

Management of metastatic tumors invading the peripheral nervous system

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Object. The authors present the results of a retrospective review of 37 surgically treated metastases to nerve (malignant peripheral non-neural sheath nerve tumors). Tumor frequencies, presentations, management, and prognosis are discussed.

Methods. Thirty-seven patients who were treated for metastases to nerve between 1969 and 2006 at the Louisiana State University Health Sciences Center were identified in a review of patient records. Notes regarding patient history and physical examination findings were reviewed to provide information on presenting symptoms and signs. Imaging and histopathological examination results were also reviewed. Cases were analyzed depending on the primary tumor and the location of metastasis.

Results. There included 37 surgically treated lesions, 16 of which originated in the breast and 10 of which originated in the lung. In two cases melanomas had metastasized to nerve, and one tumor each had metastasized from the bladder, rectum, skin, head and neck, and thyroid, and from a primary Ewing sarcoma. There was a single lymphoma that had metastasized to the radial nerve and one chordoma and one osteosarcoma, each of which had metastasized to the brachial plexus.

Conclusions. The nervous system is involved in numerous ways by oncological process. Direct involvement of the peripheral nervous system occurs mostly from direct extension, although it occasionally occurs because of distant spread from the primary tumor to nerve. Surgical excision of the metastatic lesion with margins has been useful mostly in the control of pain. Nevertheless, patients eventually succumb to their primary malignancy.

KEY WORDS • malignant tumor • metastasis to nerve • non-neural sheath nerve tumor peripheral nerve tumor

MOST MALIGNANCIES OF THE PNS result from metastases from carcinomas and lymphomas, rather than lesions originating in nerve such as neurosarcomas.^{1,6,9} Infiltration of the PNS can result from a variety of mechanisms, including direct extension of the tumor and lymphatic spread into adjacent noncompartmentalized locations. In addition, tumors can invade the PNS through hematogenous seeding. It is therefore not surprising that most of the described metastases to the PNS occur in plexi in proximal noncompartmentalized anatomical locations such as the supraclavicular areas, the axilla, the pelvic sacral area, and the groin.⁸ The supraclavicular brachial plexus is commonly involved by metastases from tumors invading the nearby lymph nodes, as in breast cancer. In contrast, metastasis to the axillary

level of the infraclavicular brachial plexus results from direct extension of the primary tumor.

Meller et al.⁸ have defined true isolated nerve metastasis as occurring when there is a histologically identified tumor beneath the nerve sheath and between the fascicles, without disintegration of the nerve trunk structure and in the absence of neoplasm in the adjacent soft tissues and regional lymph nodes. Such isolated nerve metastases are less common than tumors extending to adjacent plexi. In this paper, the term “nerve metastases” is intended to include non-neural sheath tumors that are direct extensions into adjacent plexi as well as true isolated metastases.

There are numerous case reports as well as series compilations of tumors metastatic to the PNS. The types of tumors involved include tumors of the breast, lung, rectum, bladder, head and neck, and thyroid, as well as lymphomas, chordoma, melanoma, nonmelanoma skin cancers, and osteosarcomas. Osteogenic or soft-tissue sarcomas displace or adhere to the nerve and encase it and in a few cases

Abbreviations used in this paper: LSUHSC = Louisiana State University Health Sciences Center; PNS = peripheral nervous system.

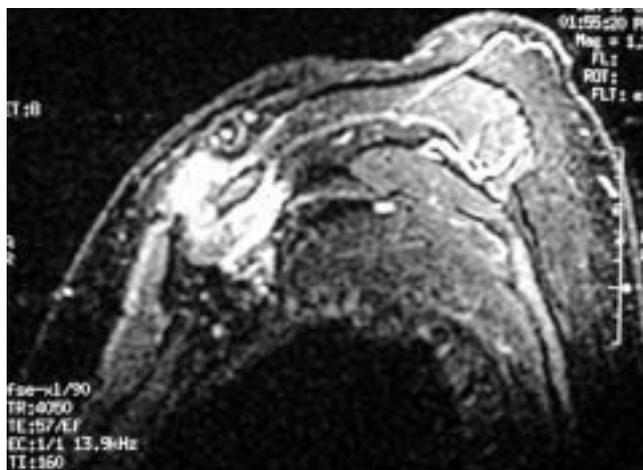


FIG. 1. A T2-weighted MR image showing invasion of branches of the brachial plexus by metastatic carcinoma.

