**Case 4: From the Plexus to the Cord: A Case of Metastatic Breast Cancer**

In 1998, a 46-year-old professional model presented with breast cancer with axillary, infraclavicular, liver, and lung metastasis. She completely responded to systemic therapy but developed brain metastasis treated in 1999 with resection and scalp-sparing whole brain radiation. She continued modeling and remained with no evidence of disease before recurring locally and undergoing lumpectomy and radiation in 2002. After a breast and infraclavicular recurrence, she received chemotherapy followed by modified radical mastectomy in 2005. She remained with no evidence of disease until a positron emission tomography/computed tomography scan in 2013 (Fig. 1a) revealed curvilinear activity in the left infraclavicular region thought to be nodal or vascular phenomena. She developed slowly progressive sensory deficits, pain, and mild weakness in the left forearm. Repeat positron emission tomography/computed tomography scan in 2014 (Fig. 1b) revealed progressive linear uptake concerning for infiltration of the brachial plexus (BP) cords. This prompted electromyography, which confirmed plexopathy. Given suspicion of metastatic BP infiltration, the infraclavicular and supraclavicular regions were treated to 40 Gy in 15 fractions, followed by BP boost of 10 Gy in 5 fractions completed in January 2015 with radiographic response (Fig. 1c). Her weakness remained stable, but imaging revealed slow progression extending to the cervical and thoracic spinal cord, which acutely resulted in ambulatory deficits in November 2018. We thus emergently irradiated her cord with 40 Gy in 15 fractions.

Fig. 1: Chronological progression of brachial plexus metastasis dated (a) December 2013, (b) September 2014, (c) January 2015, (d) June 2015, (e) January 2016, (f) October 2016, (g) May 2017, and (h) May 2018

**Expert 1: Comprehensive Assessment and Tailored Treatment for Optimal Outcomes**

A thorough diagnostic workup is crucial for differentiating malignant infiltration from radiation-induced plexopathy. This includes evaluating clinical history, performing dedicated magnetic resonance imaging (MRI) of the brachial plexus, and utilizing positron emission tomography with computed tomography (PET-CT). Accurate diagnosis will help guide an appropriate treatment plan.

Reirradiation of the brachial plexus can be considered, with a dose of 34 Gy in 15 fractions and a simultaneous integrated boost of 40 Gy in 15 fractions to the non-overlapping area of the spinal cord. While the risk of radiation-induced toxicity is present, it may be acceptable given the potential for inevitable plexopathy without further radiation therapy.

Systemic therapy options, such as targeted therapy or immunotherapy, should be explored based on genomic profiling of the tumor to control disease spread and target resistant cancer cells.

Supportive care measures, including pain management, physical therapy, and occupational therapy, are essential to maintain the patient's quality of life and functionality.

Close monitoring and regular follow-ups should be performed to track disease progression and adjust the treatment plan accordingly. Open communication with the patient about the goals of the treatment, potential benefits and risks, and the importance of a balanced approach that considers both disease control and quality of life is essential.

**Expert 2: High Reward and Low Risk**

Clinical history in combination with ultrasound, magnetic resonance imaging, and positron emission tomography (PET) can assess whether symptoms are due to neurotrophic tumor infiltrate versus radiation plexopathy or another cause. In this patient with infraclavicular disease and prior radiation, symptoms are likely from direct tumor involvement or prior radiation.

Clinically, painless upper trunk lesions with lymphedema correlate with radiation injury, whereas painful lower trunk lesions are more often related to neoplastic infiltration. On magnetic resonance imaging, both radiation plexopathy and tumor appear as hypointense on T1 and have increased T2 signal. On PET, radiation injury is only mildly avid, whereas tumor is often hypermetabolic. The PET avidity and pain in this patient is consistent with tumor.

Increased dose correlates with pain relief in patients with carcinomatous plexopathy. A biologically effective dose (alpha/beta = 10) over 30 is associated with higher rates of treatment response. Recently published large randomized trials of conventional versus hypofractionated treatment for postmastectomy radiation therapy have shown no evidence of brachial plexus injury in patients who received hypofractionation, with a median follow-up of 5 years. Therefore, the dose of 40 Gy in 15 fractions used for this patient seems appropriate for palliation, with minimal risk.

With regard to the optimal dose for reirradiation, there is data to suggest that risk of toxicity to the plexus is low in patients with a >2-year interval between radiation therapy courses. The same authors recommend a cumulative maximum dose of less than 95 Gy. As such, the reported dose of 40 Gy in 15 fractions appears safe and reasonable.

**Expert 3: Ten Percent Plexopathy Is Acceptable in This Case**

Metastatic infiltration of breast cancer into the brachial plexus (BP) is rare. Symptoms can occur years after initial diagnosis and can be confused with treatment-related complications. Diagnostic workup can include electromyography, BP magnetic resonance imaging (MRI), positron emission tomography with computed tomography and/or nerve biopsy to ensure accurate diagnosis. The gold standard in this setting is MRI, with a sensitivity of 95% for detecting perineural invasion and 63% for mapping the entire extent of perineural spread. The clinical target volume of involved nerves can be extended proximally to their site of origin—in this case, at the spinal cord levels C5 to T1.

