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Cervical lymph node metastases from remote primary tumor sites

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Abstract

Although most malignant lymphadenopathy in the neck represent lymphomas or metastases from head and neck primary tumors, occasionally, metastatic disease from remote, usually infraclavicular, sites presents as cervical lymphadenopathy with or without an obvious primary

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tumor. In general, these tumors metastasize to supraclavicular lymph nodes, but occasionally may present at an isolated higher neck level. A search for the primary tumor includes information gained by histology, immunohistochemistry, and evaluation of molecular markers that may be unique to the primary tumor site. In addition, 18F-fluoro-2-deoxyglucose positron emission tomography combined with CT (FDG-PET/CT) has greatly improved the ability to detect the location of an unknown primary tumor, particularly when in a remote location. Although cervical metastatic disease from a remote primary site is often incurable, there are situations in which meaningful survival can be achieved with appropriate local treatment. Management is quite complex and requires a truly multidisciplinary approach.

Keywords

cervical lymph node; non-head and neck cancer; unknown primary; diagnosis; neck dissection

INTRODUCTION

Cervical lymph nodes are a common site of metastases for malignant tumors that originate at primary sites in the head and neck. These include squamous cell carcinomas of the upper aerodigestive tract as well as metastases from salivary gland, thyroid, and skin cancers. Primary lymphoma in neck nodes must be considered in any differential diagnosis. Occasionally, neoplasms from primary sites outside of the head and neck region may unexpectedly metastasize to the neck. In evaluating a patient presenting with a malignant lymph node and no obvious primary site in the head and neck, it is essential to consider which tumors have a propensity to metastasize to the neck and how such disease should be managed. The mechanism leading to the occurrence of head and neck metastases from many of the distant primary tumors remains obscure, as there are often no obvious lymphatic pathways to explain their mode of spread. An experienced pathologist may be helpful in identifying specific tumor types by using specific tumor markers. The presence of lymphatic metastases in the neck from a remote primary site has significant impact on the patient's prognosis.

About 1% of all head and neck malignancies are accounted for by metastases from a remote primary site (most frequent identifiable sites include the breast, lung, gastrointestinal tract, genitourinary tract, and, uncommonly, the central nervous system). This review considers the likely individual malignancies (excluding lymphoma and melanoma) that present with cervical or supraclavicular lymphadenopathy. Also discussed are the role of neck dissection in the local treatment of the neck and the likely outcome effect of patients' so treated.

LYMPHATIC DRAINAGE

The predictable flow of the head and neck lymphatics can help localize a primary malignancy arising from organs or mucosa in the head and neck area. Level II nodes, for example, most often correspond to a primary site in the upper neck region, such as the oropharynx or the parotid gland, and level I nodes often are associated with oral cavity and salivary gland cancers.

In contrast, it is more difficult to establish the exact lymphatic pathways to the neck nodes from primary tumors arising below the clavicles, although there is a predilection for such metastases to be located to the left neck. The thoracic duct enters the central venous system in the neck at the junction of the left subclavian and internal jugular veins. The thoracic duct originates at the confluence of the cisterna chyli just below the diaphragm to the right of the aorta. The duct enters the thorax through the aortic opening of the diaphragm and travels superiorly in the posterior mediastinum. Lymphatic flow toward the left neck begins in the superior mediastinum and, as a result, the lymph nodes in the left supraclavicular region will have afferent drainage that includes the thorax, abdomen, and pelvis.¹ This left supraclavicular node, as described by the 19th century pathologists, Virchow and Troisier are generally known as Virchow's node. Blockage of lymphatic flow in the left lower cervical area may allow retrograde spread and the involvement of more superior or contralateral neck nodes. The route of drainage from the pelvis to the para-aortic nodes and into the mediastinum can also include spread through hepatic nodes.² Involvement of right-sided neck nodes may be associated with more extensive mediastinal involvement.

PRETREATMENT EVALUATION AND IDENTIFICATION OF THE NEOPLASM

As with all cancers that present as a malignant cervical lymph node, without an obvious primary tumor detectable on initial clinical examination, the search for the primary site is influenced by the location and level of the nodal mass in the neck. Additional diagnostic information is also gained by aspiration (or tissue biopsy of the node if aspiration is nondiagnostic), history, and physical examination of the entire patient and likely sites may be identified and/or confirmed by the imaging studies. As a general rule, metastatic nodes in the upper two thirds of the neck originate from primary tumors of head and neck origin, whereas the lower one third of the neck and supraclavicular nodes often represent metastatic disease from infraclavicular sites. However, there are many exceptions to this generality. Because of the low cost and high diagnostic accuracy, the combination of ultrasound and fine-needle aspiration cytology (FNAC) represents a clinically valuable and reliable method of choice for diagnosis in most cases of enlarged lymph nodes from an unknown primary in the first instant. Ultrasound-guided core biopsy may be considered as a diagnostic technique if the accuracy of FNAC is equivocal or nondiagnostic.³ Even in cases of lymphoma, for which excisional biopsy is considered standard for pathological diagnosis, core biopsy has been shown to yield an adequate diagnosis and to avoid the need for excision.⁴ When needle biopsy techniques fail to produce sufficient diagnostic information, open incisional or excisional biopsy is necessary.

Immunohistochemical as well as molecular studies can render a more accurate tissue diagnosis and can be carried out on cytology samples (from paraffin-embedded cell blocks), core biopsy samples, or tissue obtained by open biopsy (Table 1). The most challenging diagnostic problems occur in cases of adenocarcinoma, because of the multiplicity of anatomic sites that may harbor such a primary tumor. A differential diagnosis for adenocarcinoma in neck lymph nodes includes metastases from the lungs, breast, and gastrointestinal tracts.⁵ In such cases, primary salivary gland malignancies should also be considered in the differential diagnosis.

A number of relatively specific tumor markers may aid in the identification of the site of the cancer. The profiles of cytokeratin (CK)7 and CK20 are the most common CK markers used for identifying the primary location of metastatic adenocarcinomas. CK7 is detected in tumors of the lung, ovary, endometrium, and breast, but not in lower gastrointestinal tract tumors. CK20 is normally expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. The CK phenotype CK20-positive/CK7-negative favors lower gastrointestinal tract primary tumors. Certain studies have reported that 75% to 95% of colon tumors are CK20-positive/CK7-negative, whereas 85% of lung carcinomas are CK20-negative/CK7-positive. More tumor-specific immunostains are discussed in the representative sections below (see Table 1).

The advent of 18F-fluoro-2-deoxyglucose positron emission tomography combined with CT (FDG-PET/CT), has greatly improved the ability to detect the site of a previously unknown primary tumor, more so when it is in a remote location. A meta-analysis of 11 studies comprising 433 patients, most with cervical primaries but some with noncervical, Kwee and Kwee⁶ reported an overall primary tumor detection rate, pooled sensitivity, and specificity of 37%, 84%, and 84% for this modality in detecting unknown primary tumors.

SPECIFIC PRIMARY TUMOR SITES

Breast cancer

Although the occurrence of neck metastases in breast carcinoma is low (2.3% to 4.3%),^{7–10} breast cancer is the most common distant primary to metastasize to neck lymph nodes.⁹ The cervical nodes most often affected are the supraclavicular lymph nodes; jugular chain metastases are an extraordinarily rare event (0.5% of cases).¹¹ Cervical lymph node metastases can occur months to years after diagnosis of the primary tumor.¹²

Lymphatic drainage from the breast by is reported to flow by 1 of 3 principal routes: the axillary, transpectoral, and internal mammary pathways. The lymph vessels from medial breast tissue perforate the pectoral and intercostal muscles and enter the internal mammary lymph nodes. The skin, nipple, and lactiferous tubules drain into a subareolar plexus and on to the axillary nodes, but the plexus can be bypassed by metastases directly to the axilla. From the axilla, the lymphatics travel along the axillary and subclavian vein and into the jugulosubclavian confluence.¹³ Cervical lymph nodes may be involved through this pathway.

Until early 21st century, supraclavicular lymph node metastases from breast cancer were considered distant metastases and classified as stage IV disease.¹⁴ The prognosis in such cases with neck disease was historically considered to be poor, similar to that of patients with visceral metastases (5-year reported survival rates ranging between 5% and 34%), and treatment did not seem to influence overall survival.¹⁵ However, it has been more recently recognized that the outcomes of patients with regional stage IV disease (isolated regional recurrence) fared better than those of patients with visceral stage IV disease. The current revised version of the American Joint Committee on Cancer Staging System for Breast Cancer (2003) and the current classification of the International Union Against Cancer note that supraclavicular lymph node metastases be classified as pN3c (metastases in ipsilateral

supraclavicular lymph nodes) and considered stage IIIC (any T, N3, or M0) if no distant metastases are diagnosed.⁷ The question remains whether upper and middle jugular vein lymph node (levels II and III) metastases represent distant disease as opposed to isolated supraclavicular metastases. Contrary to the current staging system, Bisase and Kerawala¹⁶ conducted a survey in the United Kingdom regarding the management of breast carcinoma that had metastasized to the neck, 61% of those interviewed clinicians felt that both level V and III neck metastases represent incurable stage IV disease.

Tumor involvement of the supraclavicular lymph nodes is an unfavorable prognostic indicator.^{11,12} However, patients with breast cancer who present only with involved neck nodes have been observed to have improved survival.¹⁰ Brito et al¹⁷ conducted a study involving 70 patients with positive breast cancer supraclavicular lymph nodes who received aggressive treatment that included induction chemotherapy, surgery, and postoperative chemoradiotherapy. At a median follow-up time of 8.5 years, the disease-free survival and overall survival of these patients was equivalent to those with stage IIIB disease without distant metastases and was significantly better than patients classified as stage IV. As such, classifying supraclavicular lymph node metastases as distant metastases may lead to inadequate treatment of some patients. However, given the low frequency of supraclavicular metastases, there is no consensus regarding optimal treatment. Bisase and Kerawala¹⁶ concluded that there is a widespread inconsistency in the management of such patients, but there was a trend toward aggressive surgical treatment, including recommendations for comprehensive neck dissection despite the lack of high-level evidence. After a neck dissection, there was also no agreement as to whether giving adjuvant treatment was necessary, but the prognosis in general was better in cases managed by combined adjuvant therapies.^{8,9,18}

The histopathology of metastatic breast adenocarcinoma can range from ducts and tubules (ductal carcinoma) to single cells or cords (lobular carcinoma) to basaloid nests (basal-like carcinomas). By immunohistochemistry, the most commonly used markers to assess for metastatic breast carcinoma are estrogen receptor (ER), progesterone receptor (PR), human epidermal receptor 2 (HER2)/neu (receptor tyrosine-protein kinase erbB-2), gross cystic disease fluid protein, mammaglobin, and GATA binding protein 3 (GATA-3).^{19–23} Importantly, ER and PR expression in the primary tumor can differ from those in the supraclavicular metastases, which possibly indicates de-differentiation of the tumor.¹²

Finally, it must be remembered that there is considerable overlap in the histologic and immunophenotypic appearances of breast carcinoma and salivary gland carcinoma.²⁴ The distinction between metastases from a breast or salivary primary must, in most cases, be made clinically and/or radiographically; the availability of pathologists with expertise in distinguishing these neoplasms is important. Of particular note, salivary ductal carcinomas frequently overexpress HER2/neu and may be confused as breast cancer.