actually invade the nerve. Lymphomas and melanomas can metastasize and secondarily involve a nerve by epineurial invasion or infiltration of the subperineurial zone, the interfascicular epineurium, and eventually the actual fascicle(s).⁷

Clinical expression of PNS involvement in patients with cancer occurs in 1.7 to 16% of cases.¹ The clinical picture varies depending on the mechanism by which the PNS is affected by the metastatic process. The mechanism can involve compression or infiltration of the nerve, deleterious effects of treatment, and metabolic and nutritional factors, which frequently accompany malignancies, as well as paraneoplastic processes. Irrespective of the underlying pathophysiological processes, there is a common denominator in the clinical presentation of the patients: neuropathy. The manifestations include intractable pain and loss of function of the muscles served by the affected nerves. The results of a previous analysis of the presentation of patients with nerve metastases who were treated at LSUHSC showed that patients presented primarily with pain and/or weakness irrespective of any previous treatment.⁴

Treatment of the primary tumor usually involves local surgical excision, radiotherapy, and systemic intravenous chemotherapy.

Clinical Material and Methods

In this retrospective study, charts were reviewed and findings documented for 37 patients who underwent surgery for malignancies metastatic to the PNS, also known as malignant peripheral non-neural sheath nerve tumors or nerve metastases. Physical and neurological examinations were performed to assess the size and location of the tumor, localized tenderness on palpation of the mass, the presence or absence of a Tinel sign, and neurological deficits. Findings on CT scans and/or MR images were reviewed to document each tumor's location, margins, and relationship to adjacent structures. Patients with nerve metastases also underwent a metastasis evaluation, which included lung and abdominal CT scans and technetium liver, spleen, and bone scans. Angiograms were obtained

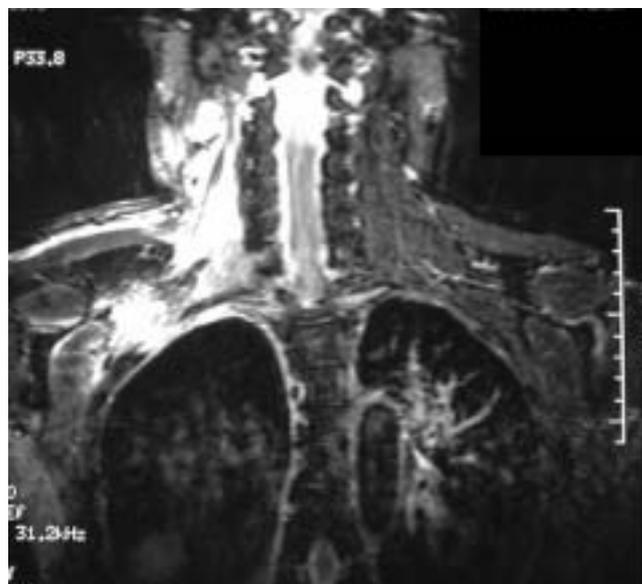


FIG. 2. A T2-weighted MR image obtained in a patient with breast cancer showing extensive involvement of the right brachial plexus from the level of the spinal roots to the cord elements. Note the sharp distinction from the lung, which suggests a breast lesion rather than a Pancoast tumor.

for all tumors of vascular origin to delineate the feeding vessels and the tumor vascularity. Myelograms were evaluated when they had been obtained in cases of tumors near the spinal cord or nerve roots.

The role of needle biopsies in the diagnosis of non-neural sheath nerve tumors remains controversial. We have had patients referred to us after either core needle or fine needle biopsies of these lesions with deficits resulting from the biopsy. We do not generally advocate the use of needle biopsy in the diagnosis of PNS tumors. The introduction of a neural deficit would be unwelcome in cases of benign tumors. In addition, tumors can be heterogeneous with certain sections being representative of a less malignant histological type while other parts have obvious malignant characteristics. The sampling error from such needle biopsies can thus lead to unfavorable decision making in the management of PNS tumors. It is also not uncommon for needle biopsies to be nondiagnostic. As a result, over the years we have favored open resection of suspected nerve metastases, in which we attempt to resect the lesion while preserving neurological function.

