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MAMOGRAFIJA SA INTRAVENSKOM PRIMENOM KONTRASTNOG SREDSTVA KAO NOVI STANDARD BRIGE O ZDRAVLJU DOJKE

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SAŽETAK

Kontrastna mamografija (KM) (eng. *Contrast-enhanced mammography* - CEM) postaje sve više prisutna metoda u dijagnostici karcinoma dojke tokom poslednjih nekoliko decenija, a posebno tokom poslednjih nekoliko godina. Sve je više dokaza o visokoj dijagnostičkoj efektivnosti i senzitivnosti KM u otkrivanju karcinoma dojke. Takođe, nova istraživanja pokazuju sličnost u efektivnosti i senzitivnosti KM u poređenju sa magnetnom rezonancom (MR), uz manje slučajeva lažno pozitivnih rezultata. Kako se primena KM sve više širi, od potencijalne njene primene u skriningu kod žena sa gustim tkivom dojke do određivanja stadijuma maligniteta dojke, sve je više neophodna dobra upućenost u ovu metodu i njenu implementaciju. Ovim preglednim radom biće sagledan značaj KM kako za skrining, tako i za dijagnostičku proceduru, sa posebnim akcentom na sagledavanje njenih prednosti i nedostataka u odnosu na ultrazvuk, standardnu mamografiju i MR.

Ključne reči: kontrastna mamografija, skrining, karcinom dojke

Uvod

Kontrastna mamografija (KM) (eng. *Contrast-enhanced mammograph*y - CEM) definiše se kao mamografija koja se realizuje intravenskom primenom kontrastnog sredstva. Stoga se ova tehnika danas smatra novom, jer koristi jodirane kontrastne materijale za vizualizaciju neovaskularnosti dojke na identičan način kao magnetna rezonanca (MR) (1). U okviru procesa angiogeneze obrazuju se krvni sudovi koji se veoma dobro ispunjavaju kontrastom (2), te stoga omogućavaju dobro kontrastno propuštanje kroz samo tkivo tumora, što dalje omogućava dobijanje kvalitetne dijagnostičke slike (3). Zahvaljujući prethodno opisanom procesu, KM omogućava da se postojanje malignih nodusa vizualizuje, čak i pri značajno velikoj gustini tkiva dojke, koje inače u standardnoj mamografiji predstavlja značajnu dijagnostičku poteškoću. Slično je i sa potencijalnim suspektnim lezijama, koje se upravo zbog gustine parenhima preklapaju sa tkivom dojke i predstavljaju izazov za dijagnostiku na standardnim mamografskim snimcima. Princip rada KM zasnovan je na aplikaciji intravenskog kontrastnog sredstva, pomoću kog se omogućava njegova akumulacija iz abnormalnih, propusnih krvnih sudova u potencijalno prisutno tumorsko tkivo dojke (4), što se jasno vizualizuje na dobijenom snimku visokog kvaliteta. U literaturi se KM naziva i kontrastno poboljšanom spektralnom mamografijom i kontrastno poboljšanom digitalnom mamografijom i kontrastno poboljšanom dualnom mamografijom. Bez obzira na naziv, reč je o savremenoj dijagnostičkoj tehnici koja obezbeđuje individualni pristup svakom pacijentu, omogućavajući da se tretman „prilagodi“ njihovim potrebama.

Prema dostupnim epidemiološkim podacima, karcinom dojke jedan je od najučestalijih karcinoma širom sveta, posebno ako se razmatraju oba pola (3). Studija *Sung*-a i saradnika iz 2020. godine pokazala je značajan porast broja novoobolelih od karcinoma dojke u odnosu na, do sada vodeći, kar-

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CONTRAST-ENHANCED MAMMOGRAPHY AS THE NEW STANDARD IN BREAST HEALTH CARE

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SUMMARY

Contrast-enhanced mammography (CEM) has become a ubiquitous method in breast diagnostics over the last few decades, especially in recent years. There is an increasing body of strong evidence regarding the high diagnostic efficiency and sensitivity of CEM in detecting breast cancer. There is more and more evidence about the high diagnostic effectiveness and sensitivity of CEM in detecting breast cancer. Also, new research has shown similarity in the efficiency and sensitivity of CEM compared to magnetic resonance, with fewer cases of false positive results. As the application of CEM expands from potential use in screening for women with dense breast tissue to the staging of known breast malignancy, it becomes increasingly important to become well-versed in this method and its implementation. This review article will perceive the importance of CEM both for screening and in the diagnostic procedure, with a special emphasis placed on the advantages and disadvantages compared to ultrasound, standard mammography and MRI.