Lung cancer

Lung cancer is generally classified as either: nonsmall cell lung carcinoma (NSCLC) or small cell lung carcinoma (SCLC). Non-small cell tumors include adenocarcinomas, which are responsible for about 40% of cases, squamous cell carcinomas (25% to 30%), large cell

carcinomas (10% to 15%), and alveolar cell carcinoma (1% to 2%). The risk of dissemination of small cell carcinoma ranges from 74% to 96%, adenocarcinoma from 50% to 82%, large cell carcinoma from 48% to 86%, and squamous cell carcinoma from 25% to 54%.²⁵ With the exception of large cell carcinomas and adenocarcinomas, lung cancers rarely metastasize to the neck. When neck metastases occurs, the supraclavicular group is most often involved, although involvement of level I and II nodes has also been reported.²⁶ Metastatic involvement of the supraclavicular lymph nodes by pulmonary malignancies is classified as N3, which is considered to be at least stage IIIB, and involvement of other cervical lymph nodes is classified as M1 (stage IV disease).¹⁴

Davis et al²⁷ reported the frequency of cervical lymph node involvement in patients with lung cancer, to vary from 1.5% to 32%, possibly because the term “cervical node” was used without site specification. High resolution ultrasound is extremely useful for imaging these patients.^{28,29} Prosch et al³⁰ assessed the utility of ultrasound evaluation and ultrasound-guided fine-needle aspiration biopsy for the diagnosis and staging of patients with lung cancer. They reported that enlarged nodes that were missed on CT in 16% of non-NSCLCs, and in 35% of SCLCs in a study of 300 consecutive patients. In these cases, ultrasound-guided biopsy examination detected malignancy and staged the disease N3 or M1, which avoided or prevented more invasive diagnostic procedures.

The curative potential and management plans of patients with lung cancer vary according to histological type and stage of disease. Patients with extensive-stage SCLC have particularly aggressive disease and a median survival on the order of 8 months and 5-year survival 10%; surgery of metastatic sites is almost never recommended. The prognosis of patients with advanced NSCLC is variable according to its histological and molecular characteristics, and treatment should be tailored to the findings of individual patients. There is no reported role for neck dissection for cervical metastases from a lung carcinoma.²⁹ For the majority of cases, surgical removal of metastatic nodes in the neck from lung cancer is not indicated because of the aggressive nature of this disease. It carries a dismal prognosis, whether or not a neck dissection is performed. However, select patients with isolated supraclavicular lymph node involvement (including those with ipsilateral primary and nodal disease completely included within a radiation portal) can be treated with curative intent with concurrent chemoradiotherapy.

Morphologically, metastatic lung cancer may be glandular (ie, adenocarcinoma), squamous, or neuroendocrine (eg, small cell carcinoma, large cell carcinoma, or carcinoid tumor). The most useful immunohistochemical tools for identifying metastatic lung adenocarcinoma are thyroid transcription factor-1 (TTF-1) and Napsin-A.^{31–33} Increasingly, molecular diagnostics (including the use of next generation sequencing technology), has identified specific subsets of advanced-stage NSCLC, which have improved prognosis with targeted therapy.

It is important to note that for nonadenocarcinomas (ie, squamous or neuroendocrine tumors), the distinction between a lung and head and neck primary cannot be made by histology or immunohistochemistry. This is particularly challenging for management for the approximately 10% of patients with a head and neck squamous cell carcinoma with

synchronous presentation of a solitary lung mass. A biopsy of the lung mass confirming a different histology would support 2 separate malignancies, but a squamous histology of both head and neck and lung lesions leave the clinician with the challenge of considering the lung lesion as a metastases or a second primary.³⁴

Esophageal cancer

Topographically, the esophagus is separated into cervical and thoracic portions. From an oncologic point of view, there are major differences between the upper two-thirds and the lower third of the thoracic portions. A submucosal plexus of lymphatics can be identified running the entire length of the esophagus with the upper two-thirds draining superiorly and the lower third inferiorly. There also may possibly be lateral lymphatic connections with the thoracic duct. With such a rich lymphatic supply, metastatic spread is unpredictable resulting in skip lesions, which are reportedly common.²⁹ Mucosal histology also differs along the regions of the esophagus, and, as a result, cancers of the upper two-thirds are usually squamous cell carcinomas but those that arise in the lower third are most often adenocarcinomas; the latter have become more common in recent years. The presence of involved regional lymph nodes is associated with significantly reduced survival, although they do not necessarily preclude long-term survival after resection.^{35,36} Long-term survival has not been reported in patients with junctional cancers who have cervical nodal disease or nodal metastases in 3 body compartments (neck, mediastinum, and abdomen).³⁶

Approximately 20% to 30% of esophageal carcinomas present with cervical node involvement.³⁷ Neck ultrasound frequently detect clinically nonpalpable metastatic nodes leading to alteration of the final pretreatment TNM staging in patients with squamous esophageal carcinoma. Twenty-eight percent of patients who present initially with no palpable cervical nodes were subsequently found to have malignant nodes after being evaluated by ultrasound.³⁸ Carcinomas of the esophagus may exhibit squamous or glandular (ie, adenocarcinoma) histology. Esophageal squamous cell carcinomas are microscopically indistinguishable from head and neck squamous cell carcinoma. Esophageal adenocarcinomas are very similar to those of the stomach, as described below.

The role of neck dissection for esophageal squamous cell carcinoma remains controversial.³⁹ Kato et al⁴⁰ found that patients who had bilateral neck dissection as well as transthoracic esophagectomy along with mediastinal and abdominal lymphadenectomy had a 5-year survival of 49% compared with 34% for those whose necks were not treated. Moreover, the prognosis for patients with positive cervical lymph nodes (26% of neck specimens) was relatively satisfactory (4-year survival of 48%). The presence of positive cervical nodes in patients with lower esophageal cancer involves a significantly worse survival.³⁷ The number of positive cervical nodes is important, as the overall survival of patients with 5 metastatic nodes is 6% compared with 45% for patients with 5 involved nodes.³⁷

Gastric cancer

Gastric carcinoma has a particular propensity to involve Virchow's node. Only a single case has been reported of gastric carcinoma that had first presented as cervical lymph node

metastases that had bypassed Virchow's node.⁴¹ Lymphatic spread is along the vascular network to nodes in the left gastric, hepatic, and splenic chains, and on to the celiac plexus and porta hepatis from where the thoracic duct is entered.²⁹

Most gastric cancers are adenocarcinoma, with lymphoma, squamous cell carcinoma, and carcinoid tumors accounting for the remaining number of malignant gastric neoplasms. Metastatic gastric carcinoma may have the appearance of an intestinal adenocarcinoma or as single discohesive cells (ie, signet ring cells). Gastric carcinomas do not have a very specific immunoprofile; they are frequently positive for caudal type homeobox-2 (CDX-2), similar to other carcinomas of the intestinal tract.^{42,43}

The presence of cervical or supraclavicular lymph nodes indicates stage IV disease, which is associated with 5-year survival of 4%. Currently, there is no evidence to support a neck dissection in these cases.⁴⁴

Hepatocellular cancer

The principal site of extrahepatic metastases of hepatocellular cancer (HCC) is the lung. Extrahepatic metastases of these tumors occurs in about 30% to 50% of patients and depends on presenting tumor stages.⁴⁵ Lymphatic spread of HCC ordinarily occurs to the hepatic hilar and peripancreatic and perigastric lymph nodes; "skip metastases" to more distal nodes is reportedly rare. However, mediastinal, axillary, supraclavicular, and cervical lymph nodes have been occasionally reported.^{46,47} Most lymph flows toward the hepatic hilum running through the hepatoduodenal ligaments. On the other hand, a small amount of flow communicates with the diaphragmatic and intrathoracic lymphatic system through the bilateral triangular ligaments. The latter pathways might be an explanation to account for the uncommon metastases to the cervical lymph nodes.

Terada and Maruo⁴⁸ examined unusual extrahepatic metastatic sites from HCC, and they identified only a single case with cervical nodal metastases. In addition, Kobayashi et al⁴⁹ described another case of HCC that presented with cervical nodal metastasis that had "skipped" the common intermediate routes of involvement.

Histologically, HCC consists of large cells with abundant eosinophilic cytoplasm arranged in sheets or trabeculae. Occasionally, the cancer cells produce a bile-like substance, which is a helpful histologic clue. The most helpful immunostains for identifying HCC are hepatocyte paraffin 1, glypican-3, and arginase.^{42,50,51}

Thus, the rarity of reported HCC metastases to cervical lymph nodes limits any ability to conclude any evidence to consider any benefit from a therapeutic neck dissection for this disease.

Gastrinoma

Gastrinoma, a neuroendocrine tumor, has a similar appearance to neuroendocrine tumors of other organs. They are characteristically positive for synaptophysin, chromogranin, and, of course, gastrin.

Gastrinomas can be either benign or malignant. Malignancy is associated with metastases to the liver and locoregional lymph nodes. Westreich et al⁵² reported a case in which a patient with refractory peptic ulcer disease and elevated serum gastrin levels demonstrated uptake on octreotide scan near the pancreas as well as a focus within the left supraclavicular neck. There was no evidence of a primary lesion or liver disease on either preoperative or postoperative imaging.

These tumors can be located in duodenum (43%), pancreas (33%), and extrapancreatic locations (27%), such as stomach, ovary, kidney, liver, and lymph nodes.⁵³ The absence of a solid organ primary and presence of skip metastases to the neck without prior liver involvement is very uncommon, but in a patient with refractory peptic ulcer disease and a left supraclavicular lymph node, this disease entity should be included in the differential diagnosis. Fine-needle aspiration or incisional biopsy may yield a definitive diagnosis.⁵² In case of isolated metastases in the neck, a neck dissection should be considered as an option.⁵²

Renal cell carcinoma

Renal cell carcinoma (RCC) is the third most common infraclavicular tumor to metastasize to the head and neck, only surpassed by breast and lung carcinomas.⁵⁴ Publications have highlighted the potential for metastases of RCC to the head and neck.⁵⁵ Metastases occurs in about 15% of patients with this neoplasm, and nearly 8% of patients present with disease in the head and neck region.^{56,57} However, only 1% of patients with RCC have metastases confined only to the head and neck.⁵⁸ These metastases may either clinically precede the diagnosis of the renal primary tumor or may occur many years after apparently successful surgery of the primary tumor. The explanation for this apparent propensity for metastases to the head and neck region remains unclear. Some of these tumors seem to have spread by a hematogenous route, bypassing the pulmonary capillary filtration mechanism, metastasizing directly to the head and neck.⁵⁸ The postulated mechanism for this phenomenon is spread through Batson's venous plexus: valveless veins connecting the pelvis and thorax to the vertebral venous plexus. This rich venous system offers little resistance to the passage of tumor emboli, especially during efforts that increase intra-abdominal or intrathoracic pressure.⁵⁹ The vertebral venous plexus can bypass the pulmonary venous system producing metastases to the head and neck region without lung involvement.⁵⁶ Tumors may also spread by lymphatics into and through the thoracic duct.

