International Journal of Community Medicine and Public Health
Siddiqui M et al. Int J Community Med Public Health. 2023 Jan;10(1):480-485
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20223316

Review Article

An overview of inflammatory breast cancer

Mohammad Siddiqui[1]*, Mustafa Alsarhan[2], Faisal Almutairi[3], Ahmed Salman[4], Dhari Alroudan[5], Saleem Alotaibi[6], Abdullah Alomran[7], Taghreed Awaji[8], Sadaf Buarish[9], Raghad Aldahlawi[10], Nizar Wali[11], Malaz Siddiqui[12]

[1]Department of General Surgery, King Fahad General Hospital, Jeddah, Saudi Arabia
[2]College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia
[3]College of Medicine, Baha University, Medina, Saudi Arabia
[4]Royal College of Surgeons in Ireland, Medical University of Bahrain, Manama, Bahrain
[5]Department of Plastic Surgery, Jahra Hospital, Kuwait City, Kuwait
[6]Department of Orthopaedic, Farwaniya Hospital, Sabah Al Naasir, Kuwait
[7]Department of Urology, Prince Saud bin Jalawi Hospital, Al Ahsa, Saudi Arabia
[8]College of Medicine, Taif University, Taif, Saudi Arabia
[9]College of Medicine, Vision Colleges, Riyadh, Saudi Arabia
[10]College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia
[11]Department of Emergency Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia
[12]College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Received: 28 November 2022
Accepted: 12 December 2022

***Correspondence:**
Dr. Mohammad Siddiqui,
E-mail: saqib16@outlook.com

ABSTRACT

Inflammatory breast cancer is an uncommon and severe malignancy that frequently goes undiagnosed at first because it presents similarly to more benign breast diseases like mastitis, resulting in delayed treatment. Inflammatory breast cancer affects 1% to 5% of all occurrences of breast cancer and accounts for 8% to 10% of all breast cancer-related deaths. Erythema, skin abnormalities, nipple inversion, edema, and warmth of the affected breast are all signs of inflammatory breast cancer. Recognized risk factors for inflammatory breast cancer include young age at the time of diagnosis, obesity and African American ethnicity. Rapid onset within 3 months and pathologic evidence of invasive carcinoma leads to diagnosis of disease further including erythema occupying at least one-third of the breast, tumour may or may not be present in this case. Chemotherapy, surgery, and radiation make up the trimodal therapy used to treat inflammatory breast cancer. A modified radical mastectomy performed as part of an aggressive surgical strategy improves survival rates. Although patients with inflammatory breast cancer have worse outcomes than those with noninflammatory breast cancer, those who complete trimodal therapy have a positive locoregional control rate, highlighting the significance of an early diagnosis. Physicians must be aware and examine any clinical manifestation of inflammatory breast cancer if present to make a prompt diagnosis and refer patient for expert care timely also awareness and cancer screening can help in prevention of disease. The purpose of this research is to review the available information about an overview of inflammatory breast cancer.

Keywords: Inflammatory, Breast, Cancer, Disease

INTRODUCTION

Inflammatory breast cancer (IBC) is a rare subtype of locally progressed breast cancer as per the tumor-node-metastasis breast cancer staging classification. IBC is categorized as T4d and is clinically distinguished by diffuse skin lesions with an erysipeloid margin, typically without an underlying mass.[1] IBC affects 1% to 5% of all

occurrences of breast cancer and accounts for 8% to 10% of all breast cancer-related deaths. IBC has a very distinctive clinical appearance when compared to other cancers. IBC is defined by a lower median progression-free survival and overall survival time than reported in non-IBC cases, and it is at least stage III at the time of diagnosis. As per recent statistical estimates, the incidence of IBC increased from 2.0 to 2.5 per 100,000 woman-years. In contrast, over the same time period, the prevalence of non-inflammatory breast cancer decreased. Regardless of the molecular subtype, the prognosis for inflammatory breast cancer is poor, with triple-negative IBC patients having the worst results and a 10-year overall survival rate of just 17.8%.[2] In 1814, Sir Charles Bell presented the first characterization of IBC in the scientific literature. The terms primary IBC and true IBC were developed in 1938 to distinguish IBC from secondary IBC, which was described as secondary changes in the breast caused by locally progressed, non-inflammatory breast cancer or breast cancer recurrence. In current clinical practice, skin changes linked to a neglected non-inflammatory breast tumour and skin changes related with IBC are routinely distinguished. As a result, the term secondary IBC now refers to a recurrence in a patient with a prior history of non-inflammatory breast cancer that is presented with clinical signs like erythema, edema, or skin abnormalities in the breast.[3]

IBC diagnostic criteria are predicated on a rapid onset of diffuse erythema and edema also referred as peau d'orange affecting at least one-third of the breast surface, whether or not there is a palpable tumour beneath. The skin changes can be the result of lymphedema caused by tumour emboli in dermal lymphatics, which may or may not be present in biopsy specimens. Despite being a defining feature of IBC, tumour emboli are only present in about 75% of patients that have been diagnosed with the disease.[4] Neoadjuvant systemic chemotherapy, surgery, radiation, and hormonal therapy are all components of the multidisciplinary management of IBC. Compared to local modalities alone, induction chemotherapy with anthracyclines and taxanes substantially benefit the prognosis and local control of patients with IBC. The development of targeted medicines including trastuzumab and lapatinib which are altering the course of this aggressive disease is made possible by advances in understanding of the basic characteristics of the illness.[5] The purpose of this research is to review the available information about an overview of IBC.

METHODS

This study is based on a comprehensive literature search conducted on 24 October 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about an overview of IBC. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

IBC is a rare and severe kind of invasive breast cancer that is distinguished from other breast cancers by its swift progression, local and distant metastases, earlier age of occurrence, and lower overall survival rates.[6] IBC incidence is noteworthy since it is steadily increasing and accounts for up approximately 10% of all breast cancer-related fatalities while having a dismal prognosis. The detection of dermal-lymphatic intrusion in a skin biopsy is often frequent although it is not necessary for the diagnosis. IBC tumours display a unique dispersion of clinical subtypes in comparison to non-IBC tumours, with hormone receptor-positive tumours which account for 30% of IBC versus 65-70% of non-IBC and triple-negative breast cancer which accounts for 30% of IBC versus 15% of non-IBC being the most prevalent subtypes. IBC patients have access to a vast array of anti-human epidermal growth factor receptor-2 therapeutic options owing to the trastuzumab deruxtecan, which has successfully revealed extraordinary efficacy in human epidermal growth factor receptor-2 positive metastatic breast cancer.[7]

Clinical picture, manifestations and diagnosis

Clinical signs of IBC include fast progress of breast tenderness, redness, and edema skin changes such as peau d'orange, frequently without a clearly defined mass. Women with IBC often have early involvement of the axillary lymph nodes in addition to significant breast involvement. The breast becomes diffusely reddened, ranging in intensity from a little blush to a fiery red, and it also becomes hot, pitted, and edematous, giving it an orange-skin appearance. Meanwhile, a widespread, poorly defined induration which represents the cancer spreads rapidly throughout the entire breast. Within a few weeks, the breast may grow to two or three times its initial volume. True primary inflammatory carcinomas can be distinguished from neglected locally advanced breast cancers that exhibit inflammatory signs in case of secondary inflammatory carcinomas based on their rate of progression. Less than half of IBCs will emerge as a distinguishable mass on a mammogram, which sets them apart from other breast tumours. However, the majority of patients also have other aberrant findings such axillary adenopathy, trabecular thickening, and thickening of the skin.[8] Clinical characteristics of IBC are depicted in (Figure 1).

The differential diagnoses for breast inflammation can be divided into benign conditions and various cancers. Up to 10% of nursing mothers get lactation mastitis, which can be distinguished from IBC by its localized discomfort, fever, and leukocytosis. Over a few days, mastitis

progressively progresses. The patient feels sick, and the erythema covers a wedge-shaped area of the breast that is painful and erythematous. Additionally, the benign conditions Mondor disease and fat necrosis might be mistaken for IBC. Phlebitis of the thoracoepigastric vein, also known as Mondor disease, typically manifests as a painful, perhaps palpable chord and is typically caused by trauma. Leukemic infiltration of the breast is one of the malignant conditions that resembles IBC. A peripheral blood smear typically confirms this uncommon diagnosis in these patients, who are typically suffering from systemic illness.[9] Conditions that are taken into account when determining an IBC differential diagnosis include misdiagnosis of IBC as bacterial infection which includes mastitis and abscess, is prevalent. These infections are uncommon in nursing women, and IBC is uncommon in young women of childbearing age; it is more prevalent in women 50 to 55 years old. Older women can develop duct ectasia; a non-lactational chronic breast abscess, but in most cases the erythema is well-contained and affects only a portion of the breast. Leukemia, sarcoma, and in particular primary non-Hodgkin lymphoma can all resemble some or all of the clinical indications of IBC, but they can all be ruled out cytologically. Another cause of erythema, post-radiation dermatitis, is restricted to the area around the radiation port and is sharply delineated as opposed to having the diffuse appearance of IBC. It can also be identified by the way it develops over time, typically starting 2 to 3 weeks following the start of radiation therapy.[10]

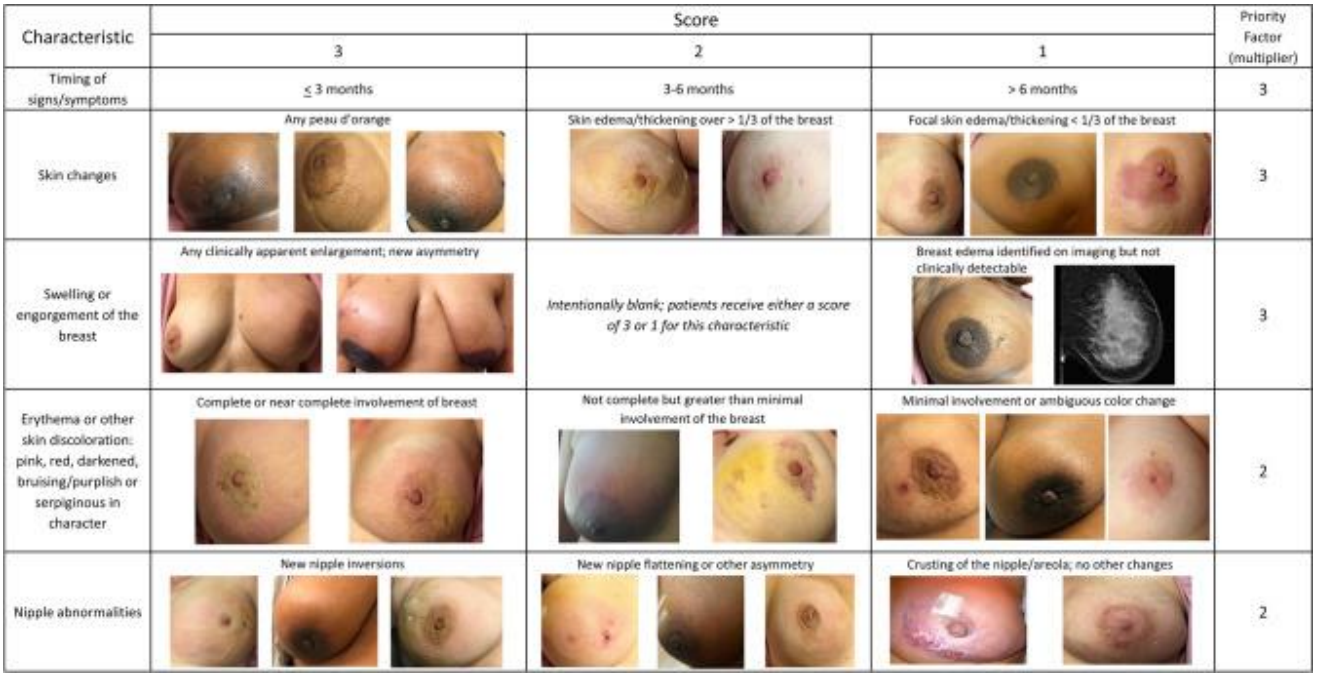

Figure 1: Clinical characteristics of IBC.[11]

The rapid onset of signs and symptoms within a 6-month period preceding to the identification of an invasive disease is the distinguishing feature of IBC. IBC is distinguished from non-inflammatory locally advanced breast cancer, which results from a more indolent subtype of invasive breast cancer and is sometimes overlooked for years, by the quick development of clinical symptoms. It should be noted that IBC should still be diagnosed if signs and symptoms develop within 6 months although a pathologic diagnosis of cancer is not made until 6 months later. The time of the symptoms' start is crucial. On mammography, IBC frequently appears as diffusely increased breast density, however on magnetic resonance imaging, same changes are described as extensive non-mass-like enhancement. Breast imaging in IBC instances should, in general, show more diffuse involvement, showing disease evidence beyond a localized mass.[11] At the time of diagnosis, almost all women exhibit lymph node involvement, and 36% have gross distant metastases. The prognosis for individuals with IBC is poor, with a median disease-free survival of fewer than 2.5 years, despite recent improvements in multimodality therapy.[12]

Clinically, IBC resembles a benign bacterial infection of the skin or breast, such as cellulitis, abscess, or mastitis. On physical examination, no signs of breast tumors or lumps are often found. The most common reason for misdiagnosis and treatment delay is treating IBC as an infection with antibiotics.[13]

The development of dermal lymphatic invasion with multiple dilated dermal lymphatic vessels loaded with tiny tumour emboli is the hallmark histological finding in IBC. This invasion is frequently localized in the papillary and reticular dermis of the skin overlaying the breast. However, cutaneous tumour emboli are not a required diagnostic criterion because only 75% of individuals with IBC-like clinical features have them. High-grade tumour

cells with a ductal character frequently form emboli. The IBC tumour may or may not form a distinct mass, making it challenging to determine the tumour's size in many instances. Additionally, there is only a limited correlation between the size, quantity, and clinical degree of inflammatory skin involvement of the emboli. High echogenicity of the breast tissue, the presence of a lump or tumor, and dilated lymphatic vessels are all frequently seen on ultrasound. These abnormalities are occasionally linked to abnormal lymph nodes in the neck and axilla. IBC frequently makes an appearance as skin changes rather than a clear mass. As a result, a skin punch biopsy is frequently employed to aid in the diagnosis.[14] Histological diagnosis of IBC is represented in (Figure 2).[15] There are no recognized risk factors for IBC at present time. Although, the investigated characteristics of IBC are clarified by numerous epidemiological research studies which include black race, high body mass index, age, and region as the most significant suspected risk factors linked to this disease.[16]

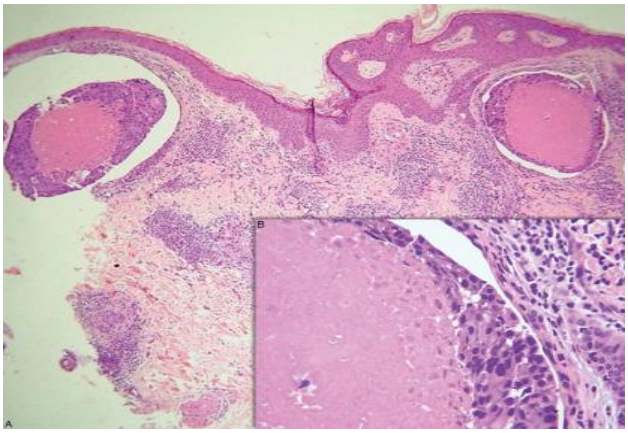

Figure 2: Histological diagnosis of IBC.[15]

Lymph node involvement

On clinical examination, metastases to the axillary or supraclavicular lymph nodes may be visible in 55% to 85% of patients. Fixed ipsilateral axillary nodes are a frequent finding in practice. Similar to non-inflammatory breast cancer, the existence of lymph node involvement is crucial information for disease stage and offers crucial prognostic data.[10] Wecsler et al described in their study that breast cancers that have positive lymph node status typically have worse prognoses than negative nodes. Nodal metastases was present in about 80% of IBC patients, which is indicative of the disease's aggressive nature. When compared to lymph node-negative and ER/PR-positive individuals, those with positive lymph nodes and ER/PR-negative tumors had lower overall survival.[17] Accurate analysis of the lymph node locations, including the axillary, supra- and sub-clavicular, or parasternal nodes, is vital piece of information that ultrasonography may provide. In 93% of cases, ultrasound appears to show axillary node involvement, an increase in node volume, a highly hypoechoic look, and the loss of fatty hilum, and in 50% of cases, it appears that the other locations listed are also involved. In contrast to clinical examination, which is believed to only detect lymph node involvement in 68% of instances, ultrasound is undoubtedly more sensitive.[18]

Management and treatment

In the last three decades, the multidisciplinary management of IBC has evolved and is now clearly established in order, with preoperative or neoadjuvant chemotherapy serving as the cornerstone of care. The most efficient cytotoxic drugs for treating initial breast cancer are anthracyclines and taxanes, which ought to be the norm for women with IBC. After receiving the necessary medical care, localized treatment, such as radiotherapy with or without surgery, continues to be important. Numerous studies into the specific molecular factors that influence IBC development have led to the discovery of several intriguing novel treatment targets. Combination treatments for IBC that contain p53 inhibitors, farnesyl transferase inhibitors, and angiogenic modulators show promising results.[19] Neoadjuvant chemotherapy based on doxorubicin was first used to treat IBC in the 1970s. Neoadjuvant chemotherapy followed by surgery and radiation therapy was shown to be effective in prospective trials. The treatment of IBC with neoadjuvant taxane-containing regimens was then examined, and the results demonstrated that taxanes mixed with anthracyclines resulted in a better response. Today, it is generally accepted that patients with IBC who were diagnosed without signs of distant metastases should receive systemic chemotherapy, surgery, and radiation therapy. Trastuzumab is recommended for those with human epidermal growth factor receptor 2+ illness.[3]

Singletary suggested in his study that for patients with IBC, multimodality therapy that combines radiotherapy, mastectomy, and main chemotherapy tends to provide the best results. The greatest candidates for surgery are those who respond well to chemotherapy; if this is not the case, radiation should be started before surgery. In order to ensure negative margins, the surgical field must be sufficiently large to include any secondary skin alterations. Patients with IBC should not undergo sentinel lymph node biopsy or breast conserving surgery. Breast reconstruction after mastectomy is not medically contraindicated, although most physicians prefer to wait until radiotherapy is finished before trying this additional surgery.[20] Neoadjuvant therapy today refers to a combination of chemotherapy, endocrine therapy, and targeted therapy. Initially, it was referred to as systemic chemotherapy for inflammatory or locally progressed breast cancer. Neoadjuvant systemic therapy is used for patients with operable breast cancer who want breast-conserving treatment but are ineligible for it due to the initial size of the tumor in relation to the size of the breast, as well as for patients with locally advanced and inoperable IBC. The surgical options in this group of patients may be impacted by neoadjuvant therapy.[21]

Bristol and Buchhloz described in their study that local management has become an essential part of the curative management of these patients since survival for those with IBC has increased with the addition and regular use of doxorubicin-based chemotherapy. Local control rates for patients with IBC have significantly increased during the past 20 years. Adjuvant chemotherapy given after a mastectomy and adjuvant chemotherapy given after accelerated hyper fractionated radiation to 66 Gy have been used to treat a disease that previously had local control rates of less than 50% and now has rates of 70–80%. The 5-year local control rates in patients whose illness responds to treatment are significantly greater. Survival has improved as a result of these gains in local control.[22] Numerous clinical studies have demonstrated that neoadjuvant chemotherapy with targeted therapy increases the pathological complete response rate for breast cancer. Due to the rarity of IBC, patients with IBC were not excluded from any of the randomized clinical trials examining the effectiveness of combining targeted therapy with neoadjuvant chemotherapy.[23] In future clinical trials are needed to assess the efficacy of various treatment options available for IBC also further research can be beneficial in development of new treatment modalities. Breast cancer screening practice shall be encouraged in women as it can successfully prevent IBC and other form of breast cancer.