Keywords: contrast-enhanced mammography, screening, breast cancer

Introduction

Contrast-enhanced mammography (CEM) is defined as mammography, which is realized with the intravenous administration of a contrast agent. Therefore, this technique is deemed to be new today because it uses iodinated contrast materials for the visualization of breast neovascularization identically as magnetic resonance (MR) (1). Within the process of angiogenesis, blood vessels, which are filled well with contrast, are formed (2), and therefore, they allow good contrast transmission through the tumor tissue itself, which further enables a high-quality diagnostic image to be obtained (3). Thanks to the previously described process, CEM allows the visualization of present malignant nodes, even with a significantly high density of breast tissue, which otherwise represents a significant diagnostic problem in standard mammography. Similar is the case with potentially suspicious lesions, which overlap with the breast tissue due to the density of parenchyma, and therefore, they are challenging for diagnosing on standard mammographic images. The working principle of CEM is based on the application of an intravenous contrast agent, which enables its accumulation from abnormal, permeable blood vessels into the potentially present tumor tissue of the breast (4), which is clearly visualized on the obtained high-quality image. In the literature, CEM is called contrast-enhanced spectral mammography and contrast-enhanced dual mammography. Regardless of the name, it is a modern diagnostic technique, which enables an individual approach to each patient, allowing the treatment to be "adapted" to their needs.

According to the available epidemiological data, breast cancer is one of the most common cancers worldwide, especially if both sexes are taken into consideration (3). A study by Sung et al. from 2020 showed a significant increase in the number of new cases of breast cancer in comparison to lung cinom pluća (4). Bez obzira na izuzetno intenzivan i značajan napredak tehnologije, dijagnostika karcinoma dojke i dalje je veoma kompleksna i nosi sa sobom veliki broj nedoumica, te zahteva kontinuirano unapređenje, razvoj i težnju ka novim dijagnostičkim tehnikama koje će omogućiti brže i efektivnije otkrivanje maligniteta u što ranijem stadijumu bolesti (2,5,6). Čak i u dobu savremene terapije, otkrivanje maligniteta dojke u ranim stadijumima ključno je za bolji ishod lećenja (7). Dijagnostičke metode za pregled dojke evoluiraju, a njihova snaga i slabosti kontinuirano se procenjuju kako bi se formulisale preporuke i smernice koje su korisne za kliničku praksu.

Ovim preglednim radom biće sagledan značaj KM kako za skrining, tako i za dijagnostičku proceduru, sa posebnim akcentom na sagledavanje njenih prednosti i nedostataka u odnosu na ultrazvuk, standardnu mamografiju i MR.

Metod

U ovom preglednom radu pretraženo je nekoliko elektronskih baza podataka: *Google Scholar* napredne pretrage, Konzorcijuma biblioteka Srbije za objedinjenu nabavku – KoBSON i platforma *PubMed*. U cilju pretraživanja literature korišćene su sledeće ključne reči: mamografija, kontrastna mamografija i karcinom dojke. Ovim preglednim radom obuhvaćene su radovi koji su publikovani u periodu 2014-2024. godine na srpskom ili engleskom jeziku, a koji su obrađivali navedenu tematiku.

Osnove kontrastne mamografije

KM tehnika je počela da se razvija postepeno i polako, počevši od 1985. godine kada je prvobitno nazvana digitalna subtrakcijska angiografija dojke. Prvobitno ova tehnika je razvijana kao neinvanzivna dijagnostička metoda za indentifikaciju tumora dojke koji je do tada najčešće bio dijagnostikovan biopsijom ili hirurškim zahvatima. Inicijalna KM tehnika izvodila se pomoću katetera koji je morao biti plasiran u regiju gornje šuplje vene kroz koji se aplikovao kontrast koji je omogućavao višeslojnu ekspoziciju i prikaz krvnih sudova unutar dojke. Opisana tehnika imala je niz nedostataka i zahtevala je prekontrastno, potom i kontrastno snimanje, zatim i kompresiju dojke, što je iniciralo dodatna tehnološka rešenja, kako bi ova tenhika bila primenjivana na efikasniji način koji bi bio bolje kontrolisan od prvobitnog i koji bi značajno kraće trajao.

KM tehnika koja koristi dualnu energiju (engl. *dual energy*) pravi razliku u apsorpciji rendgenskih zraka između tkiva dojke i joda kada se koriste spektri niske i visoke energije. Ova tehnika je prvobitno opisana tokom 2003. godine, kao alternativna tehnika subtrakciji (6). Pregledi KM sastoje se od uparenih slika niske i visoke energije dobijenih korišćenjem rendgenskih energija ispod i iznad ivice kontrasta. Iz ovih uparenih ekspozicija dobijenih pod istom kompresijom, generiše se rekonstruisana slika koristeći postupak naknadne obrade koji izoluje samo koncentraciju joda. Pre nego što se izvrši snimanje, neophodno je aplikovati nejonski kontrastni agens sa niskom osmolskom vrednošću, još u periodu dok je dojka van kompresije, kako bi se omogućio najveći protok krvi. Koncentracija joda varira od 300 mg/mL do 370 mg/mL (8). Iako standardizovani parametri snimanja za KM još uvek nisu konstituisani, generalno je prihvaćeno da se daje volumen od 1,5 ml/kg telesne mase (maksimalno 150 ml) brzinom od 2-3 ml/s, po mogućstvu korišćenjem automatskih injektora (9). Oko 2-3 minuta nakon ubrizgavanja kontrasta, dobijaju se uparene slike niske i visoke energije dojke, koja je pod kompresijom, u dve standardne projekcije - kraniokaudalne i mediolateralne kose. Dodatne projekcije mogu se dobiti unutar 10 minuta od aplikacije kontrasta. Rekombinovane slike za svaku dobijenu projekciju generišu se nakon obrade.