At the time of initial BP involvement, 40 Gy in 15 fractions (equivalent dose in 2-Gy fractions (EQD23) of 45.3 Gy) followed by a boost of 10 Gy in 5 fractions (EQD23 of 10 Gy) was delivered. Assuming an α/β ratio of 3, an initial, more fractionated regimen such as 60 Gy in 30 fractions may have allowed for dose escalation with minimally increased risk of toxicity. Of note, estimates of the α/β ratio of breast cancer range from 2.2 Gy to 10.0 Gy.

At time of recurrence, if accepting a 10% chance of BP injury, a total EQD23 of 90 Gy could be delivered to the BP.4 This would leave an EQD23 of 35 Gy that could be prescribed to the BP this time. This could be delivered as 34 Gy in 15 fractions to the BP with a simultaneous integrated boost of 40 Gy in 15 fractions to the nonoverlapping area of spinal cord. Admittedly, the use of the linear quadratic equation to estimate cumulative toxicity risk is imperfect, but given the inevitable plexopathy that may arise without further radiation therapy, this dose and fractionation with a relatively low risk of radiation-induced toxicity warrants consideration.

In summary, it is our opinion that the authors5 used an appropriate dose of radiation up front that straddled palliative and curative-intent regimens in terms of its overall risk and efficacy, which appears appropriate for this patient with apparent oligoprogression. In hindsight given the recurrence, an initial aggressive, conventionally fractionated regimen encompassing a larger portion of the BP may have optimized outcomes, although with a slightly higher risk of radiation-induced plexopathy.

**Expert 4: Don't Forget the Value of a Good History**

Differentiating malignant infiltration from radiation induced fibrosis can be challenging so taking a comprehensive history, particularly noting the previous radiation dose to the brachial plexus (BP) and time elapsed since treatment is key. Clinical presentation with both sensory and motor neurologic deficits can point more toward a malignant cause, as can intractable pain at rest and the tempo of progression. The evolution of fibrosis is a slow process. A dedicated magnetic resonance imaging BP protocol is useful to aid the clinical diagnosis. Malignant infiltration is typically less uniform in appearance compared with the linear enhancement of radiation induced fibrosis, which typically presents without a focal mass.

The intent of treatment, projected life expectancy, specifically whether late toxicity will have time to develop, and time interval between radiation courses all help inform the organ at risk constraints. Development of plexopathy is affected not only by total dose and dose/fraction but the volume of the BP receiving a high dose of radiation, the use of concomitant chemotherapy, and whether plexopathy was present at the start of treatment. Most protocols limit the BP dose to between 60 to 66 Gy2/2 with increased risk of toxicity at doses greater than 69 Gy. Chen et al4 reported increased tolerance of the BP to historically accepted constraints in the setting of reirradiation. A clinical decision may need to be made, weighing the risk that plexopathy might be an inevitable consequence of disease progression should the target volume not be adequately covered to meet constraints. These decisions are multifactorial and complex and need to be made with the patient. In the setting of reirradiation of the spinal cord using conventional fractionation, Nieder et al showed that the risk of radiation myelopathy is low, providing the cumulative biologically effective dose is ≤135.5 Gy2, the interval between radiation courses is at least 6 months, and the dose of each course is ≤98 Gy2.

**Expert 5: Systemic Therapy and Supportive Care**

This patient has shown a history of recurrent metastatic breast cancer with involvement of various sites, including the brachial plexus, and a prior history of multiple treatments, including systemic therapy, surgery, and radiation.

Our most favored therapeutic approach for this patient would be a combination of systemic therapy and supportive care. We would first recommend a thorough multidisciplinary evaluation involving a medical oncologist, radiation oncologist, and neurologist to tailor the best treatment plan.

1. The patient has shown a tendency for recurrence and metastasis, which might imply the presence of resistant cancer cells. Systemic therapy, such as targeted therapy or immunotherapy, may be more effective in controlling the spread of the disease and targeting cancer cells that are resistant to previous treatments. Additionally, genomic profiling of the tumor can guide the selection of targeted therapies.
2. Reirradiation of the brachial plexus could be considered; however, given the patient's prior radiation treatments, the risk of toxicity and complications may be higher. A thorough assessment of the benefits and risks of reirradiation should be discussed with the radiation oncologist.
3. Supportive care is essential for this patient due to the sensory deficits, pain, and mild weakness in the left forearm. This may involve pain management, physical therapy, and occupational therapy to improve the patient's quality of life and maintain functionality.
4. Close monitoring and regular follow-ups are necessary to track the disease progression and modify the treatment plan accordingly.

For reirradiation of the brachial plexus, a common approach would be to use a hypofractionated regimen, which consists of administering higher doses of radiation per fraction over a shorter period of time. One potential regimen for this patient could be 30-35 Gy in 10-15 fractions. This approach aims to minimize the risk of radiation-induced complications while still delivering an adequate dose to control the disease.

For reirradiation of the spinal cord, the situation becomes more challenging due to the risk of radiation myelopathy, a rare but potentially severe complication that can result in paralysis. The maximum recommended cumulative dose for the spinal cord is typically around 50 Gy, although the actual dose tolerance may vary depending on factors such as previous radiation treatments and the patient's overall health.

If reirradiation is deemed necessary, it is crucial to use advanced radiation planning techniques such as intensity-modulated radiation therapy (IMRT) or stereotactic body radiotherapy (SBRT), which allow for highly conformal dose delivery to the target while sparing the surrounding healthy tissue.

It is essential to have open communication with the patient about the goals of the treatment, the potential benefits and risks, and the importance of a balanced approach that considers both disease control and quality of life.