

Cervical Lymph Node Metastases from Central Nervous System Tumors: A Systematic Review

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Introduction: Lymph node metastasis (LNM) from primary tumors of the central nervous system (CNS) is an infrequent condition, and classically it was thought that CNS tumors could not spread via the lymphatic route. Recent discoveries about this route of dissemination make its knowledge necessary for surgeons and pathologists to avoid delays in diagnosis and unnecessary treatments. The aim of this paper is to review the literature and to discuss the relevant pathogenetic mechanism and the cytologic features along with recommendations for surgical treatment of these cervical LNM.

Materials and Methods: Using PRISMA guidelines, we conducted a systematic review of the literature published from 1944 to 2021, updating the comprehensive review published in 2010 by our group.

Results: Our review includes data of 143 articles obtaining 174 patients with LNM from a primary CNS tumor. The mean age of the patients was 31.9 years (range, 0.1–87) and there were 61 females (35.1%) and 103 males (59.2%), and in 10 cases (5.7%) the gender was not specified. The more frequent sites of distant metastasis were bones (23%), lungs (11.5%) and non-cervical lymph nodes (11%).

Conclusion: Cervical LNM from CNS tumors is infrequent. Pathologic diagnosis can be obtained by fine-needle aspiration cytology in most cases, giving surgeons the option to plan the appropriate surgical treatment. Given the poor prognosis of these cases, the most conservative possible cervical dissection is usually the treatment of choice.

Keywords: brain tumors, central nervous system, extraneural metastasis, extracranial metastasis, cervical lymph node metastasis

Introduction

Cervical lymph node metastases typically originate from primary carcinomas arising from mucosa of the head and neck, skin, salivary glands, or thyroid gland. In a 2–5% of the cases, cervical lymph node metastasis (LNM) may be the first clinical manifestation of an occult primary tumor.¹ While originating from a head and neck cancer in the vast majority of cases, rarely, a cervical LNM may occur from non-head and neck sites, such as lung, breast, digestive and reproductive systems, typically located in lower neck levels.²

The occurrence of cervical LNM arising from primary malignant tumors of the central nervous system (CNS) has been reported infrequently in case reports yet should be taken into consideration in diagnostic work-up of an unknown primary tumor. Despite this rare occurrence, clinical cases of cervical LNM of primary malignant CNS tumors are well documented in the literature.³ The anatomical features of the cervical lymph nodes networks and its connections with intracranial lymphatic structures through the jugular foramen represent an important possible route for the spread of cancers to and from the CNS. Based on the basic research findings on the dural lymphatic vessels transporting fluid into deep cervical lymph nodes,^{4–6} investigation of the existing clinical literature on this phenomenon has clinical importance. In addition, better awareness of this rare presentation could help in diagnosing occult primary tumor in patients presenting with cervical LNM from a clinically hidden primary tumor.

Primary malignant tumors of the CNS represent 2% of all cancers.⁷ The blood–brain barrier and the absence or paucity of lymphatic vessels are presumed to be the cause of the low incidence of metastasis outside the CNS.⁸ Historically, the presence of cervical metastasis was explained by surgical disruption of the dura mater during the primary surgery through which tumor cells could seed outside the limits of the CNS.⁹ However, the recent discovery of a dural lymphatic network⁴ undermines these historical assumptions, and may better explain cases of cervical metastasis without previous surgery nor dural invasion.¹⁰ Novel therapeutic approaches have extended the life of cancer patients and increased the risk of extracranial dissemination of CNS tumors.³ Histological types of primary CNS tumors that have reported to present with cervical LNM are glioblastoma (the most common), oligodendroglioma, ependymoma, metastasizing meningioma, medulloblastoma (most common in children), and pituitary carcinoma. In addition to the neck LNM, the most frequent extracranial sites of distant metastases are the lungs, pleura, liver and bones.³ Although cervical metastases have been described in a wide variety of CNS tumors, yet the reports are confined to case reports and limited case series.

The aim of this paper is to review the literature on the presence of metastasis in lymph nodes of the neck from CNS primary tumors and to discuss the relevant pathogenetic mechanism and the cytologic features along with recommendations for surgical treatment of these cervical LNM. For this purpose, we updated the comprehensive review published in 2010 by our group.³

Materials and Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) method was utilized to evaluate the literature.¹¹ The search strategy included full-text articles with CNS tumors that metastasized to the cervical lymph nodes. We performed a PubMed search updated to July 29, 2021 for English language publications between 2010 and 2021 including these search criteria: “extracranial metastases from CNS tumors” or “cervical lymph node” or “neck lymph node” coupled with “glioblastoma”, “medulloblastoma”, “oligodendroglioma”, “ependymoma”, “metastasizing meningioma”, “intracranial neuroblastoma”, “pituitary carcinoma”, “astrocytoma”, “germ cell tumors”, “yolk sac tumor” and “primitive neuroectodermal tumor”. The search results were reviewed for eligible studies. When there was information in the abstract addressing cervical metastasis, the full-text article was searched. This was supplemented with a hand search of the references in relevant review articles and in all retrieved full-text articles (Figure 1). Studies were selected if they met the following inclusion criteria: (a) patients with a CNS tumor with histological confirmation and (b) histological or cytological confirmation of cervical LNM. Studies without adequate evidence of the presence of a cervical LNM were excluded. Case reports were included. We considered the cases with metastases in the parotid gland as cervical LNM cases, although when compiling the data and presenting them in Table 1, the location in the parotid was specified within the rest of the metastatic sites presented by the patients. We include data from the previous review conducted by our group from 1944 to 2010 in order to complete the revision. No ethical approval was required.

Results

We identified 4182 papers but after applying our inclusion criteria, 143 were selected as summarized in Table 1.^{8,12–152} Most papers did not show cervical LNM, so they were excluded. Our review includes a period of 78 years (1944–2021) with 172 cases and we included two additional cases of LNM of glioblastoma (GBM) from one of the coauthors [Gebirim EMMS] as personal communications. There were 75 (43.1%) GBM, 27 (15.5%) medulloblastoma, 21 (12.1%)

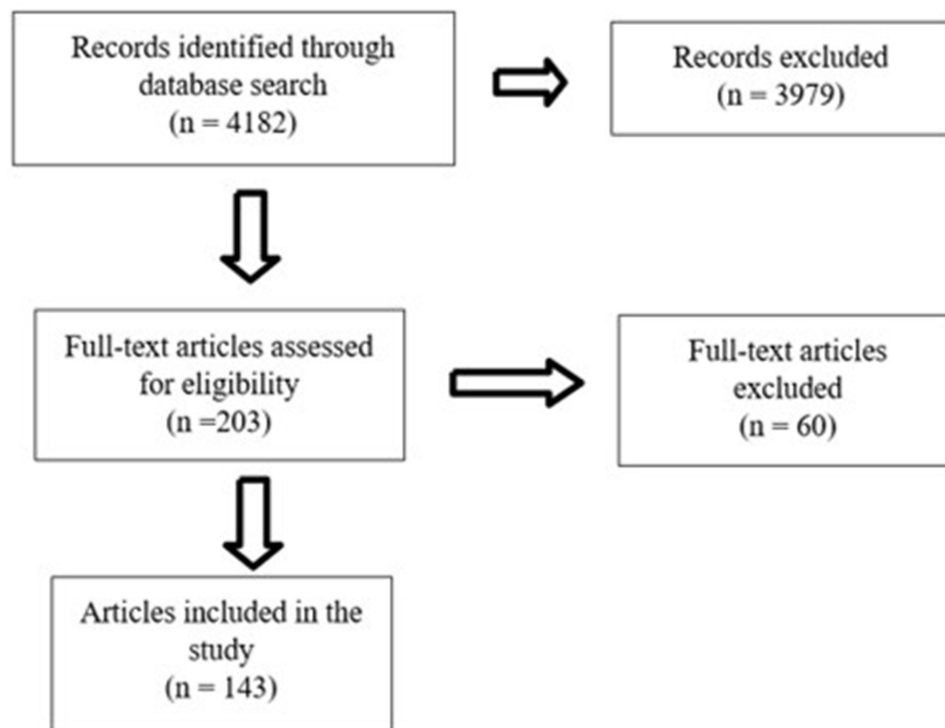


Figure 1 Flow chart showing the study selection process for our systematic review.

meningioma (including anaplastic, metastasizing, sarcomatous and rhabdoid meningioma), 13 (7.5%) pituitary carcinoma, 12 (6.9%) oligodendroglioma (including anaplastic oligodendroglioma), 10 (5.7%) ependymoma (including anaplastic ependymoma), 7 (4%) astrocytoma (including malignant, anaplastic, and grade III–IV astrocytoma), 3 (1.7%) intracranial hemangiopericytoma and 6 (3.4%) other CNS tumors (including primitive neuroectodermal tumor, germ cell tumor, yolk sac tumor, germinoma and neuroblastoma). All cases had a previous history of CNS tumor.

If all reviewed cases were considered (174 cases), the mean age of the patients with cervical LNM from a CNS tumor was 31.9 years (range, 0.1–87) and there were 61 females (35.1%) and 103 males (59.2%), and in 10 cases (5.7%) the gender was not specified. The more frequent sites of distant metastasis were bones (23%), lungs (11.5%) and non-cervical lymph nodes (11%). In 15 cases (8.6%), metastases in the parotid gland lymph nodes were described, and in only one of them the metastasis was found in the glandular tissues too.¹⁰³

In the studied period, we have detected a large increase in the number of published cases, since in the previous review there were found 128 cases in 67 years (1944–2010), and in the current one there were 46 cases reported in 12 years (2010–2021).

The reported GBM patients had a mean age at diagnosis of the primary CNS tumor of 37.2 years (range, 4–75), there were 24 females (32%) and 49 males (65.3%). The most common extracranial site of metastases, other than cervical lymph nodes, was bones (22.7%), lungs (16%), parotid (12%), non-cervical lymph nodes of the body (12%) and liver (6.7%). Medulloblastoma patients had a mean age of 8.9 years (range, 0.6–31), there were 10 females (37%) and 16 males (59.3%). Other sites of metastases were more frequently observed in bones (37%), lungs (11.1%) and non-cervical lymph nodes (11.1%). Meningioma patients were more frequently male (66.7%). The mean age of the patients was 45.7 years (range, 5–87), and the more common other sites of metastasis were lungs (14.3%), parotid (9.5%) and spine (14.3%). Pituitary carcinomas were seen with more frequency in females (53.8%). Mean age at diagnosis was 48 years (range, 16–69) and the more common other site of metastasis was the liver (15.4%). Cervical LNM from oligodendrogliomas was described in 6 females (50%) and 3 men (25%), with a mean age of 37.8 years (range, 12–54). Other metastases were described in bones (66.7%), non-cervical lymph nodes (33.3%) and scalp (25%). Ependymoma patients comprised 6 females (60%) and 4 males (40%), with a mean age at diagnosis of 16.8 years (range, 6.7–30). Metastases

Table 1 Literature Review of Studies Reporting Cervical LNM from CNS Tumors

Histology	Number of Cases	References	Mean Age Years (Range)	Gender	Other Site Metastasis (More Frequent)
Glioblastoma	75	[12,13,24,35,46,56,60–113,120,131,142]	37.2 (4–75)	24 F 49 M 2 NA	17 Bones 12 Lungs 9 Parotid 9 Other lymph nodes 5 Liver 2 Kidney 2 Scalp
Medulloblastoma	27	[8,114–119,121–130,132–135]	8.9 (0.6–31)	10 F 16 M 1 NA	10 Bones 3 Lungs 3 Other lymph nodes 1 Liver 2 Skin 1 Spine
Meningioma	21	[136–141,143–152]	45.7 (5–87)	7 F 14 M	1 Bones 3 Lungs 2 Parotid 1 Scalp 3 Spine
Pituitary carcinoma	13	[14–23,25]	48 (16–69)	7 F 5 M 1 NA	1 Parotid 2 Liver 1 Spine 1 Spleen 1 Meninges
Oligodendroglioma	12	[26–34]	37.8 (12–54)	6 F 3 M 3 NA	8 Bones 4 Other lymph nodes 3 Scalp 1 Spine 1 Vertebrae
Ependymoma	10	[36–44]	16.8 (6.7–30)	6 F 4 M	3 Bones 3 Parotid 1 Other lymph nodes 3 Scalp 1 Vertebrae 1 Skull
Astrocytoma	7	[45,47–50,61,163]	18.5 (3–42)	1 F 5 M 1 NA	1 Bones 1 Lung 2 Pleura 2 Other lymph nodes 1 Vertebrae 1 Skull
Intracranial hemangiopericytoma	3	[51,52]	47	1 M 2 NA	1 Spine
Others	6	[53–55,57–59]	9.6 (0.1–17)	6 M	1 Lung 1 Liver 1 Skin

(Continued)

Table I (Continued).

Histology	Number of Cases	References	Mean Age Years (Range)	Gender	Other Site Metastasis (More Frequent)
Total	174 cases		31.9 (0.1–87)	61 F 103 M 10 NA	40 Bones 20 Lungs 19 Other lymph nodes 15 Parotid 9 Liver 8 Scalp 7 Spine 3 Vertebrae 3 Skin 2 Skull 2 Kidney 2 Pleura 1 Meninges 1 Spleen

Abbreviations: F, Female; M, Male; NA, Not available.

were present at bones (30%), scalp (30%) and non-cervical lymph nodes, vertebrae and skull (10% each one). Astrocytoma patients had a mean age of 18.5 years (range, 3–42) and were predominantly men (71.4%). Other sites of metastases were more commonly observed in pleura and non-cervical lymph nodes (33.3% each one). Three cases of cervical LNM from an intracranial hemangiopericytoma were reported, but only one of them provided patient characteristics. The remaining 6 cases included different histologies and were grouped under the denomination “others”.

Discussion

Pathophysiology

When a patient presents with an adenopathy in the neck suspicious of metastasis, diagnostic efforts are focused on the most frequent locations of the primary tumor, among which are the upper aerodigestive tract and the thyroid gland. Rarely is the origin thought to be in more distant locations, ie, below clavicles and almost never in the primary CNS tumors. LNM from a CNS tumor should be suspected when the patient had history of such tumor, craniotomy and/or cranial irradiation.³¹ Formation of hematogenous metastases have historically been explained by disruption of the normal anatomic barriers of spread (craniotomy or tumor invasion) allowing the tumor cells to enter the lumen of vascular vessels, dissemination using the Batson’s plexus, local recurrence in the craniotomy flap with posterior lymphovascular spread and by shunting procedures commonly used in this type of surgeries. The final location of metastasis after using these pathways is usually the lungs, bones and liver.³ However, the mechanism by which CNS tumors spread via the lymphatic route is not known given the presumed absence of lymphatic vessels at the central level. In 2015, Aspelund et al⁴ reported the finding of a lymphatic vessel network in the dura mater of the mouse brain. They explained that dural lymphatic vessels absorb cerebrospinal fluid from the adjacent subarachnoid space and brain interstitial fluid via the lymphatic system. They demonstrated that dural lymphatic vessels transport fluid into deep cervical lymph nodes via foramina at the base of the skull. These findings may explain why primary brain tumors can metastasize into cervical lymph nodes. More recently, Yağmurlu et al⁶ described in humans the connection of the deep cervical lymph nodes and lymphatic tributaries with the intracranial space through the jugular foramen. In 2020, Song et al⁵ using a mouse model of GBM, were able to demonstrate a limited CD8 T-cell immunity against GBM antigen when the tumor is confined to the CNS, leading to uncontrolled tumor growth. They observed that expression of VEGF-C promotes enhanced CD8 T-cell priming in deep neck lymph nodes, CD8 T-cell migration to the tumor and rapid clearance of the GBM.

Main Histologic Types

Primary tumors of the CNS can be classified as gliomas or nongliomas. The glioma group includes glioblastoma, oligodendrogliomas and ependymomas. The non-glioma group includes benign and malignant tumors: meningiomas, pituitary adenomas, medulloblastomas.⁷

GBM is the most common and aggressive tumor in adults located in the brain.¹⁵³ GBM does not usually spread extracranially, and metastasis is rare.¹⁵⁴ We have found 75 cases of cervical LNM of GBM (Figure 2), the most common other sites of GBM metastases were bones, lungs, parotid, and non-cervical lymph nodes. Although metastases at the parotid gland level were considered as LNM in the neck, parotid gland LNM was identified to provide insights on that location particularly. In the table, we have not included rare locations of distant metastasis showed in some articles to keep the table clear. Moreover, we considered that infrequent locations are important as a clinical case but not for the purposes of this review. Pietschmann et al¹⁵⁵ in their meta-analysis suggested that extraneural metastasis from GBM and gliosarcoma occurs more often in younger patients (median age in their cohort was 42 years), most probably due to longer expectancy. This is in concordance with our observation since the mean age of GBM patients in our series was 37.2 years.