The most common histological variant of RCC is the clear cell type. However, other histological subtypes, such as papillary RCC, may occur.⁶⁰ Using immunohistochemistry techniques, the most useful marker for confirming the diagnosis of RCC is paired box gene-8 (PAX-8).⁶¹ Other markers like CD10 and RCC are sensitive but not very specific. It must be remembered that PAX-8 immunostaining is also frequently seen in thyroid carcinomas, so additional immunostaining for TTF-1 and thyroglobulin should be used to exclude a thyroid carcinoma before considering the possibility of metastatic kidney cancer.^{62,63}

The most common clinical presentation of metastatic RCC to the head and neck is as an enlarging neck mass. Nodal metastases from RCC are frequently associated with a vascular

component. Signs of such a vascular component can be demonstrated on a postcontrast CT scan, which is attributed to their vascularity and lack of tumor calcification.⁶⁴ However, the vascular nature of these metastases is not always clinically evident, and in such instances it is usually the history of a prior renal tumor that suggests the true origin of the head and neck mass.⁶⁵

Management of metastases of RCC must be tailored to the specific clinical scenario of each patient presenting. It is reasonable to attempt aggressive local control of the head and neck lesions in the absence of other metastases, provided control of the primary site can be confirmed. Pritchik et al⁵⁴ suggested that patients may benefit from effective eradication of neoplastic disease if both the supraclavicular and primary sites are controlled. Depending on the location of metastases and whether it is single or multiple, surgery may play a role in the management of these patients and local resection may improve quality of life and can provide an excellent local disease control in the neck.⁵⁴ Excision of solitary metastatic lesions of a RCC after nephrectomy has been reported to achieve 41% survival at 2 years and 13% survival at 5 years, regardless of the time interval between nephrectomy and the diagnosis of the metastatic lesion.⁶⁶ RCC has been traditionally described as a radioresistant tumor, but recent studies have reported an effectiveness of radiotherapy in the treatment of metastatic disease.⁶⁴ Although irradiation did not decrease the size of the tumor mass, it seemed to help symptom alleviation by inducing devascularization of the lesion. The systemic treatment of metastatic RCC includes immune modulating agents interleukin-2 or interferon- α along with newer treatment regimens, including sorafenib, sunitinib, and temsirolimus.⁶⁷ Partial response rates range from 5% to 20%, with complete responses generally observed in <5% of patients.⁶⁸ It may be used with the additional use of immune modulating agents and biotherapy should be considered as adjuvant therapy to treat residual disease after the resection, as discussed and supported by members of the multidisciplinary cancer team.⁵⁴

Bladder cancer

Cervical lymph node metastases of urothelial carcinoma are very uncommon and indicate widespread disease with poor prognosis. Puztaszeri et al⁶⁹ reported a case of a 44-year-old man with metastatic micropapillary carcinoma of the bladder presenting with a cervical lymph node metastases, diagnosed on FNAC. Hessian et al⁷⁰ reported similar cases presenting, but only in 3 of 207 patients (1.4%) of a case series.

Urothelial carcinoma has histologic appearance very similar to squamous cell carcinoma, so a very high index of suspicion is required to make the correct diagnose should it present as a mass in the neck. GATA-3 is the most helpful immunostain for urothelial carcinoma, although it is not entirely specific.⁷¹

There is no currently reported evidence to support therapeutic neck dissection for the management of bladder cancer metastases to the neck.

Ovarian cancer

Epithelial ovarian cancer is reported as one of the most lethal gynecological cancers and patients are usually diagnosed at advanced stage. Ovarian cancer may spread by direct

extension, by a transperitoneal, lymphatic route, and, more rarely, hematogenously. Usually, the lymphatic route of cancer dissemination involves the retroperitoneal pelvic and para-aortic lymph nodes in advanced-stage ovarian carcinoma. However, cancer spreading through the lymphatic system could result in further extension to the cervical lymph nodes. In these cases, lymph node metastases in the neck are considered to be distant metastases and are classified as International Federation of Gynecology and Obstetrics stage IV.⁷² Such cases have been rarely reported and usually have poor outcomes. In a series of 100 autopsies on female patients who died of ovarian cancer, the incidence of lymphadenopathy in the supraclavicular lymph nodes was reported to be only 4%.⁷³ Another publication reporting on a series of 35 patients with extra abdominal lymphadenopathy of ovarian cancer, 11 patients (31%) showed evidence of supraclavicular nodal metastases.⁷⁴ On rare occasions, supraclavicular metastases have been reported to be present bilaterally.^{75–77}

Lymphadenopathy in the neck may present initially before making a diagnosis of an ovarian mass.⁷⁵ In these cases, the presence of circulating tumor cells can be helpful in identifying the origin of the primary tumor.⁷⁵ Neck metastases can be discovered at the same time as initial exploration of the ovarian cancer or at the time of cancer recurrence. The interval between the diagnosis of the ovarian neoplasm and the subsequent tumor involving the neck is usually long, occurring at a mean period of 43.3 to 124 months (range, 5–240 months).^{72,76}

Ovarian serous carcinomas frequently have a micropapillary histologic appearance. Testing of the tissue using immunohistochemistry, they are positive for ER, PR, PAX-8, and Wilms' tumor-1.^{78–80} Germ cell ovarian tumors of the ovary have an identical immunoprofile to those of the testis, as described below.

Chen et al⁷² reported a case series of 20 patients with ovarian cancer with neck lymph node metastases. They concluded that a subgroup of patients with neck metastases who had presented with limited pelvic cancer had much better overall survival than those patients who had cancer spreading beyond the pelvic cavity or were diagnosed with neck lymph node metastases when the primary ovarian cancer had recurred. Isolated lymph node recurrence has been reported in about 4% to 6% of patients with ovarian cancer and thus represents approximately 10% of overall recurrences. The median survival after identification of the neck nodes was 42 months in patients with initial synchronously appearing cervical disease and 6 months in patients at whom the neck metastases was observed at the time of the primary cancer recurrence. Patients with high-grade tumors who have responded well to chemotherapy often demonstrated a complete remission of neck lymph nodes. Nevertheless, other patients seemed to have very aggressive clinical courses after the detection of their lymph node metastases. They were more likely to have low-grade histology, which was most likely to have been chemoresistant, and experienced early cancer recurrence accompanied by distant metastases resulting in death.

