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ANALYSIS OF MODERN DIAGNOSIS METHODS FOR DETECTING OCCULT BREAST CANCER.

ANÁLISE DOS MÉTODOS DIAGNÓSTICOS MODERNOS PARA DETECÇÃO DE CÂNCER OCULTO DE MAMA.

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Abstract - This research aims to identify and evaluate contemporary diagnostic options for patients with occult breast carcinoma by compiling findings from the latest literature regarding disease identification and strategies for improved patient outcomes. To achieve this purpose, a narrative literature review on the topic was conducted using manuscripts obtained from the National Library of Medicine database (through PubMed), Virtual Health Library (BVS), and Google Scholar, employing the following terms connected by the boolean operator AND: 'occult,' 'breast,' 'cancer,' 'carcinoma,' and 'diagnosis.' Clinical studies published in full in the last 10 years, in English or Portuguese, and relevant to the topic were selected. The optimal detection protocol is based on a combination of various methods for detecting occult breast cancer, but such a procedure requires treatment customization, involves higher costs, and depends on the resources available at each healthcare facility. It is anticipated that future clinical adoption will be based on safe and effective combinations of

devices and contrast agents that can be easily integrated into the surgical workflow, meet user needs, and incur lower costs.

Keywords: Occult breast cancer, diagnostics, modern methods, detection

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Resumo - O objetivo deste estudo foi identificar e avaliar as opções diagnósticas contemporâneas em pacientes com carcinoma oculto de mama, compilando achados da literatura mais recente a respeito da identificação da doença e estrategias para melhores desfechos para os pacientes. Para isto, foi realizada uma revisão narrativa da literatura sobre o tema, através da base de dados *National Library of Medicine* (via PubMed), Biblioteca Virtual em Saúde (BVS) e Google Scholar, utilizando os seguintes termos unidos pelo operador booleano *AND*: “occult”, “breast”, “cancer”, “carcinoma” e “diagnosis”. Foram selecionados estudos clínicos publicados na íntegra nos últimos 10 anos, em inglês ou português e que seguiam a temática abordada. O protocolo de detecção ideal baseia-se na combinação de diversos métodos de detecção do câncer oculto de mama, mas tal procedimento exige personalização do tratamento, implica em maiores custos e depende dos recursos disponíveis em cada unidade de atendimento em saúde. Avalia-se que a adoção clínica futura será baseada em combinações seguras e eficazes de dispositivos e agentes de contraste que são facilmente integrados ao fluxo de trabalho da sala de cirurgia, que atendam às necessidades do usuário e com menores custos.

Palavras-chave: Câncer oculto de mama, diagnóstico, métodos modernos, detecção

1. INTRODUCTION

Breast cancer is the most commonly diagnosed neoplasm and the leading cause of cancer-related mortality in women (SUNG et al., 2021; NICOSIA et al., 2023; WANG et al., 2023). Occult breast cancer is described as axillary metastatic carcinoma without detection of a primary breast lesion. Due to its very low detection rate, it poses imminent health risks as it typically lacks palpable nodules, making it difficult to detect in early stages. Consequently, diagnosis often occurs at advanced stages of the disease, reducing treatment options and chances of cure. The breast lesion may be identified, but occasionally, no primary lesion is found. Axillary carcinoma metastases arise in the absence of clinically, radiologically, or pathologically identifiable breast tumors. This is attributed to the oncological behaviour of these tumors, which is not yet fully understood. Evidence suggests that outcomes for occult breast carcinoma are similar or slightly better compared to breast cancer with corresponding nodal status; however, a few studies have shown worse outcomes for occult breast cancer (MONTAGNA et al., 2011). First described in 1907 as "axillary glands with indemonstrable breast cancer," occult breast cancer was initially defined solely by the absence of a clinical finding in the breast (NICOSIA et al., 2023). Over time, the definition

has been expanded to also include carcinomas not detectable by traditional imaging methods such as negative mammography and ultrasound (OFRI & MOORE, 2020).