The imaging modality of choice in the evaluation of nontraumatic pathological conditions of the brachial plexus is MR imaging. Wittenberg and Adkins,¹¹ in their review of the imaging findings in 104 cases of nontraumatic brachial plexopathy, found that the most common causes were radiation fibrosis (31% of cases), metastatic breast (24%), and primary or metastatic lung cancer (19%), with other types of tumors accounting for just over 25% (Figs. 1 and 2).

Radiation fibrosis occurs 5 to 30 months after completion of radiation therapy. Findings on MR images of diffuse thickening and enhancement of the brachial plexus without any focal mass suggest fibrosis. In addition T1- and T2-weighted images show changes similar to muscle,

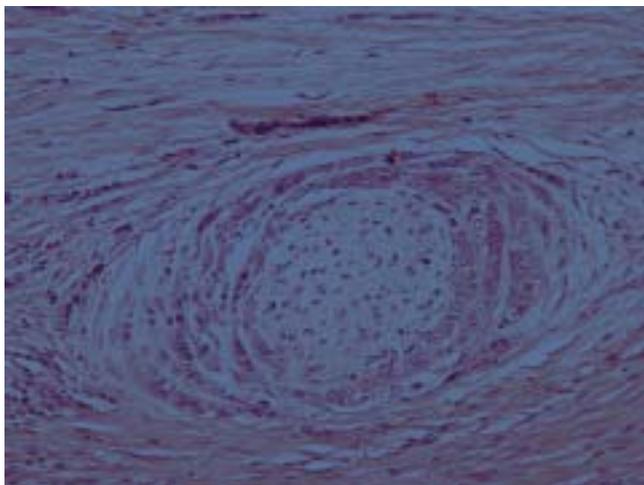


FIG. 3. Photomicrograph showing perineural invasion by metastatic carcinoma.

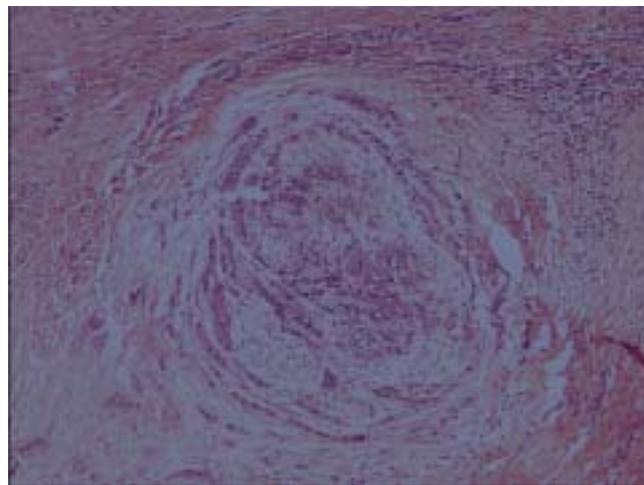


FIG. 4. Photomicrograph demonstrating intraneural invasion by metastatic carcinoma.

with radiation damage showing low signal on T2-weighted images and early infiltration by tumor showing higher intensity.¹¹ Both types of lesions can show variable amounts of enhancement, hence contrast usage does not necessarily facilitate differentiation between the two types of lesions. A major differentiating finding is the presence of myokymia on the electromyographic sampling of muscles in patients with radiation plexitis.

Breast cancer metastasis typically appears as a mass and has a low signal intensity on T1-weighted sequences with increased signal on T2-weighted sequences, although it may occasionally demonstrate low signal intensity on T2-weighted images.¹¹ Again, the presence of mass can be instrumental in differentiating radiation fibrosis from breast cancer invasion.

