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Therapeutic strategies for fungating and ulcerating breast cancers: A systematic review and narrative synthesis

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ABSTRACT

Background: To identify optimal therapeutic strategies for managing fungating, large or ulcerating breast tumors and highlight existing gaps in the literature.
Methods: We conducted a systematic search of Medline, Embase, APA, PsycInfo, CAB abstracts, Scopus, and Web of Science from inception to June 30, 2024, including studies on patients with fungating, large, or ulcerating breast cancers.
Results: The search identified 7917 studies, with 79 meeting the inclusion criteria: 62 case reports, 7 case series, and 10 cohort studies. Owing to high heterogeneity, a narrative synthesis was performed, categorizing treatment by year, molecular subtype, histology, and staging. We found that treatment modalities increased, from an average of two in luminal-B cancers to three in HER2-positive cases, with over half achieving complete response. Triple-negative breast cancers averaged two modalities, with around half showing only partial response. Cohort analysis revealed a significant positive correlation between metastasis rate and radiotherapy use (Spearman's rho = 0.828, p = 0.042) and between chemotherapy and hormonal therapy use (rho = 0.69, p = 0.04). Median survival was positively correlated with surgical treatment (rho = 0.82, p = 0.046).
Conclusions: Local treatment is crucial for symptomatic palliation in fungating or ulcerating breast tumors, and histology should guide therapeutic choices. While local treatments remain primary, emerging systemic therapies show promise and may soon become first-line options. As the first systematic review on this topic, our study faced considerable source heterogeneity, precluding a meta-analysis. Instead, we analyzed treatment trends by demographics and tumor characteristics, providing a comprehensive overview and encouraging further research in this area.

1. Introduction

Fungating, large, or ulcerating breast wounds are a rare condition that occurs as an advanced and distressing consequence of breast cancer [1]. The occurrence of locally advanced disease (LABC), classified as AJCC Stage III as per the US National Comprehensive Cancer Network [2], is likely due to delays in breast cancer diagnosis, such as challenges in accessing outpatient care that were observed during the COVID-19 pandemic [3]. Additionally, healthcare delays may also be attributable to patients' psychological unwillingness to accept their condition, low socioeconomic levels, social isolation, male gender, or elderly age [4]. This means that LABC can occur not only in developing countries but also in developed ones.

The occurrence of LABC in the fungating or ulcerated form, here on referred to as "locally disfiguring breast cancer", is a source of severe distress to patients owing to uncontrollable bleeding, recurring infections, foul smell, chronic pain, or aesthetic concerns [5]. Not only the primary tumor, but recurrences in the form of skin metastases can exhibit ulcerated and fungating features as well.

Therefore, given the limited life expectancy of these patients, the primary goal of fungating wound management is generally palliative, aiming to minimize symptoms and optimize the quality of life (QoL) rather than completely eradicate the disease, especially when neoadjuvant systemic therapies (such as chemotherapy or hormonal

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therapy) fail in the objective of shrinking the tumor mass. In such cases, surgical procedures (e.g. radical or modified mastectomy) can be performed unless impeded by underlying frailty and multiple comorbidities, or due to technical infeasibility (e.g. given the tumor size and location or the impossibility of achieving adequate margins) [6]: namely, cases in which surgical harm may outweigh the potential benefits.

As an alternative to surgical treatment, palliative radiation therapy (e.g. 30 Gy in 10 fractions, 20 Gy in 4 or 5 fractions) may be administered with the goal of providing adequate palliation of symptoms, even in patients in poor general health [7]. Furthermore, in some instances, it is possible to achieve tumor debulking, especially when employing novel radiotherapy (RT) techniques such as LATTICE radiation therapy (LRT) [8], which is a type of RT that allows the delivery of high doses to selected areas without increasing the toxicity to surrounding organs at risk [9].

In this regard, transarterial chemoembolization (TACE) has also emerged as a useful tool to control severe hemorrhage in patients who are not candidates for surgery, though patients report significant pain after the procedure [10], casting doubts over its suitability as an alternate option.

Finally, to effectively care for these patients, it is crucial to educate both patients and their caregivers on managing fungating or ulcerating wounds (e.g., accurate debridement, wound cleansing, and dressing changes) [11].

While the emergence of newer treatments such as LRT and TACE have added to the armamentarium of available therapeutic options, the decision of which treatment to use is still individualized to each patient, and there is no consensus or formal guidelines making treatment recommendations for this patient group. In order to address this gap, we performed a systematic review and narrative synthesis on the treatment of advanced fungating and ulcerating breast cancers in the literature to (i) identify strategies being chosen for optimum treatment of these tumors (ii) and highlight literature gaps.

Specifically, the objectives of this review were.

1. To review the treatment options for fungating and ulcerating breast cancers that are currently described in the literature.
2. To assess the demographic, clinical, pathological, and immunohistochemical features that determine treatment selection.

2. Methods

The systematic review and narrative synthesis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The review was also prospectively registered on Prospero (CRD42023438528).

2.1. Search strategy

The following electronic databases were systematically searched for results from inception until June 30, 2024: Medline (via Ovid), Embase, APA, PsycInfo, CAB abstracts, Scopus, and Web of Science. The search and data collection period was conducted between July 1, 2024 and August 31, 2024, given the large volume of initial records retrieved. Only human studies in the English language were included. The search results were imported into Endnote for de-duplication, and later imported into Covidence for title-abstract and full-text screening. The search string included the combination of terms breast cancer, fungating, ulcerating, management and their synonyms separated by Boolean operators. The detailed search strategy is provided in the supplementary material.