Ipak i pored svih prednosti treba naglasiti da KM ne prikazuje kinetiku i dinamiku kontrastnog pojačanja. Međutim, nekoliko publikovanih radova koji su ispitivali odloženu akviziciju dobijenu 6 do 8 minuta nakon ubrizgavanja kontrasta pokazali su poboljšanje specifičnosti KM sa 83% na 89% kod žena koje su bile podvrgnute KM radi procene odgovora na neoadjuvantnu hemioterapiju (10) i sa 80% na 92% kod žena sa denznim dojkama i suspektnim tumorskim promenama (11).

Dijagnostičke mogućnosti KM

Kao što je u samom uvodu pomenuto tehnika kontrastno pojačane mamografije se vremenom menjala, razvijala i unapređivala. Inicijalno ova tehnika snimanja prikazana je 1985. godine uz digitalnu subtrakcionu angiografiju dojke, u kojoj je bilo dominanto dobijanje prekontrastne slike, ali i slike uz kompresiju dojke nakon čega se pristupalo intravenskoj aplikaciji kontrasta (12,13). Naime, cancer, which had a leading position until then (4). Regardless of the extremely intensive and significant progress of technology, the diagnostics of breast cancer is still very complex and carries with it a large number of doubts. Therefore, it demands continuous improvement, development and striving for new diagnostic techniques, which will enable faster and more effective detection of breast malignancy at the earliest possible stage (2,5,6). Even in the age of modern therapy, detection of breast malignancy at early stages is crucial for a better treatment outcome (7). Diagnostic methods for breast examination are evolving, while their strengths and weaknesses are continually being evaluated in order to formulate recommendations and guidelines that are useful for clinical practice.

The significance of CEM for screening, as well as for diagnostic procedures will be considered in this review article, while special emphasis will be placed on realizing its advantages and disadvantages in comparison to ultrasound, standard mammography and MR.

Methods

In this review article, a few electronic databases were searched: Google Scholar advanced search, the Consortium of Serbian Libraries for Unified Procurement (Serbian: KoBSON) and the PubMed platform. The following key words were used in the literature search: mammography, contrast mammography and breast cancer. This review articles includes works published in the period 2014-2024 in the Serbian or English language, which analyzed the above mentioned topic.

Basics of contrast mammography

The CEM technique has developed gradually and slowly since 1985 when it was originally called digital subtraction breast angiography. Originally, this technique was developed as a non-invasive diagnostic method for the identification of breast tumors, which had been diagnosed by biopsy or surgical procedures until then. The initial CEM technique was carried out using a catheter that had to be placed in the region of the superior vena cava, through which contrast was administered, which allowed the multi-layered exposure and display of blood vessels inside the breast. The described technique had a number of disadvantages and it required pre-contrast, and then contrast imaging, then breast compression, which initiated additional technological solutions, so that this technique could be applied in a more efficient way, which had to be better controlled than the original one and which would be significantly shorter.

The CEM technique, which uses dual energy, makes difference in the absorption of X-rays between breast tissue and iodine, when the spectra of low and high energy are used. This technique was originally described in 2003 as an alternative technique to subtraction (6). The CEM examination consists of paired images of low and high energy obtained with the help of X-ray energies below and above the level of contrast. From these paired exposures obtained under the same compression, a reconstructed image is generated using the procedure of post-processing which isolates only the iodine concentration. Before the imaging is performed, it is necessary to apply a non-ionic contrast agent with a low osmolality value, when the breast is not under compression, in order to allow the greatest blood flow. The concentration of iodine varies from 300 mg/ml to 370 mg/ml (8). Although standardized imaging parameters for CEM have not been established yet, it has generally be accepted that a volume of 1.5 ml/kg of body mass (maximum 150 ml) is administered at a rate of 2-3 ml/s, preferably using automatic injectors (9). About 2-3 minutes after contrast injection, paired images of low and high energy of breast under compression is obtained in two standard projections – craniocaudal and mediolateral oblique viiews. Additional projections can be obtained within 10 minutes from contrast administration. Recombined images for each resulting projection are generated after processing.

