**Case 8: A Viewpoint on Isolated Contralateral Axillary Lymph Node Involvement by Breast Cancer: Regional Recurrence or Distant Metastasis?**

A 55-year-old woman was diagnosed in 2010 with mixed invasive lobular and ductal carcinoma of the left breast. Initial breast conserving surgery and sentinel lymph node biopsy revealed 2.2 cm (lobular) and 0.4 cm (ductal), grade 2, lymphovascular invasion and surrounding lobular carcinoma in situ and ductal carcinoma in situ but negative margins for invasive component. One of 1 sentinel node was positive. Subsequent mastectomy and axillary lymph node dissection revealed residual ductal carcinoma in situ, and 0 of 20 nodes were involved. Final stage was pT2N1a. Estrogen and progesterone receptors were positive but human epidermal growth factor receptor 2 was unknown. Patient received anthracycline/taxane chemotherapy and tamoxifen but discontinued due to intolerance. Adjuvant radiation therapy was not recommended. The patient underwent right contralateral prophylactic mastectomy with implant reconstruction in 2012.

In 2020, 2 firm nodes were identified in the right axilla (contralateral to the original primary) and removed along with another adjacent node in a limited resection. Pathology confirmed metastatic breast (mixed ductal and lobular) carcinoma involving 2 of 3 lymph nodes, tumor deposits measuring 0.8 cm and 1.9 cm, both showing extranodal extension, large vessel, and perineural invasion seen in perinodal soft tissue. Estrogen and progesterone were positive and human epidermal growth factor receptor 2 was negative. No primary tumor was found on resection of implants and capsules bilaterally. No distant metastasis was evidenced on restaging.

**Expert 1: Contralateral Disease Begets Contralateral Treatment**

Isolated metachronous contralateral axillary lymph node metastasis (CAM) is rare. Potential etiologies include (1) contralateral spread from the original ipsilateral cancer, (2) contralateral spread from new or recurrent ipsilateral tumor, and (3) ipsilateral spread from new contralateral disease. CAM is associated with aggressive biology but may represent regional recurrence from aberrant lymphatic drainage after axillary surgery and not distant hematogenous recurrence, warranting aggressive local therapy.

In the presented case, metachronous CAM with histology concordant with the original disease is suggestive of subclinical contralateral spread from the left primary. Aggressive treatment with radiation therapy and systemic therapy may improve progression-free survival. Regardless, the risk of right nodal recurrence is high given extranodal extension and perineural invasion and warrants right postmastectomy radiation therapy (PMRT) treating the chest wall and regional nodes (axillary, supraclavicular, and internal mammary). This may also address occult right-sided lesions and dermal lymphatics that can transmit left-sided disease.

Right PMRT is recommended regardless of systemic therapy or axillary surgery, especially given the locoregional risk from extranodal extension and perineural invasion. Systemic therapy is encouraged to mitigate distant recurrence risk and maximize PFS and overall survival. Axillary dissection may not be of benefit and does not obviate PMRT. Radiation therapy to the left side can be omitted because there is no gross disease currently, nor for the past 10 years, and the left axilla was therapeutically dissected; this avoids the risks of PMRT after extensive surgery, namely lymphedema. Overall, an interdisciplinary approach should be used to address regional and distant recurrence risk.

**Expert 2: Long Overdue “Beam-On”**

At the time of initial breast cancer diagnosis, this patient underwent suboptimal locoregional and systemic treatment due to omission of postmastectomy regional nodal irradiation (RNI) and inadequate duration of antiestrogen therapy. Although the benefits of RNI for patients with limited nodal disease were not fully appreciated in the past, subsequent clinical trials and a meta-analysis have demonstrated a clear benefit to RNI with an estimated ∼3% to 4% absolute reduction in distant metastases.

After 10 years, the patient now has contralateral axillary nodal metastases. In addition to restaging studies, we recommend bilateral magnetic resonance imaging to assess for potential primary/recurrent tumor in the residual ipsilateral or contralateral breast tissue. Because aberrant lymphatic drainage to the contralateral axilla is not uncommon after axillary lymph node dissection, and in the absence of distant metastases, the contralateral axillary nodal metastases likely represent regional spread of disease or could be the result of an occult primary tumor in the residual right breast tissue. Although data are limited, some patients with contralateral axillary nodal metastases may be cured with aggressive locoregional treatment.