Recent investigations show that the incidence rate of occult breast cancer ranges from 0.1% to 15.9% (WALKER et al., 2010; WEAVER et al., 2011; HUAND et al., 2020). Screening mammography has limited sensitivity in detecting breast cancer in dense breast tissue. Covington (2022), using data from the U.S. Food & Drug Administration for the year 2021 in the United States of America, estimated that among 38.8 million mammograms, 43% were considered to involve dense breast tissue, and the number of cancers undetected by mammography in these individuals is approximately 267,000 cases, a relatively high rate.

Historically, modified radical mastectomy has been performed for the treatment of this condition. However, less invasive approaches have been introduced more recently with promising results. Due to the limited experience of healthcare professionals with occult breast cancer, the ideal therapeutic approach has not yet been established (ABDELHAMID et al., 2022). Currently, the most recommended guidelines from the National Comprehensive Cancer Network (NCCN) designate modified radical mastectomy with axillary lymph node dissection or axillary lymph node dissection with whole-breast radiotherapy with or without nodal radiotherapy the recommended protocol to most cases (GRADISHAR et al., 2022). In conjunction with the surgical modality, current recommendations points to the use of adjuvant doxorubicin-based chemotherapy in patients with occult breast carcinoma, especially those with more than three positive lymph nodes (MACEDO et al., 2016; LENTISCH et al., 2023).

Despite improvements in breast imaging diagnostic techniques, the frequency of detecting a primary tumor in this particular context still requires advancements (WALKER et al., 2010). Imaging diagnostic technologies have been increasing in accuracy and sensitivity (HSIEH & MORRIS, 2022), and the introduction of better diagnostic techniques and more detailed pathology continues to impact the true incidence of occult breast cancer. However, the guidelines surrounding its management have not changed and are based on studies that have varied definitions of the disease depending on the level of technology used at different times (OFRI & MOORE, 2020).

Considering the low rate of occult breast carcinoma cases, there is a gap in the literature regarding effective diagnoses of this manifestation of the pathology, necessitating an expansion of the knowledge base on this topic. Thus, the objective of this study was to conduct a literature review on contemporary diagnostic options for patients with occult breast carcinoma.

METHOD

This manuscript adopts a qualitative and exploratory narrative review methodology to investigate effective diagnostic modalities for occult breast cancer. The review process comprises two distinct phases. The initial phase involves an exhaustive literature search encompassing exploratory scientific papers, retrospective analyses, clinical case series, and case reports pertinent to the diagnosis of occult breast cancer. A direct exploration of electronic databases, including the National Library of Medicine (via PubMed), Medline, and Google Scholar, was conducted using the Boolean operator AND to combine the search terms "occult," "breast," "cancer," "carcinoma," and "diagnosis." Articles are selected based on predefined diagnostic criteria that contribute to the identification of occult breast cancer cases. Exclusion criteria encompass opinion articles, manuscripts lacking suitable methodology or exhibiting inconsistent results, and those unrelated to diagnostic strategies specifically tailored for occult breast cancer. The subsequent phase involves a comprehensive examination of the selected literature, selection of the manuscripts and the synthesis of the diagnostic methods and key characteristics. During this phase, diagnostic methods are scrutinized, and a detailed discourse is undertaken to elucidate the relevant aspects of each clinical procedure, with a specific emphasis on their contributions to disclose the pathogenic mechanisms associated with occult breast cancer.

3. RESULTS

Eight academic articles were chosen as the foundational dataset for scrutinizing state-of-the-art diagnostic approaches in the context of occult breast cancers. Table 1 offers a concise synthesis of the findings, categorically organized by the methods employed for detection and diagnosis, along with their principal distinguishing features.

Table 1. Summary of findings, based on the detection and diagnostic methods and their main results and key characteristics.