Despite all the advantages, it should be pointed out that CEM does not show the kinetics and dynamics of contrast enhancement. However, a few published papers, which examined delayed acquisition 6 to 8 minutes after contrast was injected, showed the improvement of the specificity of CEM from 83% to 89% in women who underwent CEM on order to assess the response to neoadjuvant chemotherapy (10) and in 80% to 92% of women with dense breasts and suspicious tumor changes (11).

ova procedura pored toga što je bila veoma invanzivna i neprijatna, davala je suboptimalne rezultate, te njena primena nije značajno zaživela.

Nešto kasnije KM se počela razvijati uz korišćenje temporalne tehnike tokom koje je dojka takođe bila izložena kopresiji, rađena su predkontrastna snimanja i aplikovan je intravenski kontrast nakon čega je u vremenskom intervalu od 5 do 7 minuta rađeno višestruko snimanje. U odnosnu na prethodno opisanu, inicijalnu mamografiju, ova verzija je bila unapređena u segmentu što se predkontrastna slika oduzima od postkontrastne slike, pri čemu dolazi do vizuelizacije kontrastne apsorpcije. Ova tehnika pokazala se izuzetno efikasnom i uspešnom za postavljenje dijagnoze maligniteta dojke (14), ali i pored toga pokazala je niz nedostataka poput pojave artefakata zbog pomeranja pacijenta, izuzetno dugački vremenski interval akvizicije, tako da tokom jednog pregleda može biti pregledana samo jedna dojka. Svaki dodatni pogled na ipsilateralnu ili kontralateralnu dojku zahteva dodatnu dozu kontrasta. Na kraju, dojka je pod kompresijom tokom unošenja kontrasta, što može ograničiti protok krvi i rezultirati suboptimalnim poboljšanjem tkiva.

Tehnika KM koja koristi dualnu energiju razvijena je tokom 2003. godine sa ciljem da bude alternativa temporalnoj tehnici. Suština korišćenja dualne energije u ovoj tehnici je da se maksimizira iskoristivost kontrasta u smislu da se iskoriti njegova mogućnost različitog stepena apsorpcije od strane tkiva dojke i joda. Ova metoda je bila veoma prihvaćena posebno iz perspektive iskoristljivosti već postojeće opreme. Naime, kako bi se izvela ova tehnika snimanja pored standardne opreme za mamografiju bila je neophodna samo sofverski nadograditi postojeći sistem i dodatak bakarne filtracije. Ovako dopunjen standardno opremeljen uređaj omogućavao je tzv. „*dual-energy*” slikanje. Naime, ova tehnika zahtevala je da se pre nego što se izvrši akvizicija slikanja izvrši i intravenska aplikacija kontrasnog sredstva koji ima nisku osmolarnost. U ovom slučaju aplikacija kontrasnog sredstva vršena je pomoću injektora, a preporučena doza kontrasnog sredstva bila je od 1,5 ml/kg do maksimalno 150 ml/kg, obično u koncentraciji 300–370 mg joda/ml, brzinom od 3 ml/s (15). Takođe, kao i prethodna tehnika i ova tehnika zahtevala je kompresiju dojke, s tim što je u ovom slučaju kompresiju dojke bilo potrebno izvršiti tek oko dva minuta pre nego što će se završiti kompletna aplikacija kontrasnog sredstva. Na prethodno opisan način, a zahvaljujući delovanju kompresije i kontrasta omogućeno je dobijanje uparene slike niske i visoke energije u standardnim kraniokaudalnim i mediolateralnim projekcijama. KM koristi fotoelektrični efekat joda koji omogućava isticanje oblasti apsorpcije kontrasta. Sam fotoelektrični efekat zavisi od energije rendgenskog zraka i ivice materijala. Slike koje dolaze iz polja niske energije, dobijaju se ispod K nivoa joda na kVp vrednosti 28–33 i prikazuju samo tkivo dojke, dok se slike visoke energije dobijaju iznad K nivoa joda na kVp vrednosti 45–49 i prikazuju apsorpciju joda u tkivo dojke, ali nisu zahvalne za tumačenje. Nakon obrade, kreiraju se rekonstruisane slike koje naglašavaju oblasti u kojima je došlo do apsorpcije joda, odnosno naglašavaju se tzv. zone „pojačanja“, dok je signal koji dolazi iz pozadinskog tkiva potisnut. Zahvaljujući ovakvoj apsorpciji joda omogućena je vizuelizacija vaskularnosti tumora dojke. Nakon aplikacije kontrasnog sredstva najefektivnije snimanje obavlja se u vremenskom intervalu od 2 do 8 minuta (16). Ovaj vremenski raspon idealan je za snimanje jer postoje dokazi da se sam kontrast zadržava svega do 10 minuta, te dodatna snimanja zahtevaju dodatne aplikacije kontrasta (17). Takođe je važno napomenuti da nije nužno da se mamografske slike dobijaju u određenom redosledu.