Medulloblastoma represents the most common malignant brain tumor in the pediatric population.¹⁵⁶ Spread beyond the primary tumor is seen at the time of the diagnosis in more than 40% of cases. Extraneural metastasis affects more frequently bones, bone marrow, lungs, liver, and lymph nodes.¹³⁵

Meningioma is the most frequent primary CNS tumor.¹⁵⁷ These tumors are histologically divided into three grades.¹⁵⁸ The malignant transformation is possible producing a significant decrease in survival.¹⁵⁹ Although cervical node metastases from meningiomas are uncommon, 21 cases were reported according to our review.

Pituitary tumors are frequent, however, pituitary carcinoma is a rare histologic entity.¹⁶⁰ Diagnosis of pituitary carcinoma requires the presence of metastasis. Their low incidence makes it even more difficult to standardize diagnostic algorithm and treatment guidelines.²⁵

Oligodendroglioma is a diffuse glial tumor. Extracranial metastasis is infrequent, and it seems that metastasis is essentially linked to a prior neurosurgical resection.¹⁶¹ Oligodendrogliomas are characterized by multiple recurrences; however, extraneural spread is unusual with the most frequent metastatic site being bones and bone marrow, followed by lymph nodes, liver and scalp,^{32–34} as was confirmed by our review.

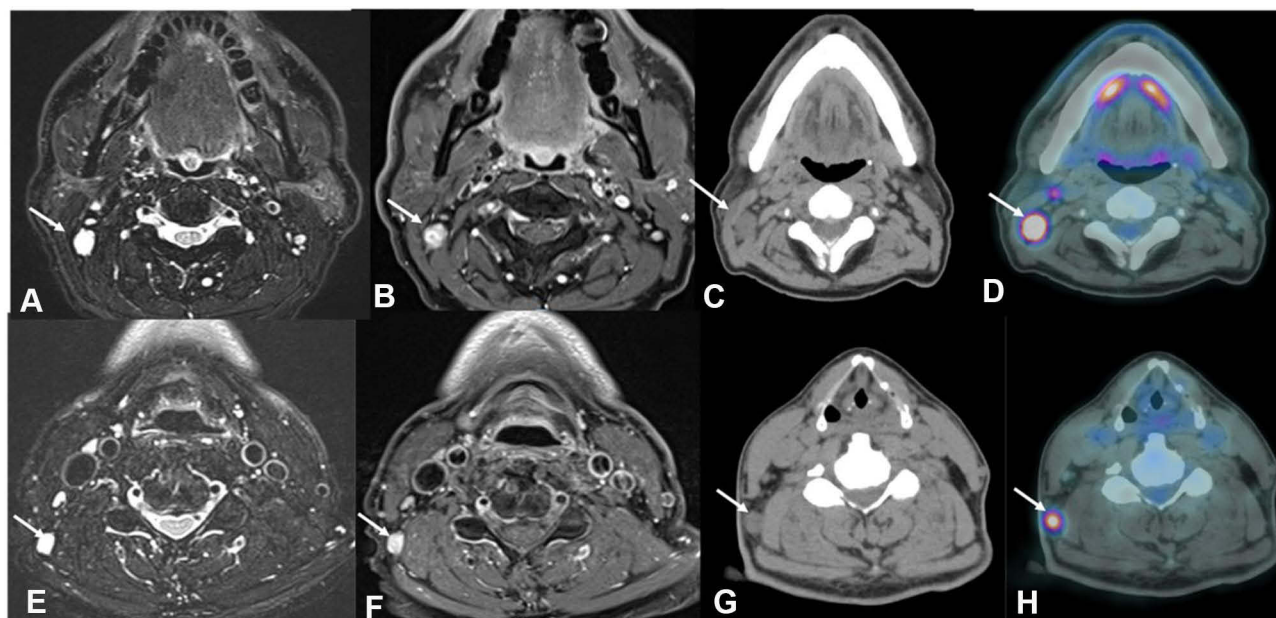


Figure 2 Male, 60 years old, cervical lymph node metastases (arrows) from a GBM. MRI axial T2-weighted sequences (A and E), MRI axial contrast-enhanced T1-weighted sequences (B and F), CT scans axial plane (C and G) and Fused Positron Emission Tomography- Computed Tomography axial plane (D and H). Observe the lymph nodes (arrows) in the right IIB (A–C) and V right level (E–G). Also, notice the increased uptake of fluorodeoxyglucose (FDG) in those lymph nodes (arrows in (D) and (H)).