Method	Authors	Main results and key characteristics
Injection of 1-3 ml of sterile aqueous suspension of 3% charcoal granules under	Farouk et al. (2022)	The method revealed the diameter and allowed differentiation between malignant and benign lesions.

ultrasound guidance.		
Portable fluorescence imaging device with or without 5-aminolevulinic acid hydrochloride (5-ALA).	Ottolino-Perry et al. (2021)	5-ALA improved tumor visualization in contrast to autofluorescence from normal tissue.
Tumorectomy using Magnetic Occult Lesion Localization Instrument (MOLLI).	Look Hong et al. (2020) Nicolae et al. (2019)	The system was deemed a reliable method, user-friendly, and accurate for minimally invasive localization of non-palpable breast lesions.
Breast magnetic resonance imaging.	Dorn et al. (2013)	Magnetic resonance imaging enabled the identification of occult breast cancer cases in a significant number of eligible patients for partial breast irradiation when compared to traditional mammography.
Molecular breast imaging.	Rhodes et al. (2015) Brem et al. (2016)	Comparable sensitivity and specificity to conventional magnetic resonance imaging. No sensitivity variation even in denser breast tissue.
Artificial intelligence-assisted imaging diagnosis (mammography).	Kim et al. (2022)	An increase in the diagnosis rate of occult breast cancers of 31.3% (confirmed by biopsy) when compared to diagnosis rates by imaging professionals.

Font: authors

Researches employing six diagnostic methods conducted prior to treatment or lesion removal were identified. The results highlight the effectiveness of all these methods, particularly when compared to traditional mammography in isolation, enabling improved detection of occult lesions and yielding positive outcomes for patients. No research reported adverse events following the procedures.

4. DISCUSSION

Breast carcinoma stands as the foremost prevalent malignant neoplasm afflicting the global female population. Therefore, the augmentation of screening initiatives and the awareness regarding their pivotal role in the early diagnosis of incipient breast carcinoma lesions substantiates an elevation in remission rates. Another challenge is how to deal with impalpable suspicious breast lesions that warrant tissue biopsy. Many techniques have been attempted for preoperative localization of the non-clinically detected suspicious lesion, depending on the availability of tools and the expertise of the physicians (ERNST et al., 2002).

Amongst the most used techniques for detecting occult breast cancer include wire localization, radioactive seed-guided material seeding within the hidden lesion, skin surface marking, intraoperative ultrasound guidance, radioimmunoguided localization, magnetically detected lesions, and dye detection, such as blue dye or aqueous charcoal detection. With practice, some disadvantages have been identified for these techniques. In the case of wire localization, wire insertion must occur shortly before surgery. Coordinating this task between the surgical team and the radiology team is challenging, and complications such as wire displacement or breakage are often observed. Another issue is wire migration to a position that can lead to chest trauma. Additionally, during surgery, the wire may be inside the tumor, and its removal with minimal damage can cause thermal injury to the skin or limit the skin incision (DUA; GRAY; KESHTGAR, 2011).

There is an approximate 18% failure rate associated with these techniques compared to newer methods using radioactive materials, which implies higher costs and specific training requirements. Radiologic detection methods require efficient coordination between the nuclear medical team and the surgical team for injecting radioactive material into the lesions, in addition to dedicated equipment. For this reason, some professional teams prefer to skip this diagnostic step and opt for direct cytology and sentinel lymph node identification if the lesion is not benign. Another technique is magnetic tumor localization, which has disadvantages, including the removal of tissue marked by the magnetic tracer, requiring cooperation between the surgeon and radiologist for accurate tumor detection (AHMED et al., 2015).

In the investigation conducted by Farouk et al. (2022), it was possible to identify that 34 patients had 36 lesions, with 16 being malignant lesions and 20 benign lesions, with an

average diameter of 10.9 millimetres, comprising 16 malignant and 20 benign lesions, demonstrating an average diameter of 10.9 millimetres. Within this set of 36 lesions, 10 were categorically designated as BIRADS 4a, 12 as 4b, 8 as 4c, and 6 as BIRADS 5. It is noteworthy that all 14 lesions classified as BIRADS 4a were subsequently confirmed as benign. The treatment of the 16 malignant lesions took diverse conducts: nine patients underwent breast-conserving surgery, five patients underwent modified radical mastectomy (including three individuals with a previous history of modified radical mastectomy, one with multicentric IDC, and one with margins involved in the conservation procedure), and one patient opted for nipple-sparing mastectomy followed by immediate breast reconstruction employing the Latissimus Dorsi Flap technique. The methodology employed by Farouk et al. (2022) entails the intradermal injection of 1-3 millilitres of a sterile aqueous suspension containing 3% charcoal granules, under the guidance of ultrasound imaging. This injection is administered at the superficial periphery of the suspicious lesion and along the trajectory between the lesion and the anticipated needle insertion site on the skin, which corresponds to the site of the subsequent incision. The activated charcoal functions as a contrast agent in ultrasound imaging, primarily due to its distinctive acoustic impedance characteristics, thereby facilitating the differentiation of tissue densities and accentuating the visibility of tumorous formations. Consequently, it serves as a guiding path between the suspicious lesion and the needle entry point on the skin. The volume of injection administered is contingent upon the number and depth of the suspicious lesions, a determination readily made during the surgical procedure.

The results from the research conducted by Farouk et al. (2022) do not indicate an escalated risk of wound infection, as the research team utilized aseptic solutions. Nevertheless, owing to the modest sample size, they advocate for the replication of the study using a larger and more comprehensive sample. While a limited number of studies in the existing literature hint at potential debates concerning impairment or challenges in histopathological evaluations of lesions marked with charcoal suspension, such issues were not discerned in the context of their investigation.

The method proposed by Ottolino-Perry et al. (2021) consists in the oral administration of 5-ALA to patients, with dosages ranging from 15 to 30 milligrams per kilogram of body weight. Stringent precautions were implemented to mitigate adverse effects, encompassing the monitoring of cutaneous photosensitivity and the monitoring of instructions to avoid prolonged exposure to intense light following 5-ALA administration. Patients applied sunblock and subjected to postoperative reviews to avoid any adverse events. Additionally, a

fluorescence-enabled device (PRODIGI) was employed for image-guided orientation during the surgical intervention. The authors observed that, in the absence of 5-ALA, tissue autofluorescence imaging lacked distinctive fluorescent contrast specific to tumorous regions. Notably, both 5-ALA dosage levels (15 mg/kg and 30 mg/kg) induced vivid red fluorescence within the tumorous tissue, markedly enhancing tumour visualisation compared to the autofluorescence exhibited by normal tissue. In the 15 mg/kg 5-ALA group, the positive predictive value (PPV) for the detection of breast cancer within and beyond the roughly delineated tumour boundary stood at 100.0% and 55.6%, respectively. In the 30 mg/kg 5-ALA group, the PPV was 100.0% and 50.0% within and beyond the demarcated tumour boundary, respectively. Ottolino-Perry et al. (2021) presented preliminary evidence of the effectiveness of a Phase II RCT demonstrating the first clinical use of 5-ALA plus PRODIGI, a prototype fluorescence imaging device, for real-time visualization of breast cancers. This was the first RCT to test a fully portable wide-field fluorescence imaging device for intraoperative real-time imaging of breast cancer in lumpectomy and mastectomy specimens and surgical cavities, as well as the first to report results for 15 and 30 mg/kg 5-ALA-induced PpIX fluorescence in breast cancer patients. Kiening & Lange (2022) conducted in-vitro investigations to evaluate the effects of 5-ALA on four distinct breast cancer cell lineages. All cell lineages demonstrated the capacity to accumulate protoporphyrin IX within a few hours, inducing fluorescence intensity equivalent to or exceeding that of ALA-Hex (the original contrast chemical agent characterised by heightened toxicity) in three of the four cell lineages. The researchers concluded that derivatives of ALA hold promise as tools for fluorescence-guided resection and may facilitate subsequent eradication of cancerous cells through blue light irradiation. These findings corroborate the potential of the methodology proposed by Ottolino-Perry et al. (2021), affirming the utility of portable fluorescence imaging devices using 5-aminolevulinic acid hydrochloride (5-ALA) for the detection of various breast cancer cell lineages.