Pregled KM obuhvata slike niske energije i rekonstruisane slike. To znači da nalaz može biti vidljiv samo na slikama niske energije, samo na rekonstruisanim slikama, ili na obema. Slike niske energije su slične slikama dobijenim standardnom digitalnom mamografijom i tumače se na isti način koristeći leksikon mamograma definisan u atlasu Američkog koledža radiologa za izveštavanje i sistem podataka o dojkama (BI-RADS) (engl. *College of Radiology Breast Imaging Reporting and Data System*-BI-RADS) iz 2013. godine (12). Rekonstruisane slike se tumače kako bi se identifikovalo svako abnormalno pojačanje koje može ili ne mora imati korelaciju na slikama niske energije. Nedavno objavljen dodatak BI-RADS atlasu iz 2013. godine dopunjuje smernice za tumačenje slika KM. U KM leksikonu su uvedena dva nova termina BI-RADS-a koja podrazumevaju i izraženu asimetriju i uočljivost lezije. Izražena asimetrija je nalaz koji je moguće uočiti u jednom pogledu, ili samo pomoću rekonstruisanih slika i/ili na obema rekonstruisanim i slikama niske energije. Uočlji-

Diagnostic possibilities of CEM

As it was mentioned at the very beginning, the technique of contrast-enhanced mammography has changed, developed and improved over time. Initially, this imaging technique was demonstrated in 1985 with digital subtraction breast angiography, in which pre-contrast images were dominant, as well as images with breast compression, after which intravenous contrast was administered (12,13). Namely, this procedure, in addition to being very invasive and unpleasant, gave suboptimal results, and therefore, its application did not proceed significantly.

A little later, CEM began to develop with the use of temporal technique, during which the breast was also exposed to compression, pre-contrast imaging was performed and intravenous contrast was applied, after which multiple imaging was done in a time interval of 5 to 7 minutes. In relation to the previously described, initial mammography, this version was improved in the segment where the pre-contrast image is subtracted from the post-contrast image, whereby contrast absorption is visualized. This technique proved to be very efficient and successful for the diagnosis of breast malignancy (14), but also it showed a number of disadvantages such as the appearance of artifacts due to the movement of patients, and a long interval of acquisition, so that only one breast can be examined during one examination. Each additional view of the ipsilateral or contralateral breast requires an additional dose of contrast. Finally, the breast is under compression during contrast administration, which can limit blood flow and result in suboptimal tissue enhancement.

The CEM technique that uses dual energy was developed in 2003 with the aim of being an alternative to the temporal technique. The essence of using dual energy in this technique is to maximize the use of contrast in the sense of exploiting its possibility of different degrees of absorption by breast tissue and iodine. This method was very well accepted, especially from the perspective of the utilization of already existing equipment. Namely, in order to carry out this imaging technique, in addition to the standard equipment for mammography, it was only necessary to upgrade the software of the existing system and add copper filtration. The standard device, which was additionally equipped in this way, enabled the so-called "dual-energy" imaging. Namely, this technique required the intravenous application of a contrast agent which has low osmolarity before the acquisition of imaging is performed. In this case, the application of the contrast agent was performed using an injector, while the recommended dose of the contrast agent was from 1.5 ml/kg to a maximum of 150 ml, usually in a concentration of 300-370 mg of iodine/ml at a speed of 3 ml/s (15). Also, like the previous, this technique demanded breast compression, but in this case breast compression needed to be performed about two minutes before the complete application of the contrast medium would be completed. In the previously described way, and thanks to the effect of compression and contrast, it is possible to obtain the paired image of low and high energy in standard craniocaudal and mediolateral projections. CEM uses the photoelectric effect of iodine, which makes it possible to highlight the areas of contrast absorption. The photoelectric effect itself depends on the energy of X-ray beam and the edge of the material. Images that come from the field of low energy are obtained below the K level of iodine at kVp values of 28-33 and show only the breast tissue, while high-energy images are obtained above the iodine K level at kVp values of 45-49 and show the absorption of iodine into the breast tissue, but they are not convenient for interpretation. After processing, the reconstructed images are created and they emphasize the areas where iodine had been absorbed, that is, they highlight the so-called zones of "amplification", while the signal, which is coming from the background tissue, is suppressed. Thanks to this absorption of iodine, the visualization of the vascularity of breast tumor is possible. After the application of the contrast agent, the most effective imaging is carried out in a time interval of 2 to 8 minutes (16). This time interval is ideal for imaging because there is evidence that the contrast itself is retained only up to 10 minutes, and therefore, additional imaging requires additional contrast applications (17). Also, it is important to note that mammographic images are not necessarily obtained in a specific order.

The CEM examination includes low-energy images and reconstructed images. This means that findings may only be visible only on low-energy images, only on reconstructed images, or on both images. Low-energy images are similar to images obtained with the help of standard digital mammography and they are interpreted vost lezije odnosi se na stepen intenziteta lezije u odnosu na pozadinsko parenhimsko pojačanje (BPE). Ovaj KM BI-RADS leksikon obezbeđuje standardizaciju izveštavanja i doslednost, što je ključno za sprovođenje KM.

