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Review

Non-hepatocellular carcinoma spinal metastases

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ABSTRACT

Metastases to the spine from non-hepatocellular carcinomas, such as cholangiocarcinoma and angiosarcoma, occur rarely. With improvements in oncologic care, the number of patients diagnosed with metastatic cancer is expected to increase. We performed a systematic review of the literature to assess the clinical presentation, treatment, outcome and survival of patients diagnosed with non-hepatocellular carcinoma spinal metastasis using PubMed, Embase, CINAHL, Cochrane Library and Web of Science. We identified 19 cases of spinal metastases from non-hepatocellular carcinomas that fit our pre-specified criteria. The mean age at presentation was 62.3 years and cholangiocarcinoma was the most common subtype. Patients frequently presented with pain, weakness or paraparesis and at the time of diagnosis, most of them had multi-level involvement of the spine. A majority of patients with spinal metastasis were treated either with radiation or chemotherapy or received no treatment. A minority of the reports included information on survival, which revealed a median survival of 1.5 months following diagnosis of the spinal metastasis. Although there is a paucity of published literature on non-hepatocellular carcinoma spinal metastasis, this systematic review provides descriptive clinical characteristics of these patients.

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1. Introduction

The skeletal system is the third most common location for metastasis and the vertebral column represents the most frequent site of metastatic spread in the skeletal system [1,2]. Although the majority of primary tumors that metastasize to the skeletal system originate from breast, prostate, lung, and kidney, more rare tumor subtypes are also known to metastasize to the skeletal system, leading to neurologic sequelae such as epidural spinal cord compression. Epidural spinal cord compression results in pain or neurological compromise from epidural tumor extension into the spinal canal [1]. With an aging population and better methods of screening, detection, diagnosis, and treatment of metastatic disease, it is expected that the number of patients diagnosed with uncommon tumor subtypes will increase.

Non-hepatocellular carcinomas are rare primary liver cancers that include cholangiocarcinoma, hepatic angiosarcoma and hepatoblastoma. It is estimated that over 45,000 cases of liver, gallbladder and intrahepatic bile duct cancers will be diagnosed in the USA in 2015 with over 17,000 deaths estimated to occur [3]. Cholangiocarcinoma is an epithelial cell malignancy arising from the biliary tree. It is the most common biliary malignancy and second most common hepatic malignancy after hepatocellular carcinoma [4,5]. Cholangiocarcinoma tends to advance locally and regionally by invading lymph nodes but distant metastases have been described [6,7]. Surgical resection followed by chemotherapy is the standard of care, however, prognosis is generally poor with a mean survival of less than 2 years [6,8]. Hepatic angiosarcomas and hepatoblastomas represent rare primary liver malignancies among adults. Hepatic angiosarcomas account for 2% of all hepatic malignancies. They progress rapidly with a uniformly fatal outcome within 6 months [9,10]. Hepatoblastomas are more common in the pediatric population with better prognosis associated with surgical resection and chemotherapy [11,12]. However, adult hepatoblastoma is rare with a worse prognosis. A recent literature review of 40 adult patients with hepatoblastoma revealed an overall median survival time of 4 months, and a 1 year survival rate of 29.6% [12]. Each of these tumors has a poor prognosis with few reports in the literature of metastases from these neoplasms to any location, and only a minority of these reports in the known literature includes metastases to the skeletal system [7,10,13,14].

Although the existing literature on clinical outcomes following a diagnosis of non-hepatocellular carcinoma metastasis to the

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spine is limited, it is expected that an increased number of patients will present with a diagnosis of metastatic disease or the sequelae of these malignancies in the future. In this manuscript, we performed a systematic review of the literature to assess the clinical presentation, treatment, clinical outcome and survival of patients diