**Case 2: One Way or Another: An Oligorecurrence After an Oligometastasis of an Estrogen Receptor-Positive Breast Cancer**

A 52-year-old woman presented with invasive ductal carcinoma of the left breast, cT3 (5.5 cm) cN1 (single axillary level 1 lymph node) cM0, grade 2, estrogen receptor (ER)-positive (70%) progesterone receptor (PR)-negative (0%) Her2/neunonamplified. Bone scan obtained at time of diagnosis revealed two lesions within the sternum (1.8 cm \*1.6 cm) and manubrium (2.9 cm \* 4.6 cm; Fig. 1). The patient received upfront chemotherapy (dose-dense adriamycin, cyclophosphamide, and paclitaxel) with interval imaging demonstrating partial response in the breast and nodes, and sclerosis of the lytic lesions suggesting response to treatment. She underwent breast conserving surgery and axillary lymph node dissection, revealing 1.8 cm of residual invasive disease in the breast and a 4 mm macrometastasis in one of nine axillary nodes without extranodal extension, ypT1c (1.8 cm) ypN1a (1/9) without extranodal extension.

The patient completed adjuvant external beam radiation therapy and was initiated on anastrozole anti-endocrine therapy. She remained without evidence of disease for 12 years, at which time she was incidentally found to have a nodule in the left upper lobe of the lung. Biopsy confirmed metastatic carcinoma consistent with breast primary, ER-positive PR-negative Her2/neu-nonamplified. She completed 12 months of palbociclib and letrozole, with recent reimaging demonstrating no new sites of disease, but further enlargement of the lung nodule to 1.5 cm (Fig. 2).

Fig. 1. Bone scan obtained at time of initial breast cancer diagnosis in 2008, demonstrating uptake within a 1.8 cm \* 1.6 cm lesion in the sternum and a 2.9 cm \* 4.6 cm in the manubrium.

Fig. 2. Diagnostic computed tomography scan at time of recent reimaging following 12 months of palbociclib and letrozole systemic therapy, demonstrating enlargement of the 1.5-cm nodule in the left upper lobe of the lung.

**Expert 1: Little Downside**

Our approach would include sequential review of this case at multidisciplinary tumor board. For patients with de novo oligometastatic disease with sustained response to therapy, we would consider radiation therapy (RT) after surgery, although the benefits from primary surgery and induction chemotherapy are unclear. Retrospective data suggested similar outcomes for patients with metastatic breast cancer limited to sternum/mediastinum treated with curative-intent and those with IIIC disease. For this patient, along with hormone therapy, we would offer 50 Gy in 25 fractions RT to the breast, regional nodes, and sternal disease with deep-inspiratory breath-hold, volumetric modulated arc radiation therapy, and lumpectomy cavity boost. Given the unresected sternal disease, we would consider a 10 to 16 Gy sequential sternal boost.

This patient presented with a single metastatic focus after a long disease-free-interval on aromatase inhibitor therapy alone, then received the same class of hormone therapy (suboptimal) combined with a cyclin-dependent kinase 4/6 inhibitor. We would favor stereotactic body radiation therapy (SBRT) over surgery for local control, and change in systemic therapy; the impact of this approach on survival is unclear. We use a risk-adapted approach for SBRT to lung metastases,3 with ablative doses used for early-stage lung cancer. For this noncentral, non-chest wall location, 1 to 3 fractions may be feasible. Surveillance includes periodic body imaging on next line hormone therapy driven by next generation sequencing, considering further targeted agents. We would tell her that she has incurable but indolent disease with additional treatment options, but that resistance to therapy will develop over time. In her case, safe, risk adapted SBRT offers little downside.

**Expert 2: A Tale of Competing Risk Management**

At the initial presentation, she was oligometastatic, and treatment to achieve durable local control to the left breast, regional nodes, and sternum and manubrium oligometastases could be justified under SABR-COMET.2 Given its proximity to the internal mammary nodal chain, we recommend inclusion of the oligometastatic lesion within the breast and comprehensive regional nodal field (50 Gy in 25 fractions) and simultaneous integrated boost to the sternum and manubrium up to 66 Gy, using VMAT with DIBH or proton radiation therapy if available.

After a significant disease-free interval, she has persistent biopsy-proven ER+ lung metastasis, without other competing health risks. Aggressive local management with radiation therapy may cytoreduce her cancer burden, although there is presently less mature evidence to support this approach.3 SBRT to the left lung lesion would be our preferred approach in lieu of surgical management given the relatively lower risk, and clinical trial enrollment would be offered. 54 Gy in 3 fractions would be prescribed using IMRT, with 4DCT motion management, and PTV coverage of D95% ≥ 100% Rx. With prior lung dose from initial radiation therapy, we recommend accounting for the cumulative EQD2 of lung V20.