Cervical lymph node metastases could be an extension of retroperitoneal lymph node metastases because these patients have similar clinical features and survival outcomes compared with patients with retroperitoneal lymph node metastases. To summarize, patients with retroperitoneal and neck lymph node metastases have better outcomes (5-year overall

survival rate of 58% to 84%) as compared those with peritoneal carcinomatosis (overall survival rate of 18% to 36%).⁸¹

Cervical and uterine cancer

Metastases from the uterine cervix to the neck lymph nodes are uncommon. In a study of 420 cases, the incidence of metastases of carcinoma of the cervix to the left supraclavicular nodes was 0.1% in patients who had not been treated and 1.5% in those who had been treated.⁸² However, occult supraclavicular lymph node metastases have been identified by FDG-PET in 8% of patients (14 of 186).⁸³

With more recent improved treatment of cervical cancer, supraclavicular lymphadenopathy has emerged as a more common manifestation of recurrent disease.⁸⁴ Manoharan et al² reported the first case of metastatic cervical carcinoma that presented as bilateral neck lymphadenopathy. Patients with involved supraclavicular nodes treated with chemotherapy have a reported 3-year and 5-year survival rate of 16.5%.⁸⁵

Cervical squamous cell carcinoma is morphologically indistinguishable from squamous cell carcinomas of other anatomic sites, including the head and neck. Most cervical carcinomas are caused by high-risk types of human papillomavirus, similar to carcinomas of the oropharynx.

Supraclavicular lymph node metastases from endometrial carcinoma are rarer than that from the uterine cervix. Oosaki et al⁸⁶ reported 5 patients (0.15%) with neck metastases from endometrial cancer of a total number of 3230 patients with neck metastases from a gynecological malignancy. Kojima et al⁸⁷ has described a neck dissection procedure performed on a woman with supraclavicular lymph node metastases from a primary endometrial carcinoma.

Prostate cancer

Carcinoma of the prostate is the most common malignancy in men. Adenocarcinoma makes up 95% of prostate malignancies and spread is by local extension, and lymphatic and hematogenous dissemination.⁸⁸ Up to 70% of patients when diagnosed may have disease that extends beyond the prostatic capsule. These tumors have a propensity to metastasize via the lymphatic system and to the axial skeleton. Based on an extensive study by Saitoh et al,⁸⁹ the most common reported sites for prostate metastases in descending order are: local pelvic lymph nodes, bones (spine and long bones), lungs, bladder, and liver. This study reported that any lymph node group in the body could be involved, with a predilection toward midline lymph nodes. Involvement of pelvic local lymph nodes can lead to intra-abdominal and then more distant involvement once para-aortic nodes are involved.

Carcinoma of the prostate can metastasize to supraclavicular lymph nodes, but has been rarely reported in 0.5% of cases.^{90,91} However, some published reports stress the need to consider metastatic prostate cancer in the differential diagnosis when confronted with a malignant lesion in the head and neck. Although prostate cancer is a diagnosis usually associated with increasing age, and supraclavicular nodes usually appear during the evolution of the disease, supraclavicular lymphadenopathy as the first presentation of

prostate adenocarcinoma has been reported in young men, which may justify use of serum prostate specific antigen (PSA) levels, or at least immunohistochemical staining of any biopsy examination for the disease.⁹² Every male patient over the age of 50 with a cervical neck mass consistent with a diagnosis of cancer of unknown primary should be evaluated with a serum PSA. If the PSA is elevated, the FNAC of the cervical node for pathological analysis should include immunohistochemical staining for prostate specific membrane antigen (PSMA). Although the PSMA stain may be weak or negative in some poorly differentiated tumors, it is still a sensitive and specific marker of prostatic differentiation and must be routinely applied.

The morphology of prostatic carcinoma consists of individual or fused glands in lower grade tumors, and sheets of cells in high-grade cancer. Prostate carcinoma typically exhibits prominent nucleoli and generally lacks the pleomorphism of metastatic cancers from other organs. The immunohistochemical panel for prostate cancer includes PSA, prostatein (P501s), NKX3.1, and PSMA.⁹³

Usually, the presence of prostatic cancer metastases heralds a poor prognosis making the discovery of prostate cancer in the head and neck an oncologically important finding. Supraclavicular or cervical nodes indicate stage IV disease associated with a 5-year survival rate of 30%.⁹⁴ However, after confirming a diagnosis of prostatic cancer involving neck nodes, the patient's outlook is not always a fatal one in the short term. Cervical lymph node metastases in cases of prostate cancer should be treated as a systemic disease and primarily treated with androgen ablation,⁹⁵ including possibly the addition with systemic chemotherapy for patients who are fit and willing. Sometimes, responsiveness to hormonal treatment is favorable and such patients attain a long-lasting remission and remain symptom free.⁹⁶ Surgical excision of an isolated resectable neck metastases may prevent the development of local symptoms in selected patients. For unresectable neck metastases, radiotherapy may be an alternative to palliate symptoms caused by neural compression or venous obstruction.⁹³ Ahamed et al⁹⁷ reported a case of prostate cancer with metastatic supraclavicular lymphadenopathy wherein the patient experienced a dramatic improvement in symptoms and a significant reduction in PSA level from 586.0 ng/mL to 251.5 ng/mL within 7 months of treatment with cyproterone acetate and leuprorelin acetate.⁹⁷ Thus, early and accurate diagnosis is important for optimal management of metastases of these tumors to the head and neck.

Testicular cancer

Testicular cancers include nonseminomatous and seminomatous germ cell tumors. The presence of neck metastases in germ cell tumors of the testis is an uncommon but well-established phenomenon. Incidence of neck metastases ranges from 2.6% to 4.5%, with a neck mass being the initial sign in approximately 5% of cases.⁹⁸ Wood et al⁹⁹ reported on 31 patients with supradiaphragmatic nodal metastases from testicular primary germ cell tumors and found neck lymphadenopathy in 10 of 11 patients with seminoma (91%) and in 13 of 20 patients (65%) with nonseminomatous germ cell tumors. Neck metastases are almost invariably left-sided.