Because both scenarios (regional spread from the left breast or occult primary in the right breast) are potentially amenable to long-term disease control with aggressive locoregional therapy, we would recommend bilateral comprehensive radiation therapy to the chest wall and RNI. Our RNI target volumes would include the undissected axillary nodal basins, supraclavicular nodes, and internal mammary nodes. Given the high risk of subsequent distant hematogenous metastases, discussion of additional systemic therapy is warranted.

**Expert 3: Making the Right Choice: Radiate Only What's Left, the Rest is Left**

Although the exact origin will never be known, we favor regional recurrence of original tumor rather than new primary or distant metastasis. Recurrent breast cancers are known to have aberrant nodal drainage, including to the contralateral axilla, and similarity of histology to the original diagnosis suggests a recurrence of the original tumor. In addition, exhaustive efforts were undertaken, including excision of implants (and assuming imaging including breast magnetic resonance imaging and positron emission tomography/computed tomography) to look for occult primary and distant metastases.

We would radiate the right-sided axillary levels 1 to 3 and supraclavicular (SCV) nodes only, 50 Gy in 25 fractions targeting the potential microscopic disease remaining after surgery.

Historically, most patients in this scenario had axillary lymph node dissection, but some have suggested that radiation therapy, rather than extent of surgery, may be more important.

Thus, the extent of axillary surgery is up to the surgeon and would not change our radiation field in this patient with higher-risk features for regional progression such as extracapsular extension and lymphovascular invasion.4 Because there is no evidence of chest wall or left-sided nodal recurrence 10 years after treatment, we would omit irradiation of the bilateral chest

walls and left axilla/SCV to reduce morbidity, as potential future isolated recurrence is salvageable, and the patient is just as likely to develop distant disease.

Systemic therapy is critical in reducing the chance of metastases, and should include endocrine and chemotherapy, and possibly a cyclin-dependent kinase 4/6 inhibitor. However, systemic therapy would not affect our radiation recommendations aside from starting radiation after any cytotoxic chemotherapy. Finally, this is a great case that illustrates the importance of

long-term follow up in breast cancer patients, both on and offprotocol. We wonder whether the outcome would have been different if the patient had radiation at initial diagnosis.

**Expert 4: Postoperative Comprehensive Radiation with Curative Intent**

Isolated metachronous contralateral axillary metastases (CAM) from breast carcinoma are rare and historically classified as distant metastatic disease. 1 However, altered lymphatic drainage patterns are common after mastectomy, particularly after axillary lymph node dissection, where spread to the contralateral axilla occurs via drainage through superficial dermal lymphatics or deep facial plexus. Patients with isolated CAM have improved prognosis compared with those with distant metastasis, and many advocate for classifying isolated CAM as a regional recurrence event. 3 Given negative systemic staging, we favor proceeding with curative intent treatment (provided this approach aligns with the patient's goals) consisting of possible axillary node dissection (depending on patient wishes and surgical recommendations), adjuvant radiation therapy, subsequent aromatase inhibitor, and likely CDK 4/6 inhibitor.

Although occult CAM at initial diagnosis with subsequent indolent growth is possible, occult ipsilateral recurrence with spread to the contralateral axilla seems more likely given lymphovascular invasion and nodal involvement at diagnosis. Tailoring to the latter possibility, we would target bilateral chest walls, and bilateral lymph node areas at risk including right axilla, left undissected axilla, and bilateral internal mammary and supraclavicular nodes.

Fifty Gy in 25 fractions would be given using a central electron IMN field matched to bilateral photon tangents. To minimize cardiac dose, the central electron field would be split with higher energy superiorly and lower energy inferiorly, in addition to use of deep inspiratory breath hold. In the absence of an axillary dissection, we would boost any undissected locoregional adenopathy seen on imaging to 60 to 66 Gy pending evaluation of brachial plexus dose.