Computed tomographic imaging of the lung is recommended every 3 to 4 months after SBRT, as well as surveillance with whole body positron emission tomography/computed tomography to monitor tumor activity, particularly bone lesions that may present as sclerosis. Metastatic disease is not considered curable as participants in oligometastatic clinical trials do eventually progress. However, based on the phenotype of her recurrence, we are hopeful she will live more years with durable disease control, assuming absence of competing health risks.

**Expert 3: The Best Defense is a Good Offense**

1. We agree with early locoregional therapy (LRT). This patient presented with low-volume, bone-only metastatic disease in the setting of an estrogen-receptor expressing (ER+) primary which portends a favorable long-term prognosis in the stage IV setting, further supported by the radiographic response of bony lesions and the absence of additional metastatic spread.

LRT to the primary in metastatic breast cancer (MBC) is controversial as 2 randomized studies have shown lack of survival and/or quality of life benefit to resecting +/-irradiating the primary site. Importantly, these studies included patients with a higher burden of metastatic disease and a heterogeneous mix of receptor statuses—populations with much poorer prognoses than the patient in question. In contrast, a large meta-analysis found a 31.8% reduction in mortality when LRT was employed4 and suggested that patients with bone-only MBC and good response to systemic therapy may derive particular benefit.

We would treat the left breast, undissected axilla, and supraclavicular/internal mammary lymph node basins (regional nodal irradiation [RNI]) with 3-dimensional-conformal RT using a deep inspiration breath hold technique. Recent experiences have demonstrated safety and convenience of moderate hypofractionation when treating whole breast irradiation + RNI. Treatment to 42.56 Gy/16 fractions to whole breast irradiation + RNI is now offered on the MA.39/Tailor RT trial, and it has become our institutional practice to offer 16-fraction courses in this setting.

We would consider including the sternum/manubrium lesions in the tangent fields if feasible without causing unacceptable dose to the heart/lungs; conversion to an intensity modulated radiation therapy plan could be considered if necessary. NRG-BR001 used 30 Gy/3 fx for osseous metastases which, using an alpha/beta of 10, is an equivalent dose in 2 Gy fractions (EQD2) = 50 Gy. However, if using alpha/beta of 4, the EQD2 = 70 Gy for 30 Gy/3 fx while EQD2 = 47.24 Gy for 42.56 Gy in 16 fx. Thus, one could also consider boosting the sternum/manubrial lesions if concern for residual disease, upwards of an additional 10 Gy/4 fx.

2. The growth of this lesion represents oligoprogression while on otherwise effective systemic therapy, and should receive local treatment. We would recommend stereotactic body radiation therapy (SBRT) to the lung metastasis. Metastasectomy can be useful to confirm malignancy/reassess receptor patterns, but as this had already been ascertained via biopsy SBRT offers a less invasive and equally effective option.

An exciting and growing body of literature supports aggressive management of oligometastases. Recently, the landmark phase II randomized SABR-COMET trial confirmed an OS benefit when ablative RT was delivered to all sites of disease in the setting of a controlled primary, and NRG-BR001 has established 45 Gy/3 fx as a safe dose for peripheral lung metastases. More recently, the SAFFRON II trial of pulmonary oligometastases has also shown promising results when SBRT is delivered in a single fraction, further increasing patient convenience. Other 3- to 5-fraction SBRT regimens achieving a BED10 ≥100 Gy would also be reasonable. We await the results of NRG-BR002 to further inform on the role of metastasis-directed SBRT in MBC.

3. As she has already experienced 2 instances of metastatic disease, we would recommend systemic imaging with positron emission tomography−computed tomography or computed tomography chest/abdomen/pelvis, every 3 to 6 months for 2 years from recurrence. With modern therapies, median survival for de novo ER + MBC may approach 5 years;5 given her time to progression, a similar estimate may be reasonable.