In Ottolino-Perry et al. (2021) inference, 5-ALA was well-tolerated and enabled the visualization of both grossly evident tumors and occult diseases in all grades (I-III) and types of tumors, including IDC and ILC, with or without in situ disease. Both tested doses were lower than the single dose previously reported for clinical use in breast cancer (40 mg/kg) (LADNER et al., 2001), consistently inducing bright red cancer fluorescence (contrasted with normal tissue autofluorescence) detected by the device.

Surgical margins stand a significant challenge in the treatment of solid cancers. Guiding principles from the Society of Surgical Oncology/American Society Radiation

Oncology/American Society of Clinical Oncology define positive margins as "ink on tumor" for invasive breast cancer and cancer within 2 mm of the margin with ink for DCIS. Surgeons disagree on recommendations, and the effect of guidelines on re-excision rates varies. Many studies still report suboptimal re-excision rates, above the internationally accepted target of 10%, underscoring the need for new imaging methods that allow surgeons and pathologists to grossly visualize occult disease in lumpectomy and surgical cavities during initial surgery (Ottolino-Perry et al., 2021).

The innovative Magnetic Occult Lesion Localization Instrument (MOLLI) procedure involves the insertion of a small ferromagnetic marker at the presumed location of the occult carcinoma to guide surgical interventions using a handheld probe. The marker is implanted under ultrasound or mammography guidance and requires no special precautions. This technique minimizes potential interference with metallic surgical instruments and allows for the identification of multiple lesions in the adjacent area. Preclinical comparative studies of MOLLI have shown significant benefits over radioactive seed localization, including direct measurement of the probe-to-marker distance with a visual and audio feedback system to assist surgeons in precise localization. In Look Hong et al. (2020) research, 17 out of 20 markers were placed directly at the centre of the lesion and were successfully removed with the specimen during surgical excision. Nicolae et al. (2019) conducted a similar investigation, finding that the three-dimensional accuracy of non-palpable lesion determination offers a valuable resource for diagnosing and staging occult breast carcinoma. In both studies, surgeons rated the guidance system as "very easy" for lesion localization. These studies represented the first human evaluations of Magnetic Occult Lesion Localization Instrument technology. A detection depth of up to 53 mm was achieved in both studies, allowing for the verification of deep suspicious lesions on the skin surface (LOOK HONG et al., 2020; NICOLAE et al., 2019). The results of this clinical trial confirm preclinical findings that MOLLI is a viable intraoperative guidance system. This method stands out for its minimally invasive and highly precise image-guided biopsy capabilities for obtaining samples for histopathological analysis (LOOK HONG et al., 2020).

The MOLLI system represents a valuable addition to the rapidly evolving field of breast localization technologies. Other products often adapt technologies from alternative, typically non-medical applications to meet the demands of breast lesion localization. In contrast, the MOLLI system is purpose-designed for wireless breast lesion localization, eliminating the need for radiation. It employs straightforward, sterilizable, and cost-effective

technology, significantly streamlining the complexity and human resource requirements of localization procedures (LOOK HONG et al., 2020; NICOLAE et al., 2019).

Current usual localization techniques, such as radioactive seed localization and wire localization, have demonstrated clinical efficacy and good tolerability. Decisions regarding localization technology selection are likely to be multifaceted, considering factors such as patient satisfaction, clinician usability, and healthcare system efficiency, as there is a delicate balance concerning clinically relevant outcomes such as margin positivity rates and the extent of resection (ZHANG et al., 2017).

Magnetic resonance imaging is a valuable imaging modality for detecting occult breast cancer, particularly when mammography and ultrasound yield inconclusive results. This technique relies on a robust magnetic field and radio waves to produce detailed images of the breast's internal structures and adjacent regions. While magnetic resonance imaging may occasionally yield false-positive results for occult breast cancer (as well as other suspicious neoplastic cases), the possibility of occult carcinoma should prompt consideration of biopsy for diagnostic confirmation (KASIVISVANATHAN et al., 2019; BANSAL et al., 2022; HAO et al., 2023; ZHANG et al., 2023). Dorn et al. (2013) observed that magnetic resonance imaging findings altered eligibility for partial breast irradiation procedures in 12.9% of patients. Additionally, tumor size ≥ 2 cm on mammography or ultrasound (P=0.02), age < 50 years (P=0.01), invasive lobular histology (P=0.01), and HER-2/neu protein amplification promoting breast gland growth (P=0.01) were associated with a higher likelihood of magnetic resonance imaging influencing eligibility for partial breast irradiation.