Ependymomas can arise in the spinal cord (adults) or intracranial (pediatrics).¹⁶² The most aggressive is the anaplastic type (Figure 3) having an infiltrating behavior and the propensity to disseminate by seeding. Extraneural metastases are rare, but they affect more commonly the bones, parotid and scalp,⁴¹⁻⁴⁴ as was confirmed also by our study.

Astrocytoma, intracranial hemangiopericytoma and the subgroup classified as “others”, rarely metastasize to cervical LNM. In fact, to our knowledge, there has been no published cases of cervical LNM of astrocytoma since 1988.

Diagnostic Work-Up and Treatment Considerations

When a cervical LNM of CNS tumor is suspected, due to the patient's history for example, fine needle aspiration cytology (FNAC) can clarify the diagnosis.^{18,23,33,93,106} Yet, without a precedent of a brain tumor, the underlying diagnosis can be difficult, due to the fact that the tumor may be similar to a sarcoma, carcinoma, or a hematopoietic neoplasm.³ In dubious cases, histologic examination of tissue obtained with core biopsy of suspicious lymph node is sometimes necessary to obtain a reliable diagnosis. Several authors have stated that FNAC may be the method of choice to detect a lymph node metastasis in the neck from a CNS tumor, since it is a safe and minimally invasive procedure that can confirm the diagnosis and eliminates the need for a more aggressive core biopsy.^{18,23,33,93,106} In the case of GBM, Gestrich et al¹⁰⁶ and Romero Rojas et al⁹³ made the diagnosis with a FNAC showing their cytomorphology as highly cellular, with pleomorphic cells arranged in small, loosely cohesive clusters and single cells. The nuclei are described as high nuclear to cytoplasmic ratios, coarsely clumped hyperchromatic chromatin, irregular nuclear membranes and prominent single or multiple nucleoli in the background of necrosis. Intranuclear and cytoplasmic inclusions and rare mitoses may be seen. The differential diagnosis includes melanoma, squamous cell carcinoma and poorly differentiated carcinoma.¹⁰⁶ For oligodendrogliomas, the differential diagnosis of primary neuroectodermal tumor and other small round cell tumors can be done when the cytopathologist is aware of the previous history of oligodendroglioma.³³ The tumor cells show round nuclei with prominent nucleoli. Fibrillary background varied and can have a cloudy appearance. Microcalcifications and a rich capillary network can help in the diagnosis, as well as necrosis, nuclear atypia, high cellularity, and mitosis in the case of anaplastic tumors.³²⁻³⁴ The cytologic differential diagnosis of the pituitary

