Contemporary surgical management of inflammatory breast cancer: a narrative review

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Objective: The purpose of this review is to outline the surgical management of inflammatory breast cancer (IBC) including the clinical decision making, operative approach and current controversies.

Background: IBC is a rare and aggressive form of breast cancer. Trimodality therapy consisting of neoadjuvant therapy, modified radical mastectomy (MRM) and radiation therapy improves survival and is the recommended course of treatment. Advancements in systemic therapy and de-escalation strategies in non-IBC have accelerated discussions regarding several aspects of care in IBC including feasibility of de-escalation of surgical care, timing of reconstruction and the role of surgery in *de novo* stage IV disease. We discuss the evidence to support the surgical approach and decision-making in this rare disease.

Methods: We reviewed existing literature using multiple electronic databases and clinical consensus guidelines to identify historical and current publications addressing current management recommendations and clinical controversies in IBC.

Conclusions: Breast conserving surgery (BCS), skin- or nipple-sparing mastectomy should not be performed in IBC as surgical resection to negative margins results in improved locoregional recurrence rates. Level I and II axillary lymph node dissection should be performed regardless of response to therapy and initial nodal status. Reconstruction should be delayed and contralateral prophylactic mastectomy (CPM) is discouraged in IBC. Surgery may be considered for *de novo* stage IV IBC patients who demonstrate durable response to neoadjuvant therapy to improve local-regional control.

Keywords: Inflammatory breast cancer (IBC); trimodality therapy; surgery; post mastectomy radiation therapy; lymphedema

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Introduction

The management of breast cancer has dramatically changed over the past 6 decades from primarily a surgical disease to leveraging a multidisciplinary approach with recognition of breast cancer as a systemic disease. Improved survival outcomes have been largely driven by sophisticated understanding of breast cancer subtypes and improved systemic therapies including targeted therapy. This has allowed for the refinement of surgical approaches including de-escalation in select patient populations. Despite this, surgery remains critically important within the multidisciplinary treatment paradigm. Specifically, surgical management not only results in excision of the malignancy but also clarifies the pathologic stage or response to treatment, provides local-regional control and remains essential for curative intent therapy.

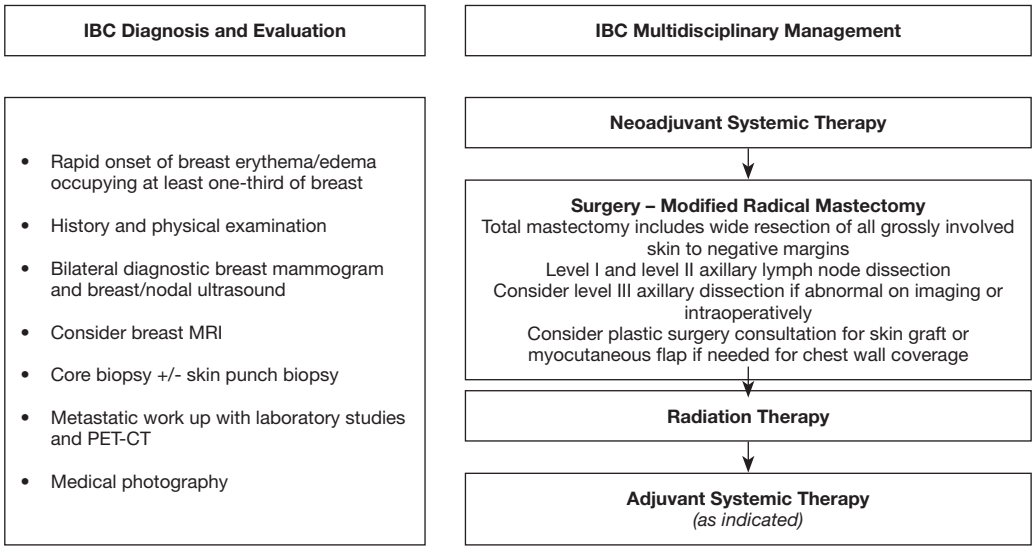

Figure 1 Diagnosis, evaluation and treatment algorithm for non-metastatic inflammatory breast cancer (IBC).

Inflammatory breast cancer (IBC) is a rare and aggressive breast malignancy accounting for approximately 2–5% of breast cancer cases (1). IBC is characterized by rapid onset of distinctive findings including erythema, peau d'orange, skin thickening and edema involving at least one-third of the breast (*Figure 1*) (2,3). These classic findings are secondary to dermal lymphatic involvement with the pathognomonic histopathologic finding of tumor emboli in the dermal lymphatics present in up to 75% of IBC cases though a positive skin biopsy is not required for diagnosis (4). IBC is a clinical diagnosis with patients classified as stage III or IV and patients often present with extensive involvement of the breast skin, breast and axillary nodes.