As previously mentioned, MR imaging remains the imaging modality of choice in the evaluation of malignancies involving peripheral nerves. Differentiating between malignancy and radiation plexopathy on the basis of imaging, even with gadolinium enhancement, remains difficult. This is especially so because both types of lesions can show enhancement upon gadolinium administration. The clinical features, including the history, electromyographic evidence of myokymia, and the usual delayed occurrence of radiation plexopathy can be useful in distinguishing between the two. In this regard, although we have not had extensive experience with positron emission tomography, it can be a useful imaging adjunct in distinguishing between radiation plexopathy and tumor. The role of this modality should be further evaluated.

Primary lung cancer also must be differentiated from intrinsic brachial plexopathy. The presence of Horner syndrome, which typically is present in about 20% of patients with Pancoast tumor, can be helpful in making the diagnosis. Moreover, imaging in various planes can be used to delineate the relationship of the tumor to the lung tissue. Tumors arising from the lung tend to have an irregular attachment to the lung parenchyma, whereas brachial plexus tumors, especially those that are benign, having a smoother border.¹¹

Electromyography was also performed in each patient. Histological diagnoses based on light microscopy studies and at times electron microscopy studies and special staining in difficult-to-diagnose cases were reviewed (Figs. 3 and 4). As noted previously, electromyography can help in differentiating radiation from tumor plexopathy, with radiation-induced plexopathy demonstrating myokymic discharges. Despite this observation, it is possible to have both irradiation plexitis and metastatic cancer especially in the brachial plexus. At times the diagnosis cannot be made on imaging or other ancillary studies, and surgical exploration and biopsy are required.

Tumors classified as malignant and of non-neural sheath origin were included, and the types of treatment of these lesions and their surgical margins were assessed.

Operative Technique for Malignant Tumors of Non-Neural Sheath Origin

If a mass was palpable and/or visualized on an imaging study in a patient with a history of primary cancer, decompression of the involved neural elements was undertaken. Although indicated for malignant peripheral neural sheath tumors, en bloc removal of tumor and adjacent tissue was seldom indicated for malignant peripheral non-neural sheath tumors involving the plexus. Unlike malignant peripheral neural sheath tumors, metastases to melanoma from melanoma and/or some other cancer could often be treated with external neurolysis and careful removal of the tumor from the epineurial level of the nerve. There were exceptions, however, in which the cancer—whether present due to true metastasis or direct extension—also invaded the nerve.

As much of the adjacent mass as possible was also removed. This usually involved external neurolysis, but exceptions existed, particularly in cases of breast cancer. Several patients with intraneural metastases from breast lesions required excision of the neural element(s) with intraneural loci. If pain was a problem, resection of the involved neural element was palliative in some cases. If pain was a problem in cases of pulmonary carcinoma,

decompressive procedures sometimes involved the spinal canal as well as the nerve roots, spinal nerves, and plexal trunks. In other cases of intraneural spread of cancer, resection was necessary for pain control.

The cases of pulmonary metastatic disease involved the brachial plexus by direct extension. Operations of the plexus were usually palliative and usually included subtotal resection of the tumor and decompression. Several were performed via a posterior subscapular approach that included resection of the first rib. Laminectomy is sometimes necessary to achieve decompression when a tumor extends into the spinal canal. A high contralateral open cervical cordotomy can also be carried out to control the pain associated with a Pancoast tumor. The main focus of this palliative operation is to decompress the spinal cord, as well as the compressed or entrapped plexal elements, to improve pain relief and only occasionally to resect the plexal elements.

In the cases of metastatic breast cancer that we have treated surgically, we removed as much of the tumor contiguous to the plexus or nerve as possible and performed a thorough neurolysis of the elements involved. Scarring secondary to irradiation made dissection difficult but not impossible. Fortunately, in 10 cases the tumors, although adherent to epineurium, had not invaded the actual nerve or neural elements. In five other cases breast cancer had invaded neural elements, and in those cases the involved neural elements were usually resected.

Results

Thirty-seven patients presented to LSUHSC between 1969 and 2006 with metastatic tumors involving peripheral nerves and underwent operations for these lesions (Table 1). The largest category of metastatic tumor was breast carcinoma, which accounted for 15 (41%) of 37 cases and usually involved the brachial plexus or one of its outflows (14 [93%] of 15 cases).

In the case of a lymphoma metastatic to the radial nerve, a physician with central nervous system lymphoma presented three years after craniotomy and cranial irradiation with a complete radial palsy at the midhumeral level. At exploration, lymphoma was found within the substance of the radial nerve. No other sign of lymphoma, either in the brain or elsewhere, was found for 5 years, and then the patient died of extensive pulmonary lymphoma.

The brachial plexus was involved in all 10 of the cases in which the primary malignancy was pulmonary, and in most of these cases, the nerve involvement was due to direct extension of the tumor rather than true metastasis. (It is important to remember that occasionally a benign nerve sheath tumor involving a lower plexus element can indent the apex of the lung and mimic a Pancoast tumor.)

A Ewing sarcoma involving the brachial plexus was removed from one patient. Occasionally a malignancy arising from blood vessels such as an angiosarcoma can secondarily involve nerve, and we have had experience with a hemangiopericytoma.

TABLE 1

Summary of 37 cases of malignancies involving peripheral nerves treated surgically at LSUHSC from 1969 to 2006*

Type & Site of Nerve Lesion	No. of Cases	LR	LRM	Repair/RT†	Improved Pain	Maintained Function	Mean FU (mos)	Deaths (MPS)
breast								
brachial plexus	15	15	0	0/0	12	10	17	5 (16 mos)
radial nerve	1	0	1	0/0	1	1	18	0
lung								
brachial plexus	10	7	0	1/0	7	7	18	5 (8 mos)
melanoma								
brachial plexus	2	2	0	0/2	2	2	27	1 (18 mos)
bladder								
brachial plexus	1	1	0	0/0	1	1	14	0
rectum								
pelvic plexus	1	1	0	0/0	1	1	12	0
skin (squamous)								
ulnar nerve	1	1	0	1/1	1	0	14	1 (18 mos)
Ewing sarcoma								
brachial plexus	1	1	0	0/1	1	1	72	0
osteosarcoma								
brachial plexus	1	1	0	0/0	1	1	13	0
lymphoma								
radial nerve	1	0	1	1/1	1	0	60	1 (60 mos)
head & neck								
brachial plexus	1	1	0	0/1	1	0	4	1 (4 mos)
thyroid								
brachial plexus	1	1	0	0/1	1	0	42	0
chordoma								
brachial plexus	1	1	0	0/0	1	0	30	0
total	37	32	2	3/7	31	24	20	14 (15 mos)

* Adapted from Kim et al., 2005. Abbreviations: FU = follow-up; LR = local resection of tumor; LRM = LR with margins; MPS = mean postoperative survival; RT = radiation therapy.

† Repair was by grafts and RT was applied by external beam from a cobalt source.

Two patients had metastatic melanoma that had spread to the brachial plexus, one involved the level of C-8 to the lower trunk, and the other the lateral cord to the musculocutaneous outflow. Gross-total excision was possible, but other metastatic lesions appeared in lung and bone 2 to 3.5 years later, even though both the original and the plexus metastatic sites were thought to be adequately treated by irradiation.

Discussion

The true incidence of plexus metastasis is largely unknown, with most reports coming from institutions with high referral volumes. In a report based on data from two large centers in which 12,000 patients presented with cancer in one year, 52 patients (0.43%) were identified as having metastases to the brachial plexus, and 85 patients (0.71%) as having metastases to the lumbosacral plexus.⁵

The neuromuscular complications of systemic cancer arise from a variety of mechanisms. One mechanism involves a direct effect of the cancer from compression or infiltration. This is especially true with plexus plexopathies because tumors can metastasize along the fascial planes. Other mechanisms involve the effect of anticancer therapies, either radiation or chemotherapy. In addition, paraneoplastic syndromes can also affect the neuromuscular system. In this paper we will focus our discussion on effects from the tumor compression/infiltration with some consideration of radiation plexopathies.

Neoplastic Plexopathies

Brachial Plexopathy. Damage to the brachial plexus from neoplastic disease is mostly seen in association with tumors metastatic from lungs and breasts. In addition, radiation-induced plexopathy should also be considered in the appropriate clinical setting. Spread of tumor is mostly through the lateral axillary lymph nodes. Pain, especially pain of a progressive nature, is a predominant complaint, with neurological examination demonstrating loss in the lower plexus. Occasionally the whole plexus is involved. The predilection for involvement of the C-8 and T-1 spinal nerves and the lower trunks can be explained by the close contact with the lymph nodes draining the lung and breast and the paucity of lymph nodes around the upper trunk and its divisions.²

Apical lung tumors lie in proximity to the C-8 and T-1 nerve roots, producing neuropathic pain along the medial aspect of the upper extremity. With continued growth of the tumor, the whole plexus may become involved. Pancoast syndrome, which occurred in seven of nine patients with pulmonary metastases to the brachial plexus, sometimes occurs as a result of local extension of a pulmonary apical tumor with involvement of the C-8, T-1, and T-2 nerves. There usually is shoulder pain radiating in the ulnar distribution of the arm, often with radiological evidence of the destruction of the first and second ribs. If pain is a severe problem, a palliative approach can consist of posterior subscapular resection of the first rib and subtotal resection of the apical tumor to decompress the lower elements of the plexus. This procedure, combined with cervical laminectomy for associated epidural metastatic disease is also palliative. Occasionally, a high contralateral

open cervical cordotomy also helps control the pain associated with a Pancoast syndrome. The main focus of this palliative operation is to alleviate pain and decompress the compressed spinal canal and or compressed plexal elements.

In addition, the tumor can invade the epidural spinal canal with attendant symptomatology. Other manifestations can include compression of the recurrent laryngeal nerve resulting in hoarseness or vocal cord paralysis.¹⁰

Breast cancer, in addition to other cancers, can infiltrate the brachial plexus by direct extension of the tumor. This infiltration may involve the infraclavicular cords of the plexus and occasionally the lower trunk producing numbness in the medial aspect of the hand and forearm and ulnar nerve involvement resulting in weakness of the intrinsic muscles of the hand.

Separating radiation plexopathy from cancer plexopathy in a patient with a known history of cancer and radiation therapy can be a challenge. Electromyography can be used to evaluate myokymic discharges, which would suggest radiation plexopathy. In addition, pain tends to be a predominant complaint in patients with cancer, while less severe pain, lymphedema, and upper plexus lesions tend to be associated with radiation-induced damage. Radiation plexopathy is dose dependent and develops as stated before in a time-dependent fashion. The use of doses per fraction in the range of 2.2 and 4.58 Gy, with total doses between 43.5 and 60 Gy, causes a significant increase in the risk of brachial plexus injury, from 1.7 to 73%.³ Overall, the risk of developing brachial plexopathy after conventionally fractionated radiotherapy is estimated to be below 1%.³

Proposed criteria thought to suggest metastatic breast carcinoma includes the presence of Horner syndrome, a history of a radiation dose less than 60 Gy, and presentation in the first few years after mastectomy. In one study, the presence of Horner syndrome was indicative of neoplastic brachial plexopathy, rather than radiation-induced plexopathy.⁷ We have seen exceptions to these criteria. For example, several women have presented with breast carcinoma within one or more plexal elements 15 or more years after initial treatment of the breast lesions.

It should be noted that the brachial plexus morbidity can also result from surgical trauma.

Lumbosacral Plexopathy. The lumbosacral plexus can be damaged by extension of tumors from intraabdominal neoplasms or metastasis. The most commonly involved malignancies are colorectal, cervical, and breast cancers, sarcomas, and lymphomas. In up to 73% of the cases of lumbosacral plexopathy associated with malignancy, there is direct extension of the tumor into the plexus, with the remaining cases involving a metastatic process.² Pain is usually the first manifestation, followed by paresthesias and weakness. Symptoms of radiation damage generally occur in a delayed fashion; the interval from radiotherapy to presentation has been described as ranging from 1 to 31 years after radiotherapy (median 5 years).² Radiation damage is typically a slowly progressive painless but debilitating condition with asymmetric bilateral involvement. Imaging is usually unremarkable. The finding of myokymia on an electromyographic examination can be used to support the diagnosis.

Cervical Plexopathy. The most common symptom at presentation is pain. Most of the neoplasms originate from carcinomas of the head and neck, lymphomas, and other systemic tumors. Phrenic nerve involvement can result in paralyzed hemidiaphragm. Involvement of the cervical sympathetic trunk can result in a unilateral postganglionic Horner syndrome.⁵ Other manifestations can include difficulties with neck movement as well as swallowing difficulties.

True Metastatic Disease

True metastatic disease rather than direct extension of cancer involving a nerve is seen with lymphoma, bladder cancer, and melanoma, although these lesions are less common than breast or pulmonary cancers. With melanomas involving the plexus, removal of the tumor from any epineurial attachment has sufficed. The surgical approach is followed by local irradiation. A similar approach is also appropriate for lymphomas, at least for palliative treatment of these tumors.

Conclusions

Metastatic plexopathy is a disabling accompaniment of advanced systemic disease. Of malignant lesions, breast and lung carcinomas are the most likely to metastasize to a nerve. Regardless of the location, carcinomatous plexopathy is typically associated with severe unrelenting and often progressive pain as the cardinal feature at presentation.⁵ The loss of function is also often unrelenting, with development of weakness, paresthesias, and numbness.

The results of radiotherapy treatment for pain have been disappointing. In one series only 46% of patients had pain relief with radiotherapy, and none had improvement of neurological signs.² Surgical indications for metastatic lesions have therefore included pain and paresthesias, progressive deficit, and usually a palpable and very tender mass.

Resection of malignant tumors is dependent on their origin and location. Even though total resection may be the goal of surgery, it is not always possible to achieve in cases of plexal malignancies without severe functional and vascular loss—even if some loss is accepted as a result of sacrifice of the element with the most involvement.⁴ If metastatic tumor involves plexus or nerve, the first order of business is decompression of the neural elements involved. En bloc removal of tumor and adjacent tissue, although indicated for malignant tumors of neural

sheath origin, is not indicated for non-neural sheath tumors involving plexi. Instead, as much tumor as possible should be removed to thoroughly decompress the neural elements.

Further treatment with irradiation or chemotherapy is individualized for each patient and involves input from an oncologist and a radiotherapist. The overall prognosis depends on the primary neoplasm and the extent of its control.

References

1. Antoine JC, Camdessanche JP: Peripheral nervous system involvement in patients with cancer. **Lancet Neurol** **6**:75–86, 2007
2. Chad DA, Recht LD: Neuromuscular complications of systemic cancer. **Neurol Clin** **9**:901–918, 1991
3. Galecki J, Hicer-Grzenkiewicz J, Grudzien-Kowalska M, Michalska T, Zalucki W: Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer—a review. **Acta Oncol** **45**:280–284, 2006
4. Ganju A, Roosen N, Kline DG, Tiel RL: Outcomes in a consecutive series of 111 surgically treated plexal tumors: a review of the experience at the Louisiana State University Health Sciences Center. **J Neurosurg** **95**:51–60, 2001
5. Jaeckle KA: Nerve plexus metastases. **Neurol Clin** **9**:857–866, 1991
6. Kelly JJ, Karcher DS: Lymphoma and peripheral neuropathy: a clinical review. **Muscle Nerve** **31**:301–313, 2005
7. Kim DH, Murovic JA, Tiel RL, Moes G, Kline DG: A series of 146 peripheral non-neural sheath nerve tumors: 30-year experience at Louisiana State University Health Sciences Center. **J Neurosurg** **102**:256–266, 2005
8. Meller I, Alkalay D, Mozes M, Geffen DB, Ferit T: Isolated metastases to peripheral nerves. Report of five cases involving the brachial plexus. **Cancer** **76**:1829–1832, 1995
9. Ramchandren S, Dalmau J: Metastases to the peripheral nervous system. **J Neurooncol** **75**:101–110, 2005
10. Wen PY, Schiff D: Neurologic complications of solid tumors. **Neurol Clin** **21**:107–140, viii, 2003
11. Wittenberg KH, Adkins MC: MR imaging of nontraumatic brachial plexopathies: frequency and spectrum of findings. **Radiographics** **20**:1023–1032, 2000

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