CONCLUSION

IBC is associated with high mortality and poor prognosis despite being a rare entity hence early diagnosis and prompt management is essential. Health promotion and education activities regarding the IBC risk factors is need of time since awareness of risk factors and routine cancer screening can significantly help in prevention of disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Sobin LH, Compton CC. TNM seventh edition: What's new, what's changed. Cancer. 2010;116(22):5336-9.
2. Hester RH, Hortobagyi GN, Lim B. Inflammatory breast cancer: early recognition and diagnosis is critical. Am J Obstet Gynecol. 2021;225(4):392-6.
3. Yamauchi H, Woodward WA, Valero V, Alvarez RH, Lucci A, Buchholz TA, et al. Inflammatory breast cancer: what we know and what we need to learn. The Oncologist. 2012;17(7):891-9.
4. Chainitikun S, Saleem S, Lim B, Valero V, Ueno NT. Update on systemic treatment for newly diagnosed inflammatory breast cancer. J Adv Res. 2021;29:1-12.
5. Dawood S, Ueno NT, Cristofanilli M. The medical treatment of inflammatory breast cancer. Semin Oncol. 2008;35(1):64-71.
6. Robertson FM, Bondy M, Yang W, Yamauchi H, Wiggins S, Kamrudin S, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin. 2010;60(6):351-75.
7. Tarantino P, Niman SM, Erick TK, Priedigkeit N, Harrison BT, Giordano A, et al. HER2-low inflammatory breast cancer: Clinicopathologic features and prognostic implications. Eur J Cancer. 2022;174:277-86.
8. Giordano SH, Hortobagyi GN. Inflammatory breast cancer: clinical progress and the main problems that must be addressed. Breast Cancer Res. 2003;5(6):284-8.
9. Molckovsky A, Fitzgerald B, Freedman O, Heisey R, Clemons M. Approach to inflammatory breast cancer. Can Fam Physician. 2009;55(1):25-31.
10. Singletary SE, Cristofanilli M. Defining the clinical diagnosis of inflammatory breast cancer. Semin Oncol. 2008;35(1):7-10.
11. Jagsi R, Mason G, Overmoyer BA, Woodward WA, Badve S, Schneider RJ, et al. Komen-IBCRF IBC Collaborative in partnership with the Milburn Foundation. Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. Breast Cancer Res Treat. 2022;192(2):235-43.
12. Kleer CG, van Golen KL, Merajver SD. Molecular biology of breast cancer metastasis. Inflammatory breast cancer: clinical syndrome and molecular determinants. Breast Cancer Res. 2000;2(6):423-9.
13. Yaghoobi R, Talaizade A, Lal K, Ranjbari N, Sohrabiaan N, Feily A. Inflammatory Breast Carcinoma Presenting with Two Different Patterns of Cutaneous Metastases: Carcinoma Telangiectaticum and Carcinoma Erysipeloides. J Clin Aesth Dermatol. 2015;8(8):47-51.
14. Mele M, Sørensen AS, Bruun J, Funder JA, Tramm T, Bodilsen A, et al. Inflammatory breast cancer: A review from our experience. Breast Dis. 2019;38(2):47-55.
15. Vallone MG, Casas JG, González VM, Larralde M. Dermoscopy of inflammatory breast cancer. Anais Brasileiros de Dermatologia. 2018;93(2):289-90.
16. Mamouch F, Berrada N, Aoullay Z, El Khanoussi B, Errihani H. Inflammatory Breast Cancer: A Literature Review. World J Oncol. 2018;9(5-6):129-35.
17. Wecsler JS, Tereffe W, Pedersen RC, Sieffert MR, Mack WJ, Cui H, et al. Lymph node status in inflammatory breast cancer. Breast Cancer Res Treatment. 2015;151(1):113-20.
18. Alunni JP. Imaging inflammatory breast cancer. Diagnostic and interventional imaging. 2012;93(2):95-103.
19. Cristofanilli M, Buzdar AU, Hortobágyi GN. Update on the management of inflammatory breast cancer. The Oncologist. 2003;8(2):141-8.
20. Singletary SE. Surgical management of inflammatory breast cancer. Semin Oncol. 2008;35(1):72-7.

21. Liu SV, Melstrom L, Yao K, Russell CA, Sener SF. Neoadjuvant therapy for breast cancer. J Surg Oncol. 2010;101(4):283-91.
22. Bristol IJ, Buchholz TA. Inflammatory breast cancer: current concepts in local management. Breast Dis. 2005;22:75-83.
23. Chainitikun S, Espinosa Fernandez JR, Long JP. Pathological complete response of adding targeted therapy to neoadjuvant chemotherapy for inflammatory breast cancer: A systematic review. PloS One. 2021;16(4):e0250057.

Cite this article as: Siddiqui M, Alsarhan M, Almutairi F, Salman A, Alroudan D, Alotaibi S, et al. An overview of inflammatory breast cancer. Int J Community Med Public Health 2023;10:480-5.