To better understand biological differences between IBC and non-IBC, genomic sequencing has been applied to identify unique gene expression profiles in IBC for potential targeted strategies (5-8). Despite these efforts, distinct genomic differences between IBC and non-IBC are yet to be clearly defined. However, the importance of cells in the tumor microenvironment such as macrophages, dendritic cells and endothelial cells (9-11), have emerged as potential pathways contributing to the aggressive nature of IBC and is under further investigation in collaborative efforts across institutions (5). Challenges include the rarity of IBC, the diverse molecular subtypes, and difficulty with obtaining tissue specimen pre-, during and post-treatment.

Though it represents a small proportion of total breast cancer cases, IBC is disproportionately responsible for approximately 10% of breast cancer deaths. Historical studies showed extremely poor prognosis with surgery alone (12). It is now well established that trimodality therapy with neoadjuvant systemic therapy followed by surgery and radiation is associated with improved survival outcomes (13-15). Additional adjuvant therapy is also often indicated in current practice depending on treatment response and approximated tumor subtype. Contemporary survival outcomes have greatly improved reaching 69% at 5 years although still are not equivalent to non-IBC (16).

The proportion of molecular subtypes in IBC differ when compared to non-IBC with IBC demonstrating a higher proportion of triple negative breast cancer (TNBC) and HER2-positive subtypes representing 30% and 40% of cases respectively, while hormone receptor (HR)-positive subtype is the predominant subtype in non-IBC. Similar to non-IBC, higher pathologic complete response (pCR) rates are observed for TNBC and HER2 positive and pCR is highly prognostic in all subtypes (5,17,18). When evaluating IBC outcomes by subtype, TNBC subtype is shown to have worse outcomes compared to other molecular subtypes. Unlike in non-IBC, HR-positive status does not confer favorable prognosis and same stage disease has significantly worse prognosis in IBC compared to non-IBC (17,19).

This article focuses on the rationale and principles guiding surgical therapy for IBC and the optimal operative approach for treating the breast primary and axillary nodes, with discussion of long-term sequalae and current controversies.

Preoperative	Intraoperative	Postoperative
• Thorough evaluation at presentation to determine extent of tumor involvement in the skin, breast tissue and nodal basins • Serial medical photography and breast imaging at presentation and during therapy to monitor response • Referral to plastic surgery if chest wall coverage with skin graft or myocutaneous flap is anticipated • Preoperative lymphedema arm measurements and counseling • Optimization of co-morbidities	• Total mastectomy to include wide resection of all grossly involved skin with goal of negative margins • Level I and II axillary lymph node dissection, consider level III lymph node dissection if abnormal nodes are identified pre- or intraoperatively • Collaboration with plastic surgery as indicated for chest wall coverage **Contraindicated** Breast conserving surgery Sentinel node dissection Targeted axillary dissection Contralateral prophylactic mastectomy Immediate breast reconstruction	• Comprehensive review of surgical pathology with multidisciplinary discussion • Re-excision to negative margins if indicated • Lymphedema arm measurements for surveillance • Provide post-mastectomy bra and prosthesis • Delayed breast reconstruction if desired by the patient

Figure 2 Surgical principles and decision-making in inflammatory breast cancer (IBC).

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/cco-21-113).

Surgical management of IBC

Modified radical mastectomy (MRM) after neoadjuvant systemic therapy remains the standard of care in the surgical management of non-metastatic IBC (20). Trimodality therapy including MRM is an independent predictor of long-term survival (15,21). MRM consists of a total mastectomy, in which the nipple, areola and central breast skin is excised with the underlying breast tissue, as well as an axillary lymph node dissection, excising the ipsilateral level I and II axillary nodes. The goal of surgery is to achieve pathologically negative margins and in IBC, it is important to excise all grossly involved skin and often results in a more extensive skin excision than non-IBC. Consultation with a plastic surgeon may be needed for skin graft or flap closure for chest wall coverage in the setting of extensive skin resection. Furthermore, if the underlying pectoralis muscle is involved this should be excised en bloc (partial or full resection). Additionally, axillary dissection is recommended regardless of response to therapy and initial nodal status. In patients with abnormal level III lymph nodes identified preoperatively or during surgery, a level III dissection may be performed. The efficacy of skin or nipple sparing mastectomy has not been demonstrated in IBC and is contraindicated given the extensive skin involvement. (*Figure 2*).