Uloga KM u ranom otkrivanju tumora

Žene koje imaju povećan rizik od razvoja maligniteta dojke imaju korist bilo od ultrazvuka ili MR. MR je najosetljiviji skrining alat, ali se trenutno preporučuje samo ženama koje imaju visok (više od 20%) rizik od razvoja raka dojke zbog visokih troškova i ograničene dostupnosti. Žene koje imaju umeren (15–20%) rizik tokom života, a uključuju žene sa porodičnom istorijom maligniteta dojke, ličnom istorijom maligniteta dojke, prethodno potvrđenim biopsijskim visokorizičnim lezijama i gustim tkivom dojke, imaju opciju da se podvrgnu dopunskom skriningu ultrazvukom, što može otkriti karcinom koji nije vidljiv na mamografiji.

Sve više podataka ukazuje da KM kao skrining test žena sa povećanim rizikom od maligniteta dojke doprinosi boljem ranom otkrivanju poremećaja zdravlja u poređenju sa digitalnom mamografijom i/ili mamografijom i ultrazvukom zajedno (19,20). Pojedini autori ističu da se dijagnostička efektivnost KM značajno približila onoj kod MR (21). Naime, 2017. godine *Jochelson* i grupa autora publikovali su prvu prospektivnu studiju koja se bavila komparativnim poređenjem KM i MR kao skrining testova za karcinom dojke (22). U pomenutoj studiji bilo je uključeno 307 žena kojima je indentifikovan umeren do visok rizik od maligniteta dojke tokom života, a koje su podvrgnute KM i MR, nakon čega su praćene tokom 24 meseca. U periodu od prve etape skrininga, koja je trajala 12 meseci, dijagnostikovana su tri invanzivna karcinoma dojke, od kojih su dva indentifikovana na obe dijagnostičke procedure, a jedan duktalni karcinom in situ je viđen samo na MR. Dakle, prema opisanoj studiji u prvoj etapi istraživanja ni jedan karcinom nije bio indentifikovan samo pomoću KM. U zaključku pomenute studije, autori su naveli da je specifičnost ispitivanih dijagnostičkih procedura u celokupnom istraživanju bila indentična (oko 94%) (22). Godinu dana kasnije, *Klang* i grupa autora publikovali su studiju u kojoj su napravili komparativno poređenje između efektivnosti KM i ultrazvuka u cilju skrininga maligniteta dojke (23). Oni su izneli da je KM pokazala veću senzitivnost (97,3%) i specifičnost (40,0%), u poređenju sa ultrazvukom (91,9% i 8,0%) (23). U okviru pomenute studije otkriveno je ukupno 37 karcinoma dojke, a autori su zaključili da ni jedan od otkrivenih karcinoma KM nije čak ni delovao benigno, dok su na ultrazvuku čak tri pokazivala benigni karakter. Kao najupečatljiviji zaključak opisane studije je da zapravo ultrazvučni skrining nakon adekvatnog pregleda KM može da rezultira samo nepotrebno indikovanim biopsijama. Značajno je spomenuti da je u maloj grupi od 132 žene sa povećanim rizikom od maligniteta dojke zbog lične istorije lobularne neoplazije, KM kao skrining test pokazao senzitivnost od 100% u otkrivanju 6 karcinoma koji su svi bili skriveni na standardnoj digitalnoj mamografiji (21). Specifičnost skrining testa je bila 88%.

Pored potencijalne ekonomske isplativosti i dostupnosti u odnosu na MR, KM ima druge prednosti u skriningu. Ženama sa povećanim rizikom od maligniteta dojke koje se ne mogu podvrgavati MR zbog klaustrofobije, metalnih implanta ili alergija na kontrast na bazi gadolinijuma može se bezbedno uraditi KM. Ako im se pruži izbor, većina pacijentkinja preferira KM umesto MR (24).

Budućnost kontrastne mamografije

U budućnosti, KM zauzima značajnu ulogu u dijagnostici maligniteta dojke sa očekivanim napretkom u nekoliko ključnih aspekata. Prvo, očekuje se dalji tehnički razvoj KM tehnologije, uključujući poboljšanje algoritma za obradu slika, povećanje rezolucije i smanjenje doze zračenja. Ovi napreci doprinose većoj tačnosti dijagnostike i poboljšavaju iskustvo pacijenata. Širenje indikacija predstavlja drugi ključni aspekt. Očekuje se da će KM proširiti svoju primenu na različite vrste patoloških promena i specifične grupe pacijenata, uz prilagođene protokole za skrining kod određenih populacija. Ovo bi omogućilo širu primenu KM u kliničkoj praksi. Edukacija i implementacija igraće ključnu ulogu u široj upotrebi KM. Potrebno je osigurati da zdravstveni radnici, uključujući radiologe, tehničare i medicinsko osoblje, budu dobro obučeni za interpretaciju slika KM i postupke u slučaju reakcija na kontrast.