**Expert 4: Stage IV or Locally Advanced Disease?**

Randomized stage IV breast cancer trials have shown no survival benefit for surgical removal of the primary. However, metastases to the sternum and mediastinum may represent a locoregional process. A retrospective review of breast cancer patients with limited sternal or mediastinal metastases reported no significant difference in local control, recurrence, or survival compared with patients with stage IIIC disease. An argument can be made to reclassify these patients as locally advanced, similar to the shift in staging for supraclavicular metastases from M1 to N3c in the sixth edition of the American Joint Committee on Cancer staging system. Definitive comprehensive radiation is recommended to the chest wall, draining nodal basins, and involved sternum/manubrium, to 50 Gy in 25 fractions, followed by a sternal boost of 10 to 16 Gy in 5 to 8 fractions, with dose dependent on imaging response to neoadjuvant treatment. Thoracic surgery consultation is recommended for consideration of metastasectomy.

The Consolidative Use of Radiotherapy to Block (CURB) study assessed stereotactic body radiation therapy (SBRT) for oligoprogression in non-small cell lung cancer and breast cancer. Surprisingly, SBRT led to a significant progression-free survival benefit for non-small cell lung cancer (44 vs 9 weeks), but not breast cancer (18 vs 17 weeks). Although a subset of patients may benefit from SBRT, it requires further study. Treatment would only be recommended as part of a trial studying SBRT for oligometastatic disease.

Computed tomography scans of the chest, abdomen and pelvis every 3 months is recommended, similar to the surveillance for the ongoing AVATAR (Audiovisual-Assisted Therapeutic Ambiance in Radiation Therapy) trial. Retrospective studies suggest 3-year survival may be ≥50% in this situation.

ChatGPT’s initial recommendation

**Expert 5: Comprehensive and Individualized Approach**

Our recommendation for this patient with a history of invasive ductal carcinoma, who developed a solitary metastatic lung nodule 12 years after initial treatment and showed progression on palbociclib and letrozole therapy, would be to consider the following approach:

* Stereotactic body radiotherapy (SBRT) for the solitary lung nodule: Since there is a solitary metastatic lesion in the lung that has enlarged despite systemic therapy, local treatment with SBRT could be considered. SBRT is a highly focused radiation therapy that delivers high doses of radiation to small, well-defined tumors, such as the lung nodule in this case. This approach could help control the local disease, potentially offering long-term disease control, and is associated with fewer side effects compared to conventional radiation therapy.
* Re-evaluate systemic therapy: As the lung nodule showed progression on the current palbociclib and letrozole regimen, a re-evaluation of the systemic treatment plan should be considered. This may involve a multidisciplinary discussion with a medical oncologist to determine the most appropriate course of action. It is possible that alternative therapies, such as switching to a different CDK4/6 inhibitor or considering other targeted therapies (e.g., PI3K inhibitors or mTOR inhibitors), may be beneficial in controlling the disease. Additionally, evaluation for potential actionable mutations through genomic profiling could provide further options for targeted therapy.
* Close follow-up and monitoring: After the implementation of the above strategies, it is crucial to closely monitor the patient for any signs of disease progression or recurrence. This should involve regular imaging and clinical evaluations. Any new lesions or progression of disease should be managed promptly with appropriate interventions.

In summary, our recommendation for this patient would be to consider SBRT for the lung nodule, re-evaluate the systemic therapy plan, and maintain close follow-up and monitoring. This approach aims to achieve local control of the solitary lung metastasis, potentially improve systemic disease control, and provide ongoing surveillance for any further disease progression.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 6: Integrating Multidisciplinary Insights**

1. Early locoregional therapy (LRT) with 3D-conformal RT using a deep inspiration breath hold technique for the left breast, undissected axilla, and regional nodal basins. Consider including the sternum/manubrium lesions within the tangent fields and offering simultaneous integrated boost to the sternum and manubrium up to 66 Gy using VMAT with DIBH or proton radiation therapy if available.
2. Stereotactic body radiation therapy (SBRT) for the lung metastasis, offering a less invasive and equally effective option compared to surgery. This addresses the oligoprogression while the patient is on otherwise effective systemic therapy. Prescribe 54 Gy in 3 fractions using IMRT, with 4DCT motion management, and PTV coverage of D95% ≥ 100% Rx, accounting for prior lung dose from initial radiation therapy.
3. Re-evaluate the systemic therapy plan in consultation with the patient's medical oncologist to optimize treatment effectiveness, potentially incorporating newer targeted agents based on next-generation sequencing results.
4. Systemic imaging with PET-CT or CT scans of the chest, abdomen, and pelvis every 3 to 4 months for 2 years from recurrence to monitor the patient's condition and detect any new metastatic lesions.

This recommendation emphasizes the importance of a multidisciplinary tumor board setting to ensure the most appropriate and tailored treatment plan is developed for the patient. The approach addresses both the primary breast cancer and the lung metastasis, providing a balanced treatment plan that aims to maximize local control and disease-free survival.