In a study of 114 patients with non-metastatic IBC, Rosso *et al.* demonstrated the importance of aggressive surgical resection to negative margins in improving LRR rates. In this cohort, approximately 40% had N2/N3 disease and all patients received trimodality therapy with curative intent. Surgical margins were negative in 99% of patients (n=113), and positive in one patient. Only 4 patients developed locoregional recurrence and 4-year probability of locoregional recurrence was 5.6% (95% CI: 2.76–14.7%) (16). In this study, 2 patients developed complications; mild incisional necrosis managed non-operatively in 1 patient, and partial incision breakdown managed with surgical debridement in another. Locoregional recurrence in IBC carries a poor prognosis and can be resistant to local and systemic therapy. As such, consensus guidelines support aggressive locoregional control with MRM, followed by post-mastectomy radiation therapy (PMRT) as essential for optimal outcomes in IBC (22).

Breast conserving surgery (BCS)

It is well established that neoadjuvant systemic therapy may be utilized to facilitate breast conservation in locally advanced non-IBC patients with exceptional response to therapy (23,24), however, there is limited data to suggest benefit in IBC. A SEER study evaluating the impact of locoregional therapy on survival in IBC demonstrated that total mastectomy was associated with improved survival (HR 0.75, 95% CI: 0.65–0.85) compared to partial mastectomy, and radiation therapy also improved survival (HR 0.64, 95% CI: 0.61–0.69) (25). A retrospective analysis investigating

the feasibility of de-escalating breast surgery in IBC evaluated 35 patients diagnosed from 1999 to 2013 (26). Neoadjuvant chemotherapy was administered to 20 patients and 14 received neoadjuvant endocrine therapy (NET). The decision for BCS was made by the treating physician based on response to therapy. After 80 months of follow up, 5-year local-regional recurrence (LRR) free survival was 87.5% (95% CI: 76.0–99.0%) and overall survival was 70.3% (95% CI: 54.8–85.8%) (26). These favorable results should be reviewed with caution as the cohort did not reflect the typical IBC patient. Most patients presented with a unifocal mass but an underlying mass is only present in about 50% of IBC cases (27). In addition, nodal burden was minimal in this cohort which is unusual for IBC (28).

Sentinel lymph node dissection (SLND)

SLND is the standard of care for axillary staging in clinically node negative breast cancer and increasingly employed in node positive patients after neoadjuvant chemotherapy. Successful SLND requires the ability to identify the SLNs with high reliability and accuracy.

The majority of IBC patients have nodal metastasis at presentation. In an analysis of a prospective institutional database, 90% of IBC patients had at least N1 disease identified on axillary ultrasound and fine needle aspiration (FNA) (28). For this reason, ALND is the recommended treatment for the axilla and de-escalation of axillary surgery is discouraged. Several trials investigating the feasibility of sentinel lymph node biopsy after NACT in IBC demonstrated a high false negative rate (FNR) ranging from 18.2 to 25% and identification rate ranging from 25–80% (29-31). Using dual-tracer technique in a prospective trial of 16 patients, DeSnyder *et al.* showed an identification rate of only 25% with three quarters of the patients with identifiable sentinel nodes having an axillary nodal PCR (30). This is in stark contrast to non-IBC where sentinel node identification rates are consistently >90%. The lack of accuracy and reliability of identification of sentinel nodes precludes this approach in IBC.

Furthermore, SLND in women with clinically node-positive breast cancer treated with neoadjuvant chemotherapy has been studied in several large prospective clinical trials with refined technique of targeted axillary dissection (TAD) increasingly employed. TAD involves removal of the sentinel lymph node(s) using dual tracer technique and selective excision of the clipped node biopsy proven axillary node has shown FNR of 2.0% (32,33). Additionally, TAD is most effective in patients with limited nodal disease. Up to a third of IBC patients have pathologically negative lymph node status (ypN0) after NACT (28). As with non-IBC, IBC patients with HER2+ disease have a high likelihood of achieving pCR after NACT approximating 64% in a single institution review (34-36). While it is tempting to extrapolate de-escalation strategies for node-positive breast cancer patients treated with neoadjuvant chemotherapy, it should be noted that the foundational studies did not include patients with IBC. These findings may inform the selection of IBC patients for de-escalation of axillary surgery however future studies are needed before adopting this approach.