Ukoliko bi se KM koristila kao alternativa za MR, dijagnostičke prakse koje se značajno oslanjaju na prihode od MR mogle bi se suočiti sa značajnim finansijskim padom. U tom kontekstu in the same way using the mammogram lexicon which was defined in the Atlas of the American College of Radiology Breast Imaging Reporting and Data System BI-RADS in 2013 (12). The reconstructed images are interpreted in order to identify any abnormal enhancement that may or does not have to correlate with the low-energy images. A recently published supplement to the BI-RADS atlas from 2013 adds guidelines for the interpretation of CEM images. In the CEM lexicon, two new BI-RADS terms have been introduced, and they imply the pronounced asymmetry and conspicuity of the lesion. The pronounced asymmetry is a finding that can be seen at a glance, or only with the help of reconstructed images and/or on both reconstructed images and low-energy images. The conspicuity of the lesion refers to the degree of intensity of the lesion in relation to the background parenchymal enhancement (BPE). This CEM BI-RADS lexicon ensures the standardization of reporting and consistency, which is important for the CEM procedure.

The role of CEM in the early detection of tumors

Women who are at increased risk of developing breast malignancy benefit from either ultrasound or MRI. MRI is the most sensitive screening test, which is currently recommended only to women who have a high (more than 20%) risk of developing breast cancer due to high costs and limited availability. Women who have a moderate risk (15-20%) during lifetime, including women with a family history of breast malignancy, a personal history of breast malignancy, high-risk lesions and dense breast tissue that was previously confirmed by biopsy, have the option to undergo additional ultrasound screening, which can detect cancer that is not visible on mammography.

More and more data indicate that CEM as a screening test for women at an increased risk of breast malignancy contributes to the early detection of health disorders in comparison to digital mammography and/or mammography and ultrasound together (19,20). Some authors point out that the diagnostic effectiveness of CEM has significantly approached the effectiveness of MRI (21). Namely, in 2017, Johelson et al. published the first prospective study, which compared CEM and MRI as screening tests for breast cancer (22). In the above mentioned study, 307 women, who were identified as having a moderate to high risk of breast malignancy during their lifetime, and who underwent CEM and MRI, were included, after which they were followed for 24 months. In the period of the first stage of screening, which lasted 12 months, three invasive breast cancers were diagnosed, two of which were identified on both diagnostic procedures, while one ductal carcinoma in situ was seen only on MRI. Therefore, according to the described study, during the first stage, there were no cancer cases that were identified only using CEM. In the conclusion of the above mentioned study, the authors stated that the specificity of the examined diagnostic procedures in the whole research was identical (92%) (22). A year later, Klang et al. published a study, in which they made a comparative analysis between the effectiveness of CEM and ultrasound aimed at screening breast malignancy (23). They reported that CEM showed higher sensitivity (97.3%) and specificity (40.0%) in comparison to ultrasound (91.0% and 8%) (23). Within the above mentioned study, a total of 37 breast cancers were detected, and the authors concluded that none of the CEM cancers appeared benign, while on ultrasound, even three showed a benign character. The most striking conclusion of the described study is that the ultrasound screening after an adequate CEM examination can only result in unnecessarily indicated biopsies. It is important to mention that in a small group of 132 women with an increased risk of breast malignancy due to a personal history of lobular neoplasia, CEM as a screening test showed a sensitivity of 100% in detecting 6 cancer cases that were all hidden on standard digital mammography (21). The specificity of the screening test was 88%.

In addition to the potential economic cost-effectiveness and availability in comparison to MRI, CEM has other advantages in screening. Women at an increased risk of breast malignancy who cannot undergo MRI due to claustrophobia, metal implants or allergies to gadolinium-based contrast can safely undergo CEM. If they are offered choice, most patients prefer CEM to MRI (24).

The future of CEM

In the future, CEM will have a significant role in the diagnostics of breast malignancy with troškovna efikasnost predstavlja bitan faktor, a ako KM ostane ekonomičnija opcija u poređenju s drugim dijagnostičkim metodama, to će povećati njenu prihvatljivost u zdravstvenim sistemima. Sa druge strane, KM bi potencijalno mogla omogućiti ekonomičnu dopunsku dijagnostičku opciju za podgrupe žena kojima je trenutno MR finansijski nepristupačan ili je iz nekog razloga kontraindikovan, kao što su žene sa srednjim rizikom od maligniteta dojke, čime bi se potencijalno povećao obim skrininga i dijagnostike, a smanjili potencijalno dodatni troškovi. Takođe, važno je u ovom segmentu napomenuti da je KM i značajno brža metoda sa aspekta izvođenja i tumačenja, kao i da ima niže troškove nabavke i održavanja opreme u poređenju sa MR.