Germ cell tumors of the testis include seminoma, teratoma, yolk sac tumor, embryonal carcinoma, or mixed germ cell tumors containing more than one type. Testing using immunohistochemistry reports that seminoma and embryonal carcinoma are positive for the markers octamer-binding transcription factor 4, placental alkaline phosphatase, and spalt-like transcription factor 4 (SALL4). Embryonal carcinoma is positive for CD30. Yolk sac tumor is positive for α -fetoprotein, SALL4, and glypican-3. Choriocarcinoma is positive for β -human chorionic gonadotropin, and the immunoprofile of teratoma is more variable.^{100–102}

The use of platinum-based chemotherapy reports the overall cure rate for testicular seminoma exceeding 90%. However, high cure rates are contingent upon early detection. Delay in diagnosis is a risk factor for development of stage III testicular cancer. Therefore, consideration of metastatic testicular carcinoma in the differential diagnosis of a supraclavicular neck mass is important as effective treatment is available. Resection of any residual postchemotherapy neck masses is indicated because of the high incidence of viable tumor (teratoma in the residual mass) and the inability to accurately predict the histology of the neck mass. Resection of residual neck masses leads to excellent local control and can contribute to long-term disease control and survival.¹⁰³

Few studies have addressed the issues of incidence, recurrence, and management of persistent neck disease. Several authors^{104,105} have recommended surgical resection in tumor marker (serum α -fetoprotein and β -human chorionic gonadotropin)-negative patients with gross residual neck disease after failure of chemotherapeutic cytoreduction of testicular carcinoma. Neck dissection has a demonstrated role in the treatment of metastatic tumors. Aggressive resection of disease is indicated, often in conjunction with thoracic surgery, to eradicate disease extending into the chest. Patients with negative preoperative serologic tumor markers have an excellent prognosis.¹⁰⁶ The only contraindication for adjunctive surgery is the presence of persistently elevated serum tumor markers after chemotherapy. Such nonresponders often have unresectable germ cell tumors and are recommended for second-line salvage chemotherapy.¹⁰⁷

Central nervous system cancers

Primary brain tumors rarely metastasize outside the central nervous system. A review of 116 cases of extraneural metastases found that the primary brain tumor that metastasizes most often is glioblastoma (41% of reported cases of metastases), followed by medulloblastoma (27%), ependymoma (16%), astrocytoma (10%), and oligodendroglioma (5%).¹⁰⁸ By immunohistochemistry, glial neoplasms, such as astrocytoma and oligodendroglioma, are positive for GFAP and OLIG2.^{33,109} Medulloblastoma is consistently positive for synaptophysin and variably positive for GFAP.¹¹⁰ Meningioma is positive for epithelial membrane antigen (EMA) and PR, and hemangiopericytoma is positive for STAT6.^{111–113}

Most cases of extracranial metastases of brain tumors have been observed after craniotomy and cerebrospinal fluid shunt procedures for treatment or diagnosis and radiotherapy. Transfer of emboli may occur between the internal jugular vein, the thoracic duct, and the right cervical lymphatic plexi, so that craniotomy seems to be the usual cause of metastases of primary brain neoplasms.¹¹⁴ However, diffusion of the disease could, in some cases, be

explained by vascular invasion because some authors have reported metastatic glioblastoma in nonoperated patients.^{115–117} Most patients with lymph node metastases have undergone repeated craniotomies. Presumably, the tumor cells gain access to lymphatics by dural or scalp extension through the surgical defect. However, there are reports of lymph node or distant metastases before surgery, with no clinical or radiologic evidence of transgression of scalp or skull. In some patients, the nature of the tumor cells themselves may predispose to metastases.¹¹⁶ Mondin et al¹¹⁸ performed a survey of metastatic central nervous system tumors to cervical lymph nodes and documented 128 cases. A clinical history of a brain tumor, craniotomy, and/or radiotherapy should prompt the surgeon to consider the possibility and provide the diagnostic pathologist with accurate background information. Even in the absence of such a clinical history, the general or head and neck pathologist, when faced with particularly “unusual” histological features in an otherwise unexplained neck mass, might consider seeking consultation with a neuropathologist if no other explanations present themselves.

Glioblastoma multiforme is a high-grade undifferentiated glial neoplasm with poor prognosis. Extracranial metastases is rare (approximately 2%) and is generally observed in adult patients.¹¹⁹ Sixty percent of extracranial metastases are to the lung, 22% to the liver (22%), and 1.5% to lymph nodes in the neck.^{114,120} Outcomes and survival in these cases are related to the age and general condition of the patient as well as to the primary lesion, effectiveness of treatment, localization of the metastatic lesion, and response to treatment.^{118,121} Despite poor prognosis, radical excision, radiotherapy, and chemotherapy has been suggested as soon as possible in these tumors.¹²²

Ependymomas account for 2% of all intracranial tumors in adults and they may be classified as low-grade ependymomas or anaplastic ependymomas. Treatment of these tumors consists of surgery and adjuvant radiotherapy. Extracranial metastases of ependymal tumors is very uncommon.¹²³ However, there have been reported cases of extraneural metastases of anaplastic ependymomas.¹²⁴ The main therapeutic modality used was radiotherapy, with only a small role for chemotherapy. Davis et al¹²⁵ reported a case with intraparotid and neck metastases; neck dissection followed by radiotherapy to the neck was carried out and neck disease was controlled. Although central nervous system tumors often respond poorly to chemotherapy, which is often explained by the poor penetration of antineoplastic agents through the blood brain barrier, extracranial disease, in contrast, may not have this limitation.¹²⁶

More than 30 cases of extracranial oligodendroglioma have been reported.¹²⁷ The number of cases has increased recently, possibly because survival times have been prolonged because of improved treatment. The bone is the most common site of metastases from oligodendroglioma (95% of cases), followed by lymph nodes (33%).¹²⁸ Noshita et al¹²⁷ reported a case of anaplastic oligodendroglioma with multiple extracranial metastases, including cervical lymph node metastases. Demonstration of oligodendroglioma-specific 1p19q codeletion on tissue section by fluorescence in situ hybridization is a reliable technique for detection of this tumor. The possibility of extracranial metastases of oligodendroglioma should be considered if this marker is found.¹²⁷