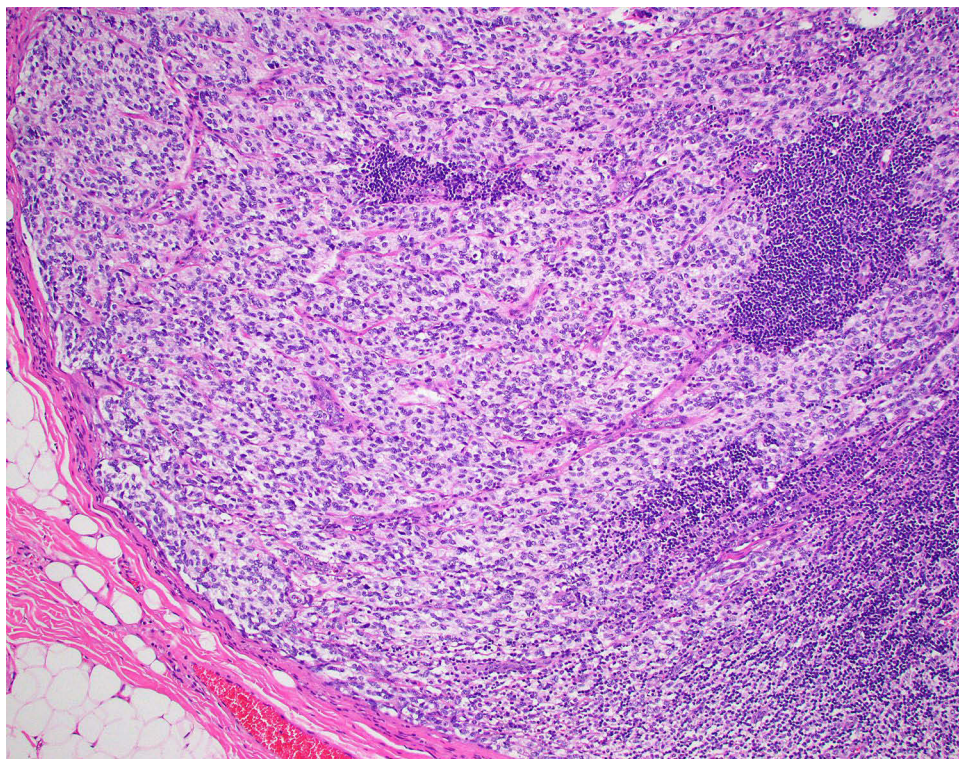


Figure 3 Microphotograph demonstrating an anaplastic ependymoma within a cervical lymph node. (Hematoxylin and Eosin, X200).

carcinoma includes hematopoietic malignancies and metastatic carcinomas.²³ The FNAC characteristics of these tumors include dispersed cells in small groups with a round to oval shape. Cells have a moderate amount of cytoplasm. Nuclear features range from minimal to marked nuclear pleomorphism with irregular nuclear contours, variable chromatin, and brisk mitoses.^{18,23} If the diagnosis cannot be made based on FNAC, a core needle biopsy or excisional biopsy is advised. Diagnosing metastatic CNS tumor is extremely challenging for pathologists. It is essential to have the clinical information of a previous CNS tumor, including the histologic type and immunophenotype. Without this information, a correct diagnosis is extremely difficult or even impossible to make. To confirm the diagnosis of a metastatic CNS tumor, immunohistochemistry must be used, for example, for GFAP, OLIG2, SOX2, etc. depending on immunophenotype of the primary tumor. However, one must keep in mind that patients with a history of a primary CNS tumor may suffer from other tumors. Moreover, markers believed to be characteristic for primary CNS tumors can be expressed in other tumor types, for example, GFAP or OLIG2 can be expressed in myoepithelial tumors, carcinomas and melanomas. Similarly, brain tumors can show aberrant expression of epithelial and other markers. A close cooperation between pathologists and clinicians, including all essential information is therefore needed to confirm the diagnosis of a metastatic CNS tumor.

Since cases of cervical lymphatic metastases from CNS tumors are rare, it is difficult to standardize treatment. Surgery is generally performed if the patient's condition is suitable and neck mass(es) operable. However, other factors to be considered are operability of primary tumor, presence of distant metastases at other sites and cyto/histological confirmation. In the reports included in this review, the treatment performed spanned from open biopsy of the neck lesion to radical neck dissection, revealing enormous variability in the treatment of these lesions that prevents its standardization. Based on our results, we believe that the most reasonable approach to these lesions is get a diagnosis first, preferentially by FNAC of the node being suspicious based on the patient's history; and secondly, if the patient condition allows, and in cases with isolated neck LNM without distant metastases (the use of positron emission tomography will be mandatory) and with primary tumor under control, the surgeon can remove all the affected lymph nodes with the least possible morbidity. Therefore, a selective or modified radical dissection would be the most appropriate. Open cervical biopsies should be avoided.

The increased number of cases in the last years (2010–2021) compared with the previous period (1944–2010) may be due to the advances in the treatment of these tumors, giving to the patients a higher chance to survive longer with a consequent increase in the risk to develop distant metastases. The low mean age of the patients in our review may also influence the life expectancy and the risk of distant relapse.

Conclusions

Cervical LNM from CNS tumors is rare. However, when the patient has a history of CNS primary tumor, this option should be considered when presented with a cervical mass. Pathologic diagnosis can be obtained by FNAC in most cases, giving surgeons the option to plan the appropriate surgical treatment. Given the poor prognosis of these cases, the most conservative possible cervical dissection is usually the treatment of choice.

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Disclosure

The authors report no conflicts of interest in this work.

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