2.2. Study selection

The title-abstract and full-text screening was performed independently by two reviewers (MH and VZ), and any differences were resolved by a third (GF). The following inclusion and exclusion criteria were used: Studies were included if they were 1. Randomized controlled trials, cohort studies, case-control studies, case reports, and case series; 2. Including patients with advanced breast cancers that were fungating, ulcerating, or bleeding (malignant wound); 3. Included tumor stages IIIB, IIIC, and IV (AJCC 8th edition); 4. Involved any tumor histology 5. Included adult patients (>/18 years); 6. Studied outcomes including survival, treatment-related toxicity, recurrence, and quality of life measures.

The exclusion criteria were as follows: 1. Non-human studies; 2. Non-English studies; 3. Systematic reviews, editorials, commentaries, protocols, book chapters; 4. Pediatric patients (<18 years); 5. Studies reporting only molecular or other biological outcomes, without reporting clinical outcomes; 6. Inflammatory breast cancers; 7. Ulceration in the breast secondary to biopsy procedures, radiotherapy, or infection; 8. Stage IIIA and below.

2.3. Data extraction

The data was extracted into a data extraction form on Excel, containing the following variables: study details (author, year, setting, design), patient inclusion and demographics (inclusion and exclusion criteria, mean patient age, patient sex), tumor details (primary/recurrent, baseline functional status, symptoms, mean size, tumor characteristics - bleeding/fungating/ulcerating, presence of metastasis, tumor histology, TNM status, hormone receptor status), treatment details (treatment intent - palliative/locoregional/systemic, treatment details of surgery, chemotherapy, radiotherapy, hormonal therapy, immunotherapy, targeted therapy), and outcomes (tumor response, recurrence, treatment-related complications, length of follow-up, median survival, and quality of life).

2.4. Data synthesis and analysis

The studies were categorized as case reports/series and cohort studies. The case reports were clustered as per molecular subtype, histology, stage, and intervention type, and the corresponding outcomes were tabulated. In case reports, it was possible to assess treatments in the form of combinations, whereas in cohort studies, owing to limitations in the reported data, the proportion of patients who underwent each treatment modality was analyzed. Spearman's correlation tests were performed to look for correlations between the proportion of people who underwent certain treatments vs. the year of study publication, treatment intent (palliative vs. curative), primary vs. recurrent tumor, and presence of metastases.

The supportive treatments provided for symptomatic control were also collated and analyzed separately.

3. Results

A total of 7917 studies were identified from various databases. After 1105 duplicates were identified and removed, 6812 studies were included in the title and abstract screening step and 348 studies were moved to the full-text screening stage. After exclusion, a total of 79 studies were finally included, comprising 62 case reports, 7 case series, and 10 cohort studies. The PRISMA flowchart is depicted in Fig. 1.

In this systematic review, case reports and case series were also included so as to increase the search yield, but were analyzed separately from cohort studies given the greater granularity of data available.

4. Case reports

A total of 62 case reports (62 patients) and 7 case series (30 patients) were included as per the selection criteria. Results of both groups of patients are described further (92 patients). The mean age of the 92

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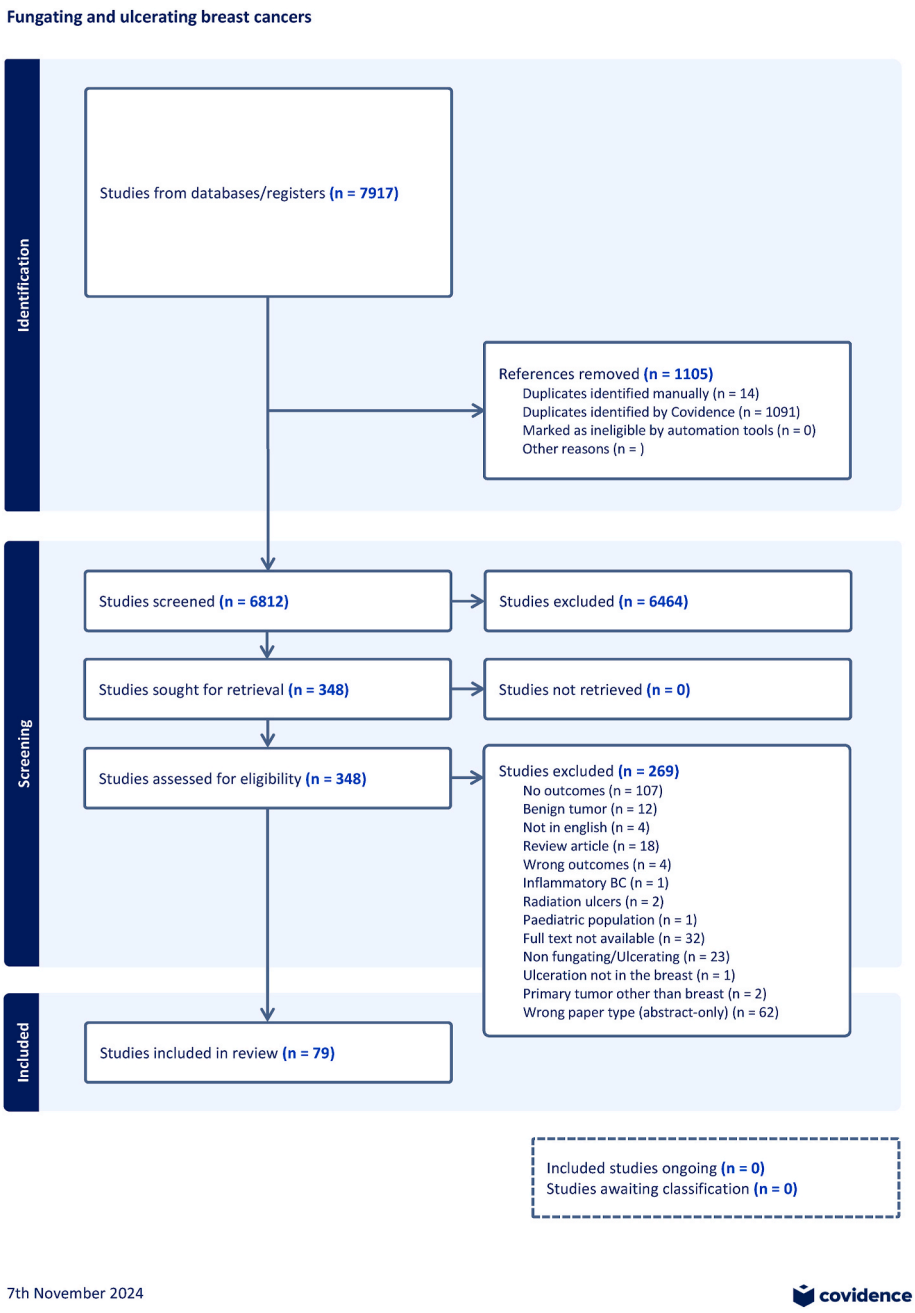

Figure 1. Fungating and ulcerating breast cancers.

patients included was 54.8 years, and 84/90 (93.33 %) patients were women, 6 (6.66 %) were men, and in 2 cases the patient sex was not reported. Baseline functional status was reported in only 14/92 (15.21 %) patients: 7 patients were reported to have a median ECOG status of 0, and 7 patients were reported to have a median WHO grade of 2. The tumor was primary in 54/71 (76.05 %) patients, recurrent in 17/71 (23.94 %) patients, and not reported in 21 (22.82 %) patients. The mean duration of tumor was 12.14 (1–72) months, reported in 50/92 cases (54.34 %). The presence of metastases was reported in 66 cases: 28 (30.43 %) patients had metastases and 38 (41.3 %) did not. Tumor histology was reported in 54/92 cases, with invasive ductal carcinoma being the most common histological subtype (Table 1).

4.1. Treatment details

Of the 92 case reports studied, 20/92 (21.73 %) of patients were treated with a palliative intent while 29/92 (31.52 %) were treated with a curative intent. About 44/92 (47.82 %) of patients underwent surgical tumor resection - which included total/modified radical mastectomy or palliative/tumor debulking procedures, and 26 did not undergo any surgical procedure; the history of surgical resection was not reported in 22 patients.

Chemotherapy use was not reported in 20, not done in 27, and done but no further details were available in 1 patient. Among those in whom details were available, chemotherapy was adjuvant in 18, neoadjuvant in 7, palliative in 11, and adjuvant/neoadjuvant in 8 cases.

As for the use of radiotherapy, RT use was not reported in 6 patients, not undergone by 34 patients, and undergone but type was not known in 7. Among those with details available, RT was definitive in 19, adjuvant in 10, palliative in 13, and neoadjuvant in 3. Similarly, the use of hormonal therapy (HT) was not reported in 13, and not used in 61 patients. Where details were available, HT was adjuvant in 9, neoadjuvant in 1,

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Table 1
Details of patient demographics, tumor features, and treatments as per included case reports and series. Data are reported as number (%) or mean (range). Abbreviations: IDC: infiltrating ductal carcinoma, TNBC: triple-negative breast carcinoma, mo: months.

Variable	No. reported (out of 92 patients)	Count (%) or Mean (range)
Age (y)	48 (52.17 %)	54.8 (28–91)
90 (97.82 %)		
Female		84 (93.33 %)
Male		6 (6.66 %)
Baseline Functional Status	16 (17.39 %)	ECOG 0: 3 ECOG 0–1: 1 ECOG 1: 2 ECOG 2: 1 WHO 1: 1 WHO 2: 4 WHO 3: 2 PS4: 1 KPS 60 %: 1
Tumor presentation	71 (77.17 %)	
Primary		54 (76.05 %)
Recurrent		17 (23.94 %)
Tumor duration (mo)	50 (54.34 %)	12.14 (1–72)
Tumor size	57 (61.96 %)	
Tumor histology	54 (58.7 %)	IDC (19) Phyllodes tumor (15) Mucinous carcinoma (5) Adenocarcinoma (4) Others: Plasmacytoma (1) Malignant fibrous histiocytoma (1) Osteosarcoma (1) Angiosarcoma (1) Infiltrating carcinoma (1) Epithelial metaplastic carcinoma (1) Stromal sarcoma (1) Medullary carcinoma (1) Mixoid colloid carcinoma (1) Pleomorphic sarcoma (1) Sarcoma + IDC (1)
Presence of metastases	66 (71.74 %)	Yes: 28 No: 38

palliative in 6, and performed without type known in 2. The other treatments utilized included TACE (3), intra-arterial chemotherapy (6), electrochemotherapy (1), imiquimod (1), and hyperthermia (4); not done or reported in 76 patients.

4.2. Number of treatments

The treatments were categorized by the molecular subtype, and on visual inspection, we found that the number of modalities used increased from an average of two in patients with luminal-B therapies to an average of three in patients with HER2-positive cancers. More than half of these tumors showed complete response. Meanwhile, TNBC tumors were treated with an average of two treatment combinations, with around half of the tumors showing only a partial response.

