in 2012 [1]. In recent years, the incidence of breast cancer has increased by 20% with a particular increase in diagnosis before the age of 50 [1]. Nowadays mammography is the only breast imaging modality with a demonstrated ability to reduce mortality. However, the method has a population-based sensitivity of only approximately 80% [2], with a much lower sensitivity that this in women with dense breasts. The sensitivity of mammography in young women with dense breasts can be as low as 40% [3-5]. For these reasons, there has been an increased research focus in Europe and in the United States on the evaluation of other imaging modalities to improve diagnostic accuracy in breast cancer diagnosis. Over the last few years, several methods, with or without the use of contrast media have been developed and evaluated in the effort to extend the capability of mammography and to detect more breast cancers. Examples of such techniques which have been proposed as adjunct breast imaging screening methods are ultrasound for dense breasts and digital breast tomosynthesis [6].

Breast cancer screening methods using contrast media are commonly based on the biological principle of the rapid formation of tumoral microvessels that render malignancy-associated vessels more permeable to contrast agent than normal tissue, resulting in tumor enhancement [7]. Contrast-enhanced spectral mammography (CESM) is a new imaging technique based on this principle. Thus CESM is based on the use of mammography in combination with iodine-based contrast agents to increase diagnostic capability via the detection of areas of increased vascularity in the breast [8]. A review of contrast-enhanced mammography techniques showed encouraging preliminary results, with a mean sensitivity of 85.2% (range 62.0-96.0%) and a mean specificity of 66.1% (range 50.0-83.3%) [7-9]. However, until now studies estimating the diagnostic performance of CESM have involved relatively small sample sizes or had mixed inclusion criteria, large confidence intervals for estimates of performance and yielded heterogeneous results.

We have therefore recently carried out a study whose purpose was to assess the potential role of CESM by estimating its diagnostic capabilities from an evaluation of the already published evidence; we performed a systematic literature review and meta-analysis. (see Reference section for details of our original paper)

Material and methods
Our review methods followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy
We identified relevant studies that assessed the accuracy of CESM through a literature search of the major medical databases available: PUBMED, Embase (ISIWeb of Science, SpringerLink, ScienceDirect and Cochrane library). Searches were performed independently by two reviewers with the assistance of a hospital librarian and were carried out up to 1st December 2015.

Inclusion & exclusion criteria
Inclusion criteria:
1. Patients older than 18 years who had undergone assessment of the breast for cancer.
2. Existence of an acceptable reference standard (surgery or pathology) for the characterisation of any lesions.
3. The availability of (or possibility of deriving adequately) at least one of the following pairs: the absolute numbers of true-positive results and false-negative results; or the numbers of true-negative results and false-positive results.

Exclusion criteria:
1. Case report or case series, review articles, letters, or comments
2. Duplicate publications

This article summarizes the findings of a recent survey and meta-analysis of publications on Contrast-Enhanced Spectral Mammography. The sensitivity of CESM was found to be high, underscoring the potential of the modality whose diagnostic performance could rival that of MRI, but with added advantages of improved accessibility and lower cost.

Contrast-enhanced spectral mammography

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3. Fewer than 10 cases confirmed by reference standard

Study selection
Two authors independently reviewed article titles and abstracts for study selection, based on the pre-defined inclusion criteria. The same authors independently read the full text of studies included in the screening and eligibility evaluation process.

We also assessed the quality of the eligible studies using the Quality Assessment of Studies of Diagnostic Accuracy Studies (QUADAS-2) checklist.

RESULTS
From 643 screened articles, 33 studies were submitted for full-text review. Out of these, 8 eligible articles reporting the accuracy of CESM were included in the systematic review. The 25 articles excluded did not meet the predefined inclusion criteria.

A number of the studies were performed in Poland (3/8) by the same group. All studies were observational: five studies enrolled participants prospectively and three studies were carried out retrospectively. In the majority of these studies, the patients had already known mammographic abnormalities; had suspicious lesions; were patients already with a confirmed diagnosis of breast cancer or were having additional imaging as part of screening or diagnostic work-up. A total of 994 lesions were evaluated in 920 patients.

Sensitivity
A very high pooled test sensitivity of 0.98 (95% CI: 0.96-1.00) was found.

Specificity
Specificity was based on six studies reporting raw data, and was calculated as 0.58 (95% CI: 0.38-0.77).

Summary ROC
The pooled ROC curve showed an area under the curve of 0.93.

Mean Lesion size
The mean size of the cancerous lesion cancer was 21.2 mm (range: 0.1-77 mm).

DISCUSSION
We estimated the sensitivity and specificity of CESM for the detection of breast cancer using a meta-analytic approach. From the evaluation of 994 lesions evaluated in 920 patients, we found that the sensitivity of the technique was very high (98%). On the other hand, specificity was relatively low (58%) and the specificity confidence intervals were very broad, indicating a large variability in specificity across the studies.

The high sensitivity of CESM is giving rise to optimism regarding the potential of the technique and its superiority over conventional mammography. The extended information obtained from the use of contrast media together with the large experience and capacity of existing mammography, means that CESM could possibly be comparable with MRI, but much more accessible.

In fact CESM can be immediately implemented in the mammography suite with minimal loss of time [9]. Therefore, CESM might be an alternative cost-effective imaging method for MRI, especially when MRI availability is limited [9]. Contrast enhanced mammography is emerging as a combined application of full-field digital mammography with intravenous injection of iodinated contrast medium. CESM also has the potential for improved lesion detection in dense breasts where the tumor could be obscured by the fibroglandular (dense) tissue.

We believe that CESM could be comparable to MRI in terms of diagnostic feasibility. CESM and MRI could have similar diagnostic performance in the diagnosis and staging of breast cancer, but most patients seem to prefer the experience of CESM to that of MRI. Indeed, in addition to the cost and accessibility issues there can also be problems with MRI such as contraindications in patients with pacemakers and in claustrophobic patients.

For these reasons, it is likely that the role of CESM will grow in the near future. However, it should be pointed out the studies published so far on the evaluation of the diagnostic performance of CESM had relatively large confidence intervals on the estimates of diagnostic performance and several discrepancies especially regarding specificity.

High-quality studies are required to assess the accuracy of CESM in unselected cases.

If CESM is going to be used in screening, or if CESM is to be considered as a potential alternative to diagnostic MRI, it will be necessary to have accuracy data derived from studies with more robust designs.

However the current evidence provides some insights on the potential of CESM to replace or complement the existing array of imaging modalities in breast cancer diagnosis.

REFERENCES


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