As reported by Poulakaki (2021), detection rates for occult breast cancers through magnetic resonance imaging vary between 43% and 86%. Combining this technique with other diagnostic resources offers an increased likelihood of identifying this type of carcinoma. The protocol-driven integration of magnetic resonance imaging and mammography has led to a higher rate of identification of clinically occult and non-palpable breast cancers in recent years (AHMED et al., 2015; GEGIOS et al., 2023).

Regarding magnetic resonance imaging, the study conducted by Dorn et al. (2013) started the prospective evaluation of the impact of this technique within a cohort of candidates undergoing partial breast irradiation. These candidates uniformly underwent magnetic resonance imaging examination combined with mammography and ultrasound. The investigation by Dorn et al. (2013) revealed that magnetic resonance imaging successfully detected clinically concealed disease foci in 12.9% of patients who met the

criteria for partial breast irradiation based on conventional imaging modalities. This observation concurs with previously reported retrospective findings, where magnetic resonance imaging identified additional disease in 10% of partial breast irradiation candidates, and with data from other researchers reporting detection rates ranging from 5.8% to 16%.

The role of magnetic resonance imaging in the preoperative staging of breast cancer patients has been extensively studied. In a systematic review, Houssami et al. (2008) found that magnetic resonance imaging identified multifocal or multicentric disease in an average of 16% of patients (range, 6%-34%). Other data revealed that initial magnetic resonance imaging does not improve outcomes in the context of whole-breast adjuvant radiotherapy. For patients without magnetic resonance imaging staging, the hypothesis is that undetected microscopic disease is eradicated with adjuvant radiation, thus reducing observed rates of local recurrence to only a fraction of the expected incidence of multicentricity or multifocality. However, magnetic resonance imaging studies in the setting of standard breast conservation therapy cannot be extrapolated to the partial breast irradiation population, in which patients may have different disease characteristics and would have additional foci of disease left untreated in the absence of whole-breast adjuvant radiotherapy (DORN et al., 2013).

In summary, the techniques employed for the detection of occult breast carcinoma exhibit effectiveness and have continued to evolve over time. The identification of supplementary disease manifestations in a substantial proportion of patients holds promise for reducing the occurrence of clinically occult foci within the breast. Furthermore, the confirmation of unifocal disease through diverse methodologies may empower healthcare practitioners to confidently administer more efficacious treatment regimens to patients, even those with characteristics traditionally associated with a poorer prognosis (Dorn et al., 2013).

A research conducted by Brem et al. (2016) examined a group of 849 women with one or more risk factors for breast cancer, including a personal or family history of breast cancer, atypical or high-risk breast biopsy, known genetic predisposition to breast cancer, and prior axillary or mediastinal radiation therapy. The use of Molecular Breast Imaging was evaluated. This technique is based on the detection of gamma radiation emitted by a radiopharmaceutical injected into the patient's bloodstream. The radiopharmaceutical is preferentially taken up by breast cells, allowing for the visualization of affected areas in the breast. Breast-specific gama-imaging is particularly effective in detecting very small lesions

(subcentimetre) and breast cancers that are not visible on conventional mammography, making it a valuable tool for early and precise breast cancer diagnosis. It exhibits sensitivity and specificity comparable to conventional magnetic resonance imaging, rendering it an important option in the array of diagnostic methods for breast diseases. Molecular Breast Imaging detected 14 mammographically occult cancers, resulting in a cancer detection rate of 16.5 per 1000 examined individuals. This elevated cancer detection rate can be attributed to a selection bias toward women who have additional risk factors for breast cancer beyond breast density alone. It is noteworthy that mammographic breast density did not affect the diagnostic performance of Molecular Breast Imaging, with 78.6% (11 out of 14) of mammographically occult cancers detected by Molecular Breast Imaging occurring in women with either heterogeneously dense or extremely dense breasts.

Rhodes et al. (2015) examined 1651 asymptomatic women with dense breasts through screening mammography and Breast-specific Gamma Imaging. They conducted a prospective supplemental screening study with Molecular Breast Imaging in women with dense breasts using an updated system designed for a lower radiation dose. The overall cancer detection rate (per 1000 screened) increased from 3.2 with mammography alone to 12.0 when both imaging modalities were combined (an increment of 8.8 per 1000 screened). These results reveal that the use of Molecular Breast Imaging as a complement to mammography is effective in detecting mammographically occult breast cancers (RHODES et al., 2016; BREM et al., 2015).

Molecular Breast Imaging-guided biopsy may offer a simplified, cost-effective, and more efficient strategy in managing patients with occult breast cancer, providing guidance for tumor localization (RHODES et al., 2015; BREM et al., 2016; SMITH et al., 2023, LOEVEZJIN et al., 2023).

A recent technology that is opening new frontiers in medical diagnosis can also useful in the diagnosis of occult breast cancer. Kim et al. (2022) reported the results of diagnosing occult breast cancer through artificial intelligence-assisted image analysis (AI-assisted diagnostics). Out of a total of 1890 breast cancer cases, 6.8% (128/1890) were imperceptible in mammography examinations by expert medical assessment. Among these 128 cases, 38.3% (49/128) yielded positive results in the AI analysis, of which 40 were confirmed through biopsy, resulting in an accuracy rate of 81.6% and an incremental diagnostic rate of occult cancers by 31.3% through computerized mammography image analysis. It is anticipated that with the augmentation of artificial intelligence systems with larger databases of mammography, ultrasound, and magnetic resonance images, cross-analysis of these data

for each patient will significantly enhance the detection rates of occult breast cancers through deep learning methods and machine learning guided by human expertise based on positive histopathology findings (BAUGHAN et al., 2022; AIZAZ et al., 2022; AVENDAÑO et al., 2023; ALSHARIF, 2023).

Combined therapies are promising (POULAKAKI, 2021; JESUS et al., 2023; GEGIOS et al., 2023) but demand treatment customization, may constitute a costly approach, and sometimes are unavailable at low resource setting health facilities. Preemptive resection of cancerous tissues can be executed; nevertheless, achieving precise tumor localization and complete tumor removal represents, in most instances, demands security margin in surgical interventions to avoid neoplasia recurrence. According to Yamauchi et al. (2018), out of 1527 patients who underwent mammography, 11.3% were diagnosed with occult breast cancer after histopathological examinations of the mastectomy removed tissue, even after receiving presumed negative results from magnetic resonance imaging. They suggested the requirement for histopathological examinations to lastly confirm negative diagnostics in patients with an established risk of mammary carcinoma. The surreptitious presentation of the disease demands a multimodal approach to enhance diagnostic confirmation with heightened certainty, thereby assisting healthcare professionals in determining the most suitable therapeutic intervention with minimized patient harm or risk, to the extent of the available clinical resources.

5. CONCLUSIONS

From the analysis of the most modern methods for detecting occult breast cancers, it can be concluded that such methods can be considered effective to varying degrees, but no method can be deemed entirely effective. Emerging current techniques show significant potential for improving clinical outcomes in patients with occult breast cancer. Detecting this pathology is hindered for various reasons, such as the small size of lesions, variations in breast density among some patients affecting the detectability in imaging studies, technical limitations of these methods, the variety of clinical presentations of the disease, and the imprecise, diffuse, or elusive localization of carcinoma cells. New device designs can help translate this approach to other cancer surgeries where margin assessment and image-guided resection are valuable. The ideal detection protocol is based on a combination of various methods for detecting occult breast cancer, but such a procedure requires personalized treatment, entails higher costs, and depends on the resources available at each

healthcare facility. It is envisaged that future clinical adoption will be based on safe and effective combinations of devices and contrast agents that can be easily integrated into the surgical workflow, meet user needs, and incur lower costs.

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