Medulloblastoma is the most common primary central nervous system malignancy in childhood, but is rare in adults. This tumor has a marked potential for extracranial spread, and insertion of a shunt is associated with a significantly earlier appearance of metastases in both children and adults.¹²⁹ The most commonly involved sites are bone, bone marrow, and cervical lymph nodes. A complete workup at initial diagnosis is recommended to screen for early metastases.¹³⁰ Extracranial dissemination is a very poor prognostic sign and requires aggressive systemic therapy for disease control.¹³¹ Rickert¹³² published a survey of 245 cases of extraneural metastases of pediatric brain tumors and noted that the most frequent site of lymph node metastases was cervical (22 cases: 63.6% were from medulloblastoma, 13.6% from glioblastoma multiforme, 9.1% from germ cell tumor, and 13.6% from other entities).

Cervical node metastases from meningioma¹³³ and intracranial hemangiopericytoma¹³⁴ are uncommon. Cervical node metastases from intracranial neuroblastoma¹³⁵ appear exceptionally rare as do nodal metastases from the rare pituitary carcinomas¹³⁶ and primitive neuroectodermal tumors.¹³⁷

SUMMARY AND CONCLUSIONS

Although most metastatic neck nodes arise from primary tumors of the head and neck, isolated supraclavicular and/or inferior neck lymphadenopathy should alert the clinician to consider the likely possibility of a non-head and neck primary neoplasm. The most common remote primary tumors associated with neck lymph node metastases include cancers of the breast, lung, kidney, cervix, and testis. The lymphatic anatomy supports a predilection for metastases to left-sided lymph nodes.

An accurate tissue diagnosis is critical, taken in context with clinical presentation. Although a neck lymph node biopsy suggesting adenocarcinoma often suggests a remote primary malignancy, the possibility of salivary gland malignancy should be considered in the differential diagnosis. Similarly, squamous cell carcinoma nodal metastases may be consistent with a lung or cervical cancer primary tumor.

Given that cervical lymph node metastases from remote primary tumors are rare, evidence-based recommendations for optimal management are lacking. The level of scientific evidence is low, limited to published case reports and small case series. The limited data available obviously limits the strength of our recommendations, but several trends in management are apparent.

Cervical lymph node involvement from remote primary tumors represents advanced-stage disease. The goals of treatment are to improve quantity and quality of life, and the choice of treatment depends on the tumor histology, the extent of disease, as well as consideration of patient comorbidities, functional status, and treatment preferences. Multidisciplinary care cancer team environment and case-by-case discussion should provide optimal treatment recommendations, including consideration for surgery, radiotherapy, chemotherapy, hormonal, or biological therapy, as well as recommending palliative care when and where appropriate.

To that end, surgical management of neck disease may be an important diagnostic and therapeutic modality in the management of patients. Although ultrasound and FNAC are important staging and diagnostic tools, even in the clinically negative neck, the tissue obtained may be inadequate for molecular testing; core biopsies and surgical excision of neck lymph nodes may be necessary for molecular testing (eg, next generation sequencing technology) that may predict the likely benefit of treatment with novel molecularly or targeted therapies (precision medicine).

Neck dissection may also be indicated in selected cases of cervical lymphadenopathy from distant primaries, but each case with their associated comorbidity must be considered on case-by-case basis. Importantly, supraclavicular lymph node involvement in select patients with breast and lung cancers represents stage III disease for which locoregional therapy can be considered with curative intent. In some cases of esophageal cancers (particularly for cancers of the cervical esophagus), resection of neck metastases has shown a beneficial role. In other cancers, there is no current reported evidence to support therapeutic neck dissection for the management of cancer metastases to the neck, but surgical excision of isolated resectable neck metastases may be beneficial in preventing or minimizing local symptoms in selected cases. In carefully selected cases, aggressive treatment to help to control metastatic disease in the neck may be indicated, particularly for bulky tumors that cause functional impairment and wound-care issues.

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TABLE 1

Immunohistochemical markers associated with the origin of neck metastasis.

Tumor origin	Marker
Bladder	GATA-3
Breast	ER, PR, GCDFP, GATA-3, mammaglobin, HER2/neu
Central nervous system	- Gliomas: GFAP, OLIG2 - Medulloblastoma: synaptophysin, +/- GFAP - Meningioma: EMA, PR - Hemangiopericytoma: STAT6
Cervix	p63, p40, CK5/6, p16, high-risk HPV
Esophagus	- Squamous cell carcinoma: p63, p40, CK5/6 - Adenocarcinoma: CDX-2
Gastrinoma	Synaptophysin chromogranin, gastrin
Kidney	PAX-8
Liver	HepPar1, glypican-3, and arginase
Lung	- Squamous cell carcinoma: p63, p40, CK5/6 - Adenocarcinoma: TTF-1, Napsin-A
Ovary	PAX-8, ER, PR, WT-1
Prostate	PSA, P501s, PSMA, NKX3.1
Stomach	CDX-2
Testis	OCT4, SALL4, PLAP, CD30 (embryonal), glypican-3 (yolk sac)

Abbreviations: GATA-3, GATA binding protein 3; ER, estrogen receptor; PR, progesterone receptor; GCDFP, gross cystic disease fluid protein; HER2, human epidermal receptor 2; GFAP, glial fibrillary acidic protein; EMA, epithelial membrane antigen; HPV, human papillomavirus; CDX-2, caudal-related homeobox transcription factor-2; PAX-8, paired box gene 8; HepPar1, hepatocyte paraffin 1; TTF-1, thyroid transcription factor-1; WT-1, Wilms' tumor-1; PSA, prostate-specific antigen; PSMA, prostate specific membrane antigen; OCT4, octamer-binding transcription factor 4; SALL4, spalt-like transcription factor 4; PLAP, placental alkaline phosphatase.