Dalja istraživanja i klinički radovi biće ključni za potvrdu dugoročne efektivnosti KM, identifikaciju novih indikacija i usavršavanje protokola primene. Povezivanje s tehnologijama veštačke inteligencije takođe ima potencijal da unapredi interpretaciju slika KM i ubrza proceduru izvođenja. U suštini, budućnost KM obećava dalji napredak u otkrivanju maligniteta dojke, nudeći napredne metode sa sve većim fokusom na preciznost, tačnost, dostupnost i udobnost pacijenata.

Zaključak

Očekivanja u vezi s globalnim prihvatanjem KM kao standarda u otkrivanju maligniteta dojke zavise od više ključnih faktora. Najpre, dalja klinička ispitivanja su ključni koraci kako bi se potvrdila njegova efektivnost na široj populaciji. Ako KM pokaže doslednu dijagnostičku preciznost i tačnost, kao i prednosti u poređenju sa dosadašnjim metodama, to će snažno podržati njegovo globalno prihvatanje. Pored toga, edukacija i osposobljavanje zdravstvenih radnika igraju ključnu ulogu u uspešnom uvođenju KM. Ekonomska održivost takođe će biti presudna, te ako KM pruži visoku dijagnostičku efektivnost uz prihvatljive troškove, olakšaće se njegova integracija u zdravstvene sisteme širom sveta. Regulativni okviri takođe predstavljaju neizostavnu kariku, pružajući jasne smernice i standarde za sigurnost i efikasnost KM. Informisanost pacijenata i edukativne kampanje su od suštinske važnosti.. Konačno, globalno prihvatanje zahtevaće saradnju između različitih zdravstvenih sistema, uključujući javne i privatne ustanove. Ukoliko KM ispuni očekivanja u ovim ključnim oblastima, postoji potencijal da postane globalni standard za rano otkrivanje raka dojke. Međutim, dinamika i brzina prihvatanja zavisiće od napretka u istraživanjima, obrazovanju, ekonomskoj opravdanosti i saradnji između različitih aktera u oblasti zdravstvene nege

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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expected advances in several key aspects. First, further technical development of CEM technology is expected, including the improvement of the algorithm for image processing, increase in resolution and decrease in radiation dose. These advances contribute to greater diagnostic accuracy and improve the patients' experience. The expansion of indications is another key aspect. CEM is expected to expand its application to different types of pathological changes and specific groups of patients, with adapted screening protocols in specific populations. This would enable a wider application of CEM in clinical practice. Education and implementation will play a key role in the wider use of CEM. It is necessary to ensure that healthcare professionals, including radiologists, technicians and medical staff are well trained in the interpretation of CEM images and procedures in case of contrast reactions.

If CEM were used as an alternative for MRI, diagnostic practices, which rely significantly on revenues gained from MRI, could face a significant financial decline. In that context, cost effectiveness is an important factor, and if CEM remains a more economical option compared to other diagnostic methods, it will increase its acceptability in healthcare systems. On the other hand, CEM could potentially provide a cost-effective additional diagnostic option for subgroups of women, for whom MRI is currently financially not accessible or contraindicated for some reason, such as women with an intermediate risk of breast malignancy, thus potentially increasing the scope of screening and diagnostics, and reducing additional costs. Also, it is important to note in this segment that CEM is a significantly faster method in terms of its execution and interpretation, as well as that it has lower costs in terms of purchase and maintenance of equipment in comparison to MRI.

Further research and clinical studies will be crucial to confirm the long-term effectiveness of CEM, identify new indications and improve the application protocols. Connecting with artificial intelligence technologies also has the potential to improve the interpretation of CEM images and accelerate the procedure. In essence, the future of CEM promises further advances in the detecting of breast malignancy, offering advanced methods with an increasing focus on precision, accuracy, availability and patients' comfort.

Conclusion

Expectations related to the global acceptance of CEM as a standard in the detection of breast malignancy depend on several key factors. First, further clinical trials are key steps to confirm the efficiency in the wider population. If CEM demonstrates consistent diagnostic precision and accuracy, as well as advantages compared to current methods, its global acceptance will strongly be supported. In addition, education and training of health workers play a key role in the successful introduction of CEM. Economic sustainability will also be crucial, and therefore, if CEM shows high diagnostic effectiveness with acceptable costs, its integration into health systems around the world will be facilitated. Regulatory frameworks are also an indispensable link, providing clear guidelines and standards for the safety and effectiveness of CEM. Patients' awareness and educational campaigns are essential. Finally, global acceptance will require the cooperation between different healthcare systems, including public and private institutions. If CEM fulfills expectations in these key areas, it has the potential to become the global standard for the early detection of breast cancer. However, dynamics and speed of acceptance will depend on the progress in research, education, economic justification and cooperation between different actors in the field of healthcare.

Competing interests

The authors declared no competing interests.

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