Immediate post-mastectomy reconstruction

Immediate post-mastectomy reconstruction has been associated with several advantages including improved patient satisfaction and body image. To facilitate immediate reconstruction, skin or nipple sparing mastectomy is typically performed to preserve the skin envelope for placement of a tissue expander/implant or autologous flap. In IBC given the extensive skin involvement, skin sparing and nipple sparing approaches are contraindicated. Immediate breast reconstruction is not recommended in IBC due to the high risk of recurrence, potential to delay receipt of PMRT and the complexity of the reconstruction needed secondary to extensive resection (37). PMRT is essential for optimal oncologic outcomes in the management of IBC however, it may result in complications during reconstruction and worse cosmetic outcomes as well as suboptimal patient satisfaction (38,39). As such, delayed reconstruction with autologous flap approach is recommended in IBC patients who desire post-mastectomy reconstruction. The optimal timing of reconstruction after PMRT is uncertain although one study showed fewer complications with a 12-month delay (40).

Contralateral prophylactic mastectomy (CPM)

In the United States, national trends indicate increased utilization of CPM despite advances in adjuvant therapy (41-44). While effective as a strategy for risk reduction of breast cancer in women with high-risk for breast cancer, this approach has shown no survival advantage in average-risk women with unilateral breast cancer (45-46). The competing risk of mortality from the index malignancy is an important decision-making factor when considering CPM. In 2016, the American Society of Breast Surgeons (ASBrS)

Table 1 Retrospective studies evaluating primary tumor surgery in *de novo* stage IV Inflammatory breast cancer

Studies	Years	N	Site of metastasis	Therapy	Clinical outcomes
Dawood 2012, (21)*	2004–2007	722	–	–	*Survival:* HR 0.49, 95% CI: 0.34–0.70; P<0.0001
Akay 2014, (55)#	1994–2009	172	Bone only 34 (71% in surgery group)	NACT: 100% Surgery: 46% Surgery + RT: 40%	*Survival:* HR 0.25, 95% CI: 0.08–0.82; P=0.02
Takiar 2014, (56)	2006–2011	36	–	NACT: 100% Surgery: 100% RT: 100%	*Survival:* 50% *Local-Regional Control:* 86%
Weiss 2018, (57)	2010–2013	1,266	–	Surgery 41%	*Survival* Matched: HR 0.72, 95% CI: 0.56–0.93; P<0.011
van Uden 2020, (58)	2006–2016	Unmatched 580 Matched 202	Bone only Unmatched 157 (34.4% in surgery group) Matched 66 (54.5% in surgery group)	NACT Unmatched: 70.9% Matched: 83.2% Surgery Unmatched: 23.9% Matched: 50% RT Unmatched: 22.4% Matched: 40.1%	*Survival* Unmatched: HR 0.56, 95% CI: 0.42–0.75 Matched: HR 0.62, 95% CI: 0.44–0.87
Partain 2021, (59)	2007–2016	97	–	NACT: 100% Surgery: 53.6% RT: 48.5%	*Survival:* HR 0.48, 95% CI: 0.45–0.51, P<0.001

*, therapy and site of metastasis data provided included stage III patients. No data on HER2 status or trastuzumab therapy; #, trastuzumab after 2001. NACT, neoadjuvant chemotherapy; RT, radiation therapy.

published a consensus statement on CPM and determined that for patients with IBC, given the aggressive primary malignancy, routine CPM is discouraged (47). Furthermore, several studies have shown increased risk of complications following bilateral mastectomy as compared to unilateral mastectomy in addition to higher costs (48-51). In IBC this is highly clinically relevant as surgical complications can delay essential adjuvant therapies such as post-mastectomy radiation and delay in treatment may result in suboptimal oncologic outcomes. Furthermore, CPM can be deferred to the time of definitive breast reconstruction if strongly desired by the patient and there is no evidence of disease (NED).

Rationale for surgery in *de novo* stage IV IBC

Surgery in stage IV breast cancer remains controversial with NCCN guidelines indicating the decision should be made in a multidisciplinary setting on a case by case basis (3). Traditionally, this was reserved for palliation of symptoms given no known survival benefit. However, this a heterogenous patient population with improving outcomes particularly those who achieve NED status. While several retrospective studies have shown a survival benefit for surgery in *de novo* stage IV breast cancer, prospective studies have shown conflicting results.

Approximately 30% of IBC patients present with *de novo* stage IV disease compared to 6–10% in non-IBC disease (52-54). While current recommendations support surgical therapy in stage III disease where the treatment approach is for curative intent, there is less consensus on the role of surgery in stage IV disease particularly given prospective studies have not shown a survival benefit. Current practice remains to prioritize systemic therapy as the primary treatment modality and consider local regional therapy in patients with a significant and/or durable treatment response.

Neoadjuvant systemic therapy with anthracycline-based chemotherapy and dual anti-HER2 targeted therapy in HER2+ disease remains first line treatment in stage IV IBC despite the results of several retrospective studies (20,21,55-59) (*Table 1*). In IBC where there are extensive skin and chest

wall findings, surgery in combination with radiation may be considered for local control due to significant morbidity associated with uncontrolled chest wall disease. In a retrospective analysis, Partain *et al.* evaluated the role of MRM in a contemporary cohort of *de novo* stage IV IBC treated with systemic and targeted therapy (59). After a median follow up of 70 months, LRR occurred in 6 of 47 patients who received trimodality therapy. Five patients had clinical partial response, and one had clinical complete response and also had pCR (59). In an inverse probability weighted analysis, favorable response to NAST with partial or complete response compared to stable or progressive disease (HR 0.49, 95% CI: 0.46–0.52, P<0.001) and surgical intervention with MRM (HR 0.48, 95% CI: 0.45–0.51, P<0.001) were independently associated with decreased risk of death. In a nationwide population–based cancer registry in the Netherlands using propensity score matching, surgery was also independently associated with improved survival (HR 0.62, 95% CI: 0.44–0.87) (58).

Several randomized controlled trials in non-IBC assessing impact of surgical therapy in stage IV disease report conflicting findings (60-62). Soran *et al.* demonstrated improved survival with locoregional therapy after 5 years in patients with no prior systemic therapy. Patients who underwent surgery did have higher rates of ER+ tumors and single bone metastasis compared to patients in the systemic chemotherapy arm. Furthermore, the sequence of surgery prior to systemic therapy in stage IV disease is unlikely in this era (61). This contrasts with the recent ECOG-ACRIN 2108 trial demonstrating no difference in 3-year OS for surgery *vs.* no surgery in *de novo* metastatic breast cancer patients without progression after NAST (68.4% *vs.* 67.9%; HR 1.09; 95% CI: 0.80–1.49; P=0.63) (62). There was also no significant difference in quality of life at 30 months after randomization. One critique of the study is the advanced disease stage in the patient population and the 20% margin positivity rate in patients who underwent surgery (62).

De novo Stage IV disease with isolated contralateral axilla metastasis (CAM) occurs in 8.3% of IBC patients (63). In this scenario, comprehensive local regional treatment with axillary dissection and radiation can achieve NED status.

In the absence of clinical trials to inform practice in IBC patients, we recommend local-regional therapy with surgery and radiation should be considered in patients who demonstrate durable response to NAST and remain an option for patients with rapidly progressing or symptomatic disease. It is important that this decision is made in the context of a multidisciplinary team as well as disclosure to the patient regarding the benefit for local-regional control with unclear impact on survival, operative risks and long-term side effects including lymphedema and body image concerns.

Long-term sequalae of surgery: lymphedema

With improving survival outcomes, long term sequelae from surgical therapies are becoming increasingly important and significant for breast cancer survivors. Breast-associated lymphedema is characterized by progressive swelling of the chest/upper extremity following breast cancer therapy due to impairment of lymph drainage via lymphatic channels. This may develop immediately after therapy or decades after treatment. Locoregional treatment with ALND (64-66) and regional nodal irradiation (67,68) are independent risk factors for the development of lymphedema and reported to be as high as 60% when both therapies are combined (69,70). While there is paucity of data regarding incidence of lymphedema in IBC, patients with IBC are considered especially high risk given locoregional therapy with surgery and PMRT is standard of care. In patients who have developed lymphedema, management includes compression therapy and therapeutic exercises with trained lymphedema therapists (71). Microsurgical techniques such as lymphovenous bypass and vascularized lymph node transfers have been investigated as therapeutic and prophylactic interventions in high-risk patients with favorable outcomes (72). Another technique known as reverse axillary mapping involves injection of blue dye into the subcutaneous upper extremity and to identify the blue arm lymphatics in the axilla and anastomosing the arm lymphatics with adjacent veins at the time of surgery. An 80% decrease rate has been reported when axillary reverse mapping and lymphovenous bypass are performed (73-75). We recommended patient education, early screening and consideration of preventive methods with expertise in microsurgery in IBC patients.

Conclusions

Surgery remains a critical element in the multidisciplinary management of IBC. Standard of care remains trimodal therapy, including neoadjuvant systemic therapy followed by MRM and post-mastectomy radiation therapy as supported by international consensus guidelines (22). BCS, SLND, skin and nipple sparing mastectomy, immediate

breast reconstruction and CPM are not recommended treatment strategies. Local-regional therapy with surgery and radiation improves local-regional outcomes in patients with *de novo* stage IV disease. Future studies are needed prior to adopting de-escalation strategies in this patient population with aggressive high-risk disease biology and where continued strides in survival outcomes are needed.

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