**Expert 5: Patient’s History is as Important as Current Pathology Findings**

The patient has locally recurrent breast cancer with contralateral axillary lymph node involvement. Considering the patient's history and pathology findings, our recommendation for the therapeutic approach would include the following:

* Systemic therapy: Given that the patient has hormone receptor-positive (ER/PR+) and HER2-negative disease, initiating endocrine therapy with an aromatase inhibitor (AI) would be my first choice. In addition, considering the prior discontinuation of tamoxifen due to intolerance, AI would be a better option for this patient. Additionally, since the patient has locally advanced and recurrent disease, I would also recommend adding a CDK4/6 inhibitor, such as palbociclib, ribociclib, or abemaciclib, in combination with the AI to improve the efficacy of treatment.
* Radiation therapy: As the patient has not received radiation therapy in the past and given the involvement of contralateral axillary lymph nodes with extranodal extension, we would recommend considering regional nodal irradiation, which includes the chest wall (in the case of a mastectomy) and regional lymph nodes (axillary, supraclavicular, and internal mammary). This will help in reducing the risk of further local-regional recurrence and may improve overall survival.
* Close monitoring: The patient should undergo regular follow-ups with physical examinations, and imaging as needed, to closely monitor her response to the treatment and to detect any signs of disease progression or new metastases.
* Supportive care: It is essential to address any potential side effects or complications of the treatments mentioned above, such as fatigue, bone health issues, and lymphedema. This would involve coordinating with a multidisciplinary team of healthcare professionals including medical oncologists, radiation oncologists, surgeons, physical therapists, and other supportive care services.

In summary, our favored therapeutic approach for this patient would be the combination of endocrine therapy with an aromatase inhibitor and a CDK4/6 inhibitor, regional nodal irradiation, close monitoring, and appropriate supportive care. This recommendation is based on the patient's hormone receptor-positive, HER2-negative status, prior treatment history, and the need to address local-regional disease control while minimizing the risk of further recurrence.

**Expert 6: A Favorable Entity Warranting the Right Therapy**

This vignette describes a patient with an ER/PR-positive, HER-2-negative, pT2N1a, mixed histology left breast carcinoma presenting 10 years after initial diagnosis with an isolated contralateral axillary metastasis (CAM). Next steps should include thorough multidisciplinary review. Completion axillary lymph node dissection and a retrial of hormone therapy are strongly recommended.

Although traditional viewpoints would suggest palliation, contemporary evidence has identified CAM as a distinct entity with favorable outcomes in comparison to other areas of dissemination. Further, her molecular subtype and prolonged trajectory from diagnosis to recurrence suggest a favorable biology. These factors warrant the use of aggressive salvage therapy with the goal of improving survival and maximizing local control.

Right-sided locoregional radiation therapy would be recommended. In many Canadian or UK centers, this would entail a hypofractionated dose (42.5 Gy/16 or 40 Gy/15) daily to the chest wall and regional lymph nodes. Full coverage of nodal levels, including the internal mammary nodes, would be encouraged given the concerning pathologic features, although a modified volume could be considered based on results of the axillary lymph node dissection. The provision of chemotherapy would not alter this recommendation.

CAM likely results from aberrant drainage secondary to blockage of normal lymphatic routes, providing some slightly controversial rationale for radiating the original left side. However, for this patient the toxicity of radiation therapy to this area, although minimal, would likely outweigh the benefit.

This case highlights the exciting, everchanging landscape of metastatic breast cancer, which requires comprehensive clinical consideration to ensure high-quality patient-centered care.

**Expert 7: Bilateral Radiation and Systemic Therapy for Optimal Disease Control**

The patient presents with contralateral axillary nodal metastases 10 years after the initial diagnosis, suggesting a need for a more comprehensive approach due to the suboptimal locoregional and systemic treatment received initially. Considering the patient's history and current situation, the following course of action is recommended:

1. Perform thorough imaging, including bilateral magnetic resonance imaging, to assess for potential primary or recurrent tumors in the residual ipsilateral or contralateral breast tissue.
2. Administer bilateral comprehensive radiation therapy to the chest wall and regional nodal irradiation (RNI), targeting undissected axillary nodal basins, supraclavicular nodes, and internal mammary nodes. This aggressive locoregional therapy addresses the risk of residual disease on the left side and the possibility of aberrant lymphatic drainage after the axillary lymph node dissection.
3. Initiate systemic therapy, including endocrine therapy with an aromatase inhibitor, a CDK4/6 inhibitor, and discuss the possibility of chemotherapy to mitigate the risk of distant recurrence and maximize progression-free survival and overall survival.
4. Conduct close monitoring and long-term follow-up to detect any signs of recurrence or progression early and provide appropriate supportive care.

By targeting both sides and incorporating systemic therapy, the treatment plan aims to optimize disease control and improve the patient's prognosis.