Table 2 schematically depicts the patterns of treatment combinations provided for patients with fungating or ulcerating cancers, classified according to the histology, tumor molecular subtype, and staging.

5. Cohort analysis

A total of 10 cohort studies (340 patients) were included as per the inclusion criteria (Tables 3a and 3b). The majority of studies were single-center retrospective studies (8/10, 80 %), with one analyzing both retrospective and prospective data, and one being prospective. All studies included patients with advanced primary or recurrent breast cancer with skin involvement. In cases where not all patients had skin symptoms in the study, only those with fungating/ulcerating lesions among the entire cohort were included in the analysis.

The sex of the patients was reported in only 4 studies, with a predominance of female patients (326/340, 95.88 %). The tumor was primary in 2 studies, primary or recurrent in 2 studies, recurrent in 4 studies and not reported in 2 studies. The median tumor size was reported only in 3 studies as follows: 5.5 cm, 7.6 cm and 6.5 cm, respectively. Tumor histology was reported in 5 studies, with infiltrative ductal carcinoma being the most common subtype. Regarding hormone receptor status, in the seven studies in which it was reported, the range of patients reported to be triple-negative ranged from 32 to 46 % of the study cohort.

Owing to lack of availability of individual patient-level data, the proportion of patients who underwent each treatment modality was extracted from each study and used for correlation analysis.

5.1. Determinants of treatment selection

Only 3/10 (30 %) studies reported the baseline ECOG status and TNM status, making it difficult to interpret the role of these factors in treatment selection. Furthermore, 6/10 (60 %) of studies reported the tumor histology, and 5/10 (50 %) studies reported history of metastasis.

5.2. Chronological trends

Among the cohort studies included in the analysis, Spearman's correlation looking for trends between the year of study publication and the proportion of patients who underwent surgery, radiotherapy, chemotherapy, targeted therapy, and hormonal therapy revealed that with each passing year, the proportion of patients who underwent radiotherapy and targeted therapy increased significantly (Spearman's rho = 0.67, $p = 0.045$ for radiotherapy and rho = 0.768, $p = 0.026$ for targeted therapy). Similarly, the proportion of those undergoing chemotherapy was found to fall, albeit non-significantly.

5.3. Factors influencing selection of treatment modality

When looking for non-parametric correlations between the proportion of patients who underwent a certain treatment and their clinical features, it was found that a higher proportion of metastases in the cohort was positively correlated (Spearman's rho = 0.828) with the use of radiotherapy ($p = 0.042$). In studies in which a higher proportion of patients underwent chemotherapy, patients were also more likely to undergo hormonal therapy (rho = 0.69, $p = 0.04$), indicating that these two treatment modalities were used frequently in combination with each other.

Median survival was also significantly positively correlated with use of surgery as a treatment modality (rho = 0.82, $p = 0.046$). No other statistically significant correlations were found.

6. Discussion

Patients with fungating tumors represent a particularly challenging cohort due to the complexities of managing tumor-associated symptoms such as pain, exudate, malodor, bleeding, infections, and aesthetic distress. Consequently, individuals with advanced fungating and/or ulcerated breast tumors experience a significant deterioration in their quality of life (QoL) [7].

This condition may be related to healthcare delays, which can also be attributed to patients' psychological reluctance to accept their condition, advanced age, and male gender [4]. Diagnostic delays can also be linked to the fear of accessing the healthcare system or the suspension of breast screening programs, as occurred during the COVID-19 pandemic

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[12]. During the epidemic, especially at the beginning, to minimize the risk of infection, patients were advised to temporarily suspend their screening schedules and to seek hospital care only when absolutely necessary. Both the fear and the slowdown in diagnostic procedures led to diagnostic delays, resulting in a higher incidence of advanced-stage tumors in the subsequent years [13]. Similarly, Mentrasti et al.

Table 2
Details of treatments for case reports and series. Abbreviations: IDC: infiltrating ductal carcinoma, TNBC: triple negative breast carcinoma, CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease, RT: radiotherapy, MPTB: malignant phyllodes tumor, SU: surgery, CH: chemotherapy, HT: hormone therapy, CDKI: cyclin-dependent kinase inhibitors, E-CH: electrochemotherapy, H: hyperthermia, I: imiquimod, T: trastuzumab, I-CH: intra-arterial chemotherapy, NA: not applicable, NR: not reported.

	Study	Stage	Histology	SU	CH	RT	HT	CDKI	I-CH	E-CH	T	H	I
Molecular subtype													
Luminal A (n = 0)													
Luminal B (n = 3)													
	Rudlowski (2019)	IV	IDC										
	Ishikawa (2022)	IV	Mucinous carcinoma										
	Michalopoulos (2023)	IIIB	IDC										
Patients for which a subgroup analysis between Luminal A and Luminal B was not possible (n = 10)													
	Kanoh (2000)	IV	IDC										
	Fiegl (2001)	NR	IDC										
	Yoneyama (2003)	NR	Mucinous carcinoma										
	Melhem (2007)	IV	IDC										
	Ugras (2015)	NR	NR										
	Ballal (2018)	NR	Medullary carcinoma										
	Alawami (2020)	IIIB	IDC and squamous carcinoma of the skin										
	Nguyen (2020)	IV	Infiltrative adenocarcinoma										
	Wiliams (2021)	IV	IDC										
	Hirshad (2022)	IIIB	IDC										
HER2 positive (n = 11)													
	Esposito (2020)	NR	NR										
	Anwar (2020)	IV	Mixoid colloid carcinoma										
	Grewal (2018)	NR	IDC										
	Kawaguchi (2009)	IV	IDC										
	Li (2018)	IIIB	IDC										
	Lin (2021)	IIIC	IDC										
	Quackenbush (2017)	IV	NR										
	Yan (2022)	IV	NR										
	Gao (2017)	NR	IDC										
	Matsuki (2022)	NR	NR										
	Salemis (2018)	IIIB	Metaplastic breast carcinoma with mesenchymal differentiation										
TNBC (n = 10)													
	Aksoy (2016)	NR	NR										
	Carlucci (2012)	IV	Epithelial metaplastic carcinoma										
	Hirowatari (2010)	IV	Mucinous carcinoma										
	Hong (2023)	IV	IDC										
	Ishikawa (2001)	IIIB	Mucinous carcinoma										

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	Liu (2023)	IIIB	IDC										
	Majumdar (2021)	NR	Adenocarcinoma										
	Takeuchi (2021)	IIIB	IDC										
	Tampakis (2017)	IV	Adenocarcinoma with a predominant metaplastic squamous carcinoma and a spindle cell (sarcomatoid) carcinoma of the breast										
	Yamaguchi (2021)	NR	IDC										
Molecular subtype unknown/not reported (n = 6)													
	Davidson (1987)	NR	Adenocarcinoma										
	Noe (1978)	IV	Mucinous carcinoma										
	Amhad (2019)	IV	IDC										
	Murakami (2001)	IV	Mucinous carcinoma										
	Nash (1999)	IV	IDC										
	Bufil (1994)	NR	Adenocarcinoma										
Fibroepithelial tumor (n = 14)													
	Gebrim (2020)	IIIB	MPTB										
	Franceschini (2017)	IV	MPTB										
	Hamdy (2019)	IV	MPTB										
	Bourke (2015)	IIIB	MPTB										
	Bruce (2023)	IIIB	MPTB										
	Chang (2017)	IIIB	MPTB										
	Khanal (2018)	IIIB	MPTB										
	Kim (2018)	IIIB	MPTB										
	Liu (2016)	IIIB	MPTB										
	Schillebeeckx (2016)	NR	MPTB										
	Szraida (2011)	NR	MPTB										
	Testori (2015)	NR	MPTB										
	Takenaka (2011)	IIIB	MPTB										
	Syrnioti (2011)	NR	MPTB										
Mesenchymal tumors (n = 4)													
	Hoshi (2020)	IIIB	Pleomorphic sarcoma										
	Tomas (2009)	IIIB	Low-grade periductal stromal sarcoma with myxoid features										
	Chien (2010)	NR	Sarcoma + IDC										
	Liu (2013)	IIIC	Malignant fibrous histocytoma										
Others (n = 4)													
	Gafumbegete (2016)	IIIB	Osteosarcoma										
	Pereira (2023)	NR	Breast malignant neoplasm with features of high-grade B cell lymphoma										
	Naqash (2015)	NR	Plasmacytoma										

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	Trichia (2016)	IIIB	Myoepithelioma												

Key	
CR	
PR	
SD	
PD	
NA	

Papers whose outcomes were not explicitly reported were excluded from the table.

The order in which patients underwent treatment has not been depicted (for example, adjuvant or neoadjuvant radiotherapy).

The tumor response was classified as per the WHO criteria in papers published before the year 2000, and the RECIST criteria in papers published post 2000.

The tumor response as per WHO or RECIST CRITERIA does not deal with upfront surgery; when surgery was performed as primary treatment we used the term "NA" (not applicable).

conducted a multicenter study to assess the impact of COVID-19 on cancer diagnoses. They concluded that in 2020, fewer early-stage cancer diagnoses were made, and fewer cases were discussed in multidisciplinary settings [14].

Regarding this specific condition (fungating or ulcerated tumors), we retrieved all papers focusing on locally advanced breast cancer (LABC), excluding those in which the tumor was neither ulcerated nor fungating, or where these characteristics were not clearly defined. From these papers, we manually identified cases in which fungation/ulceration/bleeding was reported. This strategy was necessary because the AJCC definition of LABC includes cases both with and without these characteristics [2]. In order to specifically address this group, we therefore conventionally termed this condition "locally disfiguring breast cancer" (LDBC) throughout the manuscript. Despite the significant challenges associated with treating this condition, there is paucity of literature on the optimum management; there are also no treatment guidelines available. To the best of our knowledge, this is the first review specifically devoted to the management of breast cancers with fungating/ulcerating/bleeding symptoms.

For LDBC, no standardized treatment approach is currently available. Therefore, it is crucial that optimal management is discussed within a multidisciplinary team. From the systematic review, it emerged that the primary approach to managing LDBC generally involves surgical intervention, including total or modified radical mastectomy, or palliative procedures aimed at tumor debulking. Accordingly, out of the 430 patients included in this review, 217 underwent surgery. However, this procedure is also associated with a high complication rate, as shown by Abdallah et al. [6].

When surgery is not feasible—whether due to technical limitations, patient refusal, or contraindications—radiotherapy is typically employed [15]. It served as the treatment of choice for 170 patients and was often combined with other treatment modalities such as intra-arterial chemotherapy [16], hyperthermia [17], or systemic therapies [18], with the goal of achieving rapid tumor mass reduction and alleviating associated symptoms. It is precisely the presence of such symptoms that necessitates timely and effective loco-regional treatment. As a result, the response time of neoadjuvant chemotherapy alone is often inadequate for managing these cases effectively.

Radiotherapy, therefore, is commonly employed—at least as a palliative approach—in this subset of patients. Various treatment regimens are used. For example, the use of hypofractionated radiotherapy (36.63 Gy in 11 daily fractions) in a 67-year-old woman resulted in complete resolution of a fungating and ulcerated mass, accompanied by pain relief and restoration of normal daily activities [19]. Similarly, conventional fractionation (50 Gy in 25 fractions) proved equally effective in treating a fungating tumor in a 63-year-old woman, leading to complete pain resolution [20]. As such, radiotherapy has demonstrated efficacy in various settings, including symptom palliation, bleeding control, and achieving local disease control.

Due to the heterogeneity of the studies in this review, we refrained from correlating the doses and radiotherapy regimens with the therapeutic response. Nonetheless, we observed that where radiotherapy was employed, it adequately addressed the desired symptom palliation. Although the superiority of hypofractionation over standard fractionation in cases of fungating or ulcerated tumors has not been demonstrated, hypofractionation offers radiobiological advantages, delivering a higher dose per fraction while shortening the overall outpatient treatment time [21]. This reduction in treatment time proved especially beneficial during the COVID-19 pandemic and is particularly suitable for patients with limited life expectancy. Furthermore, this approach does not significantly delay the initiation of systemic therapy.

In the context of radiotherapy used as a means to achieve effective symptom palliation, although it was not included in our review as it was published later, it is important to mention the study by Ferini et al. [8]. This is the first study in which patients with fungating breast tumors were treated with LATTICE radiotherapy technique. Among 10 patients treated with radiotherapy±systemic therapy, effective symptom palliation was achieved. Furthermore, four patients experienced a complete response, with a 6-month local control rate of 75 % and a cancer-specific survival rate of 89 %.

This technique appears to meet the need for a rapid tumor response, as it delivers high-dose radiation to specific points, known as "vertices," leading to a rapid improvement in the patients' QoL. Simultaneously, it ensures sparing of organs at risk by delivering lower doses to the remaining tumor volume [9]. Additionally, the use of high-dose fractions lead to the activation of the immune response by priming lymphocytes, activating immune cells, and inducing immune-mediated damage at sites distant from the treatment field, known as the abscopal effect, which could be beneficial in metastatic patients [22, 23].

Regarding our analysis of case reports, as reported in the results, treatments were categorized based on molecular subtype, histology, and staging. We observed that the number of therapeutic modalities

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Table 3a
Demographic and tumor details of the included participants from cohort studies.

Study ID	Pts demographics			Tumor details						
	No. of pts	Mean pts age (range)	Pts sex M/F	Presentation: Primary or Recurrent	Baseline functional status	Median tumor size (cm)	Metastases (no. of pts)	Tumor histology (no. of pts)	TNM status (no. of pts)	Receptor status (no. of pts and/or %)
Abdallah (2022)	82	60.8 ± 14.2 (31–86)	M 2 F 80	-Primary 82	NR	5.5 (2–20)	54/78	-DCIS 1 -IDC 70 -ILC 3 -Mixed 1 -Mucinous 2 -Medullary 1 -Undifferentiated 1 -Metaplastic 1 -Intracystic papillary with invasion 1	-IIb 1 -IIIa 1 -IIIb 15 -IIIc 7 -IV54	-ER− 25/69 -ER+ 44/69 -PR− 27/68 -PR+ 41/68 -HER2 = 3 + 20/63
Andersen (2009)	11	61 (47–72)	F 3 other NR	-Primary 1 -Recurrent 10	NR	NR	NR	-Adenocarcinoma 1 -Carcinoma 3 -Sol. scirrhous carcinoma 3 -Sol. carcinoma 1 Intracanal carcinoma 1	NR	NR
Bichoo (2020)	79	55 ± 11 (35–86) of all pts	F 76 M 3	-Primary 70 -Recurrent 9	NR	7.6 ± 2.8	33	-IDC 73 -ILC 1 Mucinous carcinoma 1 -IDC with neuroendocrine differentiation 1 -IDC with sarcomatoid differentiation 1 -Invasive papillary carcinoma 1 -Secretory carcinoma 1	-IIIB 44 -IIIC 2 -IV33	-HR+ 44 % -HER2 = 3 + 40 % -TNBC 32 %
Chia (2016)	35	59 (40–91)	NR	NR	-ECOG 0–1 = 28 -ECOG ≥2 = 4 -NR = 3	NR	9	NR	NR	NR
Hoeltgen (2023)	26	61 (25–83)	NR	Primary and recurrent but the no. of pts was NR	ECOG 0 17.4 % ECOG 1 52.2 % ECOG 2 17.4 % ECOG 3 8.7 % ECOG 4 4.3 %	NR	23	NR	NR	-HR+, HER2− 44.0 % -HR+, HER2 = 3 + 12.0 % -HR−, HER2 = 3 + 12.0 % -HR−, HER2− 32.0 %
Kakagia (2004)	4	NR (67–83)	NR	-Primary 4	NR	NR	None	IDC 4	NR	-ER+ 100 %
La Verde (2013)	23	63 (31–86)	NR	-Recurrent 23	median KPS 90 (50–100)	NR	23	-IDC 20 NR 1 other histologies 2	NR	-ER+ 9 -ER− 9 -PR+ 8 -PR− 10 -HER2− 16 -HER2 = 3 + 2
Merino (2015)	47	60 (30–89)	NR	-Recurrent 47	NR	6.5	NR	NR	NR	-ER+ 21 -PR+ 12 -NR 14
Shaugnessy (2015)	20	57 (39–85)	NR	-Primary 9 -Recurrent 11	NR	NR	11	IDC 20	NR	-ER+ 60 % -PR+ 30 % -HER2 = 3 + 20 %
Vempati (2016)	13	64 (34–95)	F	NR	NR	NR	NR	NR	NR	-ER+, PR+, HER2−: 4 (RT-naïve group) -ER+, PR−, HER2−: 2 (prior RT group), 1 (RT-naïve group)

(*continued on next page*)

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Table 3a (*continued*)

Study ID	Pts demographics			Tumor details						
	No. of pts	Mean pts age (range)	Pts sex M/F	Presentation: Primary or Recurrent	Baseline functional status	Median tumor size (cm)	Metastases (no. of pts)	Tumor histology (no. of pts)	TNM status (no. of pts)	Receptor status (no. of pts and/or %)
										-ER−, PR−, HER2−: 4 (prior RT group), 2 (RT-naïve group)

Data are reported when available as number (%) or mean (range). Abbreviations: M:male, F:female, pts: patients, DCIS: ductal carcinoma in situ, IDC: infiltrating ductal carcinoma, ILC: infiltrating lobular carcinoma, NR: not reported, ECOG: eastern cooperative oncology group, HR: hormone receptor, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, RT: radiotherapy treatment.

increased from an average of two in patients with luminal B tumors to an average of three in those with HER2-positive cancers, with more than half of the latter achieving complete response. In contrast, triple-negative breast cancer (TNBC) tumors were managed with an average of two treatment combinations, with approximately half of these cases exhibiting only partial response. A possible explanation for this observation is that TNBC is known to be more aggressive, exhibits greater tumor heterogeneity and higher proliferative capacity, and demonstrates higher levels of acquired chemoresistance compared to other subtypes, thereby necessitating a more intensive therapeutic approach [24]. Thus, these patients generally have a poorer prognosis compared to those with other subtypes.

For instance, in elderly patients with early-stage, hormone receptor-positive breast cancer, adjuvant radiotherapy may be safely omitted due to the typically slower tumor growth; however, this approach is not applicable for TNBC within the same demographic group [25]. This highlights the need for distinct treatment algorithms for hormone receptor-positive cancers versus TNBC, even in cases of LDBC. Consequently, a more intensified and timely treatment strategy may be warranted for patients with TNBC, comparable to the approach used for other aggressive histologies such as sarcoma [26].

These observations are derived from the studies included in our analysis, where chemotherapy was the predominant treatment for the majority of TNBC cases. However, given the high immunogenicity of TNBC, the therapeutic approach for these tumors is increasingly shifting towards immunotherapy. Notably, immunotherapy has recently been approved for the treatment of locally advanced or metastatic PD-L1-positive breast cancer, demonstrating promising outcomes [27]. Consequently, this shift may also influence prognosis and, in turn, impact future treatment decisions. Prognosis may also improve in light of the demonstrated efficacy of combining immunotherapy with radiotherapy, which has shown effects not only on targeted lesions but also on distant metastases through the abscopal effect [28]. This combination could thus become a valuable treatment option for LDBC patients with TNBC histologies requiring intervention also at metastatic sites.

Conversely, an interesting finding that emerges from the analysis of cohort series, is the statistically significant trend favoring the use of radiotherapy and targeted therapies over the years. These findings underscore that surgery was the cornerstone of treating fungating breast cancer. However, over the years, the growing need for personalized cancer treatments has led to the incorporation of targeted therapies, such as trastuzumab and pertuzumab, for HER2-positive patients [29]. In general, these therapies (namely targeted therapy or chemotherapy) are administered in a neoadjuvant setting with the aim of achieving a better pathological response, thereby increasing the likelihood of obtaining clear resection margins. However, neoadjuvant systemic therapies do not always yield these outcomes; in some cases, patients may continue to experience disease progression despite treatment, or response may not be rapid enough, potentially leading to the onset of complications [30]. For these reasons, as highlighted by our analysis, radiotherapy has gained increasing prominence in recent years, offering a local treatment option that can at least provide symptom palliation.

Local therapy for the primary tumor may be particularly beneficial for LDBC patients with metastases as well, notwithstanding the well-known debate on its utility [31]. Indeed, it is well established that those treated with chemotherapy alone for cytoreduction face a high likelihood of recurrence and mortality with the risk of debilitating their overall condition [32]. This raises the question of whether a solely systemic treatment approach as primary treatment is optimal for patients with metastatic, fungating, and/or ulcerated tumors.

To date, there are insufficient studies determining whether treatment of the primary tumor can have a positive impact on overall survival in metastatic breast cancer patients. Several retrospective series appear to be in favor of this approach [33]. However, a prospective study suggests that there is no benefit in overall survival [34]. In this study, the number of randomized patients may not be large enough to reveal significant differences in subgroup analyses. Thus, we await more robust evidence to better understand the utility of a local treatment in this patient setting, whether purely palliative or potentially beneficial to survival outcomes.

Nonetheless, a locoregional approach could be considered as the primary therapeutic option for patients with metastatic LDBC, both to address the potential for systemic therapy failure, as previously discussed, and to provide an immediate improvement in QoL, thereby minimizing the considerable distress associated with a fungating tumor.

Optimum wound care is another crucial aspect of managing these patients with LDBC. As emerged from our review of the literature, the management of malignant wounds is typically supported by therapies aimed at preventing infections, controlling bleeding, and eliminating malodor. For example, metronidazole gel and neomycin or bacitracin solutions were employed for these purposes [20,35]. Silver nitrate ($AgNO_3$) has also been successfully used to control bleeding [18]. Proper wound cleansing is equally important, along with the application of appropriate wound dressings [36].

In conclusion, patients with LDBC represent a particularly complex group requiring careful management. Local interventions are essential in these cases to at least palliate symptoms. Tumor histology should play a central role in therapeutic decision-making, with special consideration given to triple-negative tumors due to their higher acquired chemoresistance and increased proliferative index. For these patients, a timely local treatment and multimodal approach may be most effective. Other crucial factors in the treatment algorithm include patient age (elderly age is typically associated with slower-growing tumors [37]) and disease stage. Stage IV patients, given their high likelihood of recurrence with the use of chemotherapy, may benefit from prioritizing local interventions. Currently, it may appear that a local approach could serve as the first therapeutic step; however, it is important to note that new treatments, such as targeted therapies and immunotherapy, are emerging in the scientific landscape [38,39]. With encouraging therapeutic responses, these modalities may become the first-line option for these patients' cohort.

This is the first review on this topic in the literature. Unfortunately,

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Table 3b
Treatment details and outcomes of the included participants from cohort studies.

Study ID	Intervention - palliative intent?	Surgery (no. of pts)	Chemotherapy - adjuvant/ neoadjuvant/ palliative (n/% of pts)	Radiotherapy - definitive, adjuvant or neoadjuvant (n/ % of pts)	Hormonal therapy - adjuvant/ neoadjuvant (n/ % of pts)	Median FU duration (months)	Median survival (months) (range)	Final FU - Quality of life (% of pts)	LC (median months)
Abdallah (2022)	Yes	Mastectomy ± lymphadenectomy 81	Adjuvant and neoadjuvant	No	Adjuvant	18 (0–101)	Estimated mean OS: 55 (41.98–69.9)	NR	NR
Andersen (2009)	NR	No	Palliative	No	Concurrent 10	NR	NR	NR	NR
Bichoo (2020)	No	Mastectomy 70	- Neoadjuvant (84 %) - Adjuvant (10 %)	- Neoadjuvant 4/59 - Adjuvant 47/59 - Palliative 8/59	Adjuvant 33	40 (2–93)	36	Ulcer healing	NR
Chia (2016)	NR	No	Palliative post-RT 42.9 %	Palliative	Palliative pre- and post-RT 23	11.7	11.7 (95 % CI 0.8–22.7)	94.28 % achieved symptom palliation	10
Hoeltgen (2023)	NR	No	No	Palliative	No	6.5	10.9	- 95 % of pts achieved symptoms palliation - Reduction of analgesic intake in 28.6 % of pts	4.7
Kakagia (2004)	NR	No	Palliative	No	Palliative	NR	NR	Ulcer healing and returning to daily life in all pts	NR
La Verde (2013)	NR	No	Palliative	No	12	8.7	9.1 (95 % CI: 7.0–not applicable)	- Worsening of KPS (median KPS: 80, range: 40–100) - Improvement of cutaneous symptoms	NR
Merino (2015)	NR	18 (11 mastectomy, 7 local excision)	NR	Palliative re-irradiation	23	78.6	NR	Symptomatic response after treatment: - Pain 83.33 % - Ulceration 44.44 % - Bleeding 16.66 % - Brachial plexus involvement 44.44 % - Lymphedema 27.77 % - Bad odor 11.11 %	28.9
Shaugnessy (2015)	NR	4	Concurrent with radiation	Both definitive and palliative	No	25.3 (range: 1.6–42 months)	NR	NR	11.2 (range: 8–27.1)
Vempati (2016)	NR	NR	NR	NR	NR	NR	4.6 for prior RT group, 4.5 for naïve group. Median survival for both groups 4.5	- 50 % of pts from the group with prior RT experienced benefit from the palliative treatment and - 42.85 % of pts from the RT-naïve group experienced benefit from the palliative treatment. - 69 % of pts who received 30 Gy or more reported clinical improvement, whereas none of the 4 pts who received less than 30 Gy reported any benefit.	NR

Data are reported when available as number (%) or mean (range). Abbreviations: Pts: patients, DCIS: ductal carcinoma in situ, IDC: infiltrative ductal carcinoma, ILC: infiltrative lobular carcinoma, NR: not reported, FU: follow-up, LC: local control, RT: radiotherapy treatment.

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as anticipated, we found considerable heterogeneity in the baseline clinical parameters, tumor size, histology, staging, duration of follow-up, and treatment, and how outcomes are reported. Therefore, we refrained from performing a meta-analysis to determine the optimal treatment for patients with ulcerating or fungating tumors, finalizing our systematic search with a narrative synthesis of the retrieved results. Indeed, we used the wealth of available data to analyze trends in selection of treatment strategy based on demographics, baseline tumor parameters and chronology. Ultimately, this review provides a broad understanding of the therapeutic options available for these patients, with the hope of encouraging further research in this field.

CRediT authorship contribution statement

Valentina Zagardo: Writing – original draft, Validation, Resources, Methodology, Investigation, Data curation. **Mandara Harikar:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Gianluca Ferini:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Conceptualization.

Informed consent

Not applicable.

Data availability

No new data were created. The datasets are available upon request to the corresponding author.

Ethical approval

An approval was not required for this review of previously published studies.

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Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103870.

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