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Case Report

Palliative radiotherapy for leptomeningeal metastases after photon-based intensity-modulated radiotherapy in a nasopharyngeal cancer patient

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Abstract

Leptomeningeal metastasis is a rare in nasopharyngeal carcinoma, affecting less than 5% of patients with a poor prognosis. The aim of this case report was to present management of palliative radiotherapy in leptomeningeal metastasis of nasopharyngeal carcinoma patient. A 33-year-old female presented with nasopharyngeal carcinoma with stage III, T3N3M0, WHO type III. The patient has received chemoradiation with photon-based intensity-modulated radiotherapy (IMRT) technique at the dose of 70 Gy in 33 fractions and showed a satisfactory outcome in 12 months follow-up. Later, at 18 months after chemoradiation completion, the patient complained of worsening bilateral sciatic pain, particularly during coughing, with slight limitations in bilateral hip flexion observed during straight leg raises. The whole spine contrast-enhanced magnetic resonance imaging (MRI) examination showed nodular enhancement of leptomeningeal thickening at the T4 level of the spinal cord lower than S3. Palliative radiation therapy utilized a three-dimensional conformal radiation therapy (3D-CRT) technique producing 35 Gy in 14 fractions placed in a field spanning the T4-S3 vertebral bodies. Methotrexate was administered intravenously every two weeks for three cycles to ensure central nervous system penetration. After four months of follow-up, no evidence of disease was found at the primary site and metastatic areas on subsequent physical examination or imaging with MRI and there was satisfactory improvement in neurologic symptoms. In conclusion, leptomeningeal metastases with primary nasopharyngeal carcinoma are rare and typically cause neurological impairments in patients. Hematogenous or cerebrospinal fluid-mediated spread of the cancer is considered the most likely pathway for leptomeningeal dissemination. Strategic modalities, such as radiotherapy with chemotherapy, may improve outcomes in symptoms and quality of life.

Keywords: Leptomeningeal metastasis, NPC, palliative, quality of life, radiotherapy

Introduction

Leptomeningeal metastases occur in 5–10% of individuals with solid tumors, such as nasopharyngeal carcinoma (NPC), as late-stage consequences of systemic malignancies [1]. Neoplastic cells invading the leptomeninges of the brain, cranial nerves, and spinal cord are known as leptomeningeal carcinomatosis [1]. In 2020, NPC is the fourth most common cancer in Indonesian men and is linked to the Epstein-Barr virus (EBV) [2]. The prevalence of NPC in Indonesia reached 6.2/100,000, with more than 12,000 new cases annually [2]. Squamous cell

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Received: June 1, 2023 - Accepted: August 28, 2023 - Published online: October 12, 2023

carcinoma (SCC), non-keratinizing squamous cell carcinoma, and undifferentiated non-keratinizing carcinoma were the three forms of NPC that the World Health Organization (WHO) identified in 1978 [3]. While direct extension from the nasopharynx to the skull base is a rare occurrence in locally advanced disease, metastasis to the central nervous system (CNS), whether through a hematogenous route or cerebrospinal fluid (CSF), is frequently observed [4-9]. CNS metastasis from NPC is uncommon (3.3%) [10], with spinal metastases accounting for 0.5–1% of intramedullary seeding in systemic malignancies [11]. Symptoms often include weakness, sensory loss, sphincter dysfunction, discomfort, and sensory disturbances, with an average duration between tumor diagnosis and intramedullary spinal cord metastases of 13 to 17 months [12].

Radiotherapy remains the primary treatment for NPC [13]. Leptomeningeal metastases are generally resistant to cytotoxic chemotherapy and these tumors have a poor prognosis. Despite the fact that improvements in imaging and treatment methods contributed to larger incidences of spine leptomeningeal metastases and longer survival in oncological patients, the best course of therapy remains uncertain. Modern techniques such as intensity-modulated radiation therapy (IMRT) significantly improves the precision of radiation delivery, provides good tumor control results and reduces toxicity in modern cohorts. The currently accepted international standard radiotherapy delivery method for localized NPC is photon-based IMRT [13-16]. International consensus guidelines are already in place to coordinate variations in tumor target definition and to prioritize the radiation dose for NPC [15-17].

In this case study, we present a case of leptomeningeal metastasis with NPC in an adult female treated with IMRT. The key outcomes were pain relief, improved quality of life, including satisfactory neurological symptom improvement, and no evidence of disease at the primary or metastatic sites.

Case

A 33-year-old female presented with NPC stage III, T3N2M0, WHO type III was initially treated by association chemoradiation using the IMRT method, at a dose of 70 Gy in 33 fractions. The cancer was well controlled during a 12-month follow-up period.

Eighteen months after completing chemotherapy, the patient complained of worsening bilateral sciatica pain, exacerbated during coughing. On physical examination, the straight leg-raising test showed mild restriction in bilateral hip flexion; decreased proprioception and vibratory sensation in lower extremities bilaterally; and normal muscle tone, and a Karnofsky score of 70. The whole spine contrast-enhanced magnetic resonance imaging (MRI) examination showed nodular enhanced leptomeningeal thickening extending from the lower spinal cord T4 level to the cauda equine, suggestive of leptomeningeal metastasis.

Palliative radiation therapy was administered using a three-dimensional conformal radiation therapy (3D-CRT) technique, delivering 35 Gy in 14 fractions to a field encompassing the T4-cauda equina area. This radiotherapy method was considered for patients with pain because of the shorter treatment duration compared to IMRT. Additionally, methotrexate was administered intravenously every two weeks for three cycles to ensure CNS penetration.

The patient was restrained, with both arms at the sides and the body fastened in a supine position. Computed tomography (CT) simulation images were obtained at 2.25 mm slice intervals with intravenous contrast (**Figure 1**). Digital imaging and communications in medicine (DICOM) pictures from the CT simulation were sent to Monaco Treatment Planning for use in treatment planning. The treatment planning system firmly registered all pre-treatment imaging data with the CT simulation dataset after importing it all.

A region encompassing the fourth equina of the thoracic region irradiation was planned using the Monaco treatment planning system (Electa Medical Systems) utilizing a 3D conformal method with three fields and a 6MV photon beam. An anisotropic analytic algorithm with a grid size of 1.25 cm was employed for the computation of dosage for all plans (**Figure 1**). The target volume's exact center, where the isocenter was positioned.

Further beam placement in the gantry angle directions 145°, 180°, 215° with isodose planning radiation planning target volume (PTV) coverage of 98% = 99.23%, 95% coverage = 99.98% (**Figure 1**). A 120-leaf high-definition multi-leaf collimator was used to administer the treatment

on the Sinergy (Electa Medical Systems) platform. To ensure accurate delivery, daily imaging verification was done before delivery. Translational errors larger than 1mm were addressed using a treatment couch with four degrees of freedom.

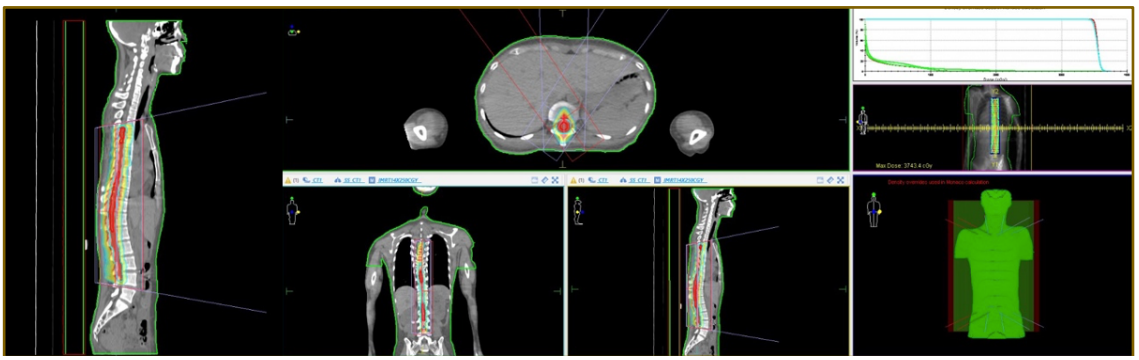

Figure 1. Three-dimensional conformal radiation therapy (3D-CRT) of leptomeningeal metastasis from thoracic to cauda equine.

After six months of follow-up, the prominent results were pain relief and high quality of life such as satisfactory outcomes in neurological symptoms (motoric improvement) and the tumor showed no evidence of disease at the primary site and metastatic areas.

Discussion

NPC, which has a proclivity for hematogenous and lymphatic dissemination, rarely presents with leptomeningeal carcinomatosis. Pathological causes of intramedullary spinal cord metastasis (ISCM) include hematogenous spread, meningeal carcinomatosis, and direct invasion by malignant neoplasms. Most cases (whether via the arterial route or spinal venous plexus) are caused by hematogenous dissemination. The second pathway is associated with CSF-mediated leptomeningeal spread. Cancerous meningitis-related tumor cells have the ability to invade the spinal cord parenchyma, enter the Virchow-Robin vascular space, and pierce the pial membrane. The third mechanism is an invasion of nearby structures directly. Despite the dura's ability to prevent malignant neoplasms from invading the spinal cord, direct tumor growth eventually metastasizes from the extradural space of the spine, CSF, or nerve roots, through the dura, and into the umbilical cord. It also spreads from the perineural space into the subarachnoid space and the umbilical cord parenchyma [18]. Leptomeningeal metastasis in this patient was most likely caused by direct infiltration of nasopharyngeal cancer into the brain. Tumor cells then followed the CSF flow down to the spinal cord.

Leptomeningeal carcinomatosis typically presents with non-specific symptoms such as headache, nausea, vomiting, altered mental status, and seizures, all linked to increasing intracranial pressure. Personality changes, dysphasia, apraxia, and hemiparesis can also result from cerebral leptomeningeal metastasis. Reduced visual acuity, diplopia, trigeminal sensory or motor loss, cochlear dysfunction, and facial weakness can all be brought on by cranial nerve involvement. Back pain, limb weakness, paresthesia, and incontinence could result from spinal cord meningeal involvement [21]. This patient presented with only bilateral sciatica pain that worsened with coughing.

A median survival rate without therapy of 4 to 6 weeks was observed in leptomeningeal metastatic disease from solid tumors [19-21]. Intrathecal chemotherapy administered through an intraventricular reservoir or by lumbar puncture has been the cornerstone of treatment for meningeal carcinomatosis, along with targeted radiation to the main sites of involvement. Unfortunately, the only available intrathecal chemotherapeutic agents are thiotepa, cytosine arabinoside, with methotrexate being the most frequently used. Seizures, acute chemical arachnoiditis with headache, nausea, vomiting, mental changes, subacute onset of motor and sensory problems, and delayed necrotizing leukoencephalopathy are only a few of the major side effects associated with the administration of methotrexate. There are not any conclusive clinical data on how systemic chemotherapy affects leptomeningeal carcinomatosis. Radiation therapy is

frequently administered to symptomatic locations or areas with significant illness to improve intrathecal chemotherapy delivery, address poor CSF flow caused by significant CNS involvement, or both, in an effort to enhance quality of life [19,22,23].

The objective of intrathecal chemotherapy is to cross the blood-brain barrier (BBB) and expose tumor cells for a sufficient amount of time to a sufficient concentration of chemotherapy effluent. Retrospective studies have demonstrated that chemotherapy of any kind improves survival rate when used to treat CNS diseases [19,21]. Squamous cell carcinoma of the head and neck has been treated with methotrexate as a single agent, with a response rate of 10% to the standard regimen of 40 mg/m^2/week [19,24]. Despite this, methotrexate is considered a first-line treatment for leptomeningeal metastasis due to its moderate response rates and ability to remove malignant cells from CSF in up to 60% of cases [19,21,25,26]. A common intrathecal methotrexate regimen includes weekly treatment of 10 to 12 mg for four weeks, then twice-weekly administration for four to eight weeks, which causes a consistent distribution throughout the neuroaxis [19,27-31].

A case report described the involvement of lumbosacral spinal nerve roots in an NPC patient, with histology of the excised tissue demonstrating NPC metastases [10]. Palliative radiation was administered to reduce the symptoms. As the patient was diagnosed with CNS metastases, after undergoing surgery and a second round of radiation therapy for persistent spine lesions, the patient lived for nearly 40 months. Surgical intervention, with or without radiotherapy, was recommended to alleviate neurological impairment in NPC patients with CNS metastases due to accumulating evidence of this entity [10,31].

A previous case report presented a case of leptomeningeal metastasis of NPC, which was successfully treated using the CNS lymphoma paradigm [19]. Six years later, the patient was still asymptomatic and showed no signs of a clinical illness. Future clinical trials for the treatment of NPC with CNS involvement should consider systemic methotrexate, according to the report. This patient may have been exceptional with a successful outcome despite medical treatment and an exceptional prognosis [19]. Another study described the median overall survival rate following diagnosis was found to be four months, with a small survival advantage of six months, and over five months for surgical patients receiving conservative care [18]. In the palliative group, where patients only get medication for symptom relief and no active medical treatment, such as radiotherapy or chemotherapy, is used to improve outcomes, the median survival rate is one month [18].

Once symptoms are evident, a thorough evaluation and proper therapy should be carried out. In patients with spinal metastases, such as leptomeningeal metastasis, it is crucial to carefully monitor neurologic changes and neurological symptoms. However, if radiation therapy is necessary, it is crucial to choose the right form of radiotherapy based on the patient's overall prognosis and the disease's stage [32]. The 3D-CRT is becoming a common therapeutic option for spinal metastases. The main objective of 3D-CRT is to provide a conformal dose distribution to the target volume while limiting radiation exposure to normal tissues [32]. IMRT requires a few days more than 3D-CRT from the commencement of treatment planning to the onset of therapy. As it impacts the patient's quality of life, the time gap between the radiotherapy plan and the start of therapy is considered a critical factor in choosing the radiotherapy technique [32,33]. If necessary, radiotherapy is required as soon as possible. Treatments like IMRT are not always the best option; 3D-CRT, a traditional RT approach, may be more suitable [32,33].

Conclusion

The rare leptomeningeal metastases from NPC typically cause neurological impairments in patients. Hematogenous or CSF-mediated spread of the tumor is considered the two most likely pathways for leptomeningeal dissemination. Leptomeningeal metastases may involve several distant organs. Surgery, palliative chemoradiotherapy, and optimal supportive care are examples of optional treatment. However, these patients typically have a poor prognosis due to inevitable tumor growth.

Ethics approval

The patient provided written informed consent to be published as a case report.

Competing interests

The authors declare that there is no conflict of interest.

Acknowledgments

We would like to express our gratitude to all participants elaborated in this study.

Funding

This study received no external funding.

Underlying data

All data underlying the results are available as part of the article and no additional source dataare required.

How to cite

Marlina YS, Novirianthy R, Beočanin A. Palliative radiotherapy for leptomeningeal metastases after photon-based intensity-modulated radiotherapy in a nasopharyngeal cancer patient. Narra J 2023; 3 (3): e266 - http://doi.org/10.52225/narra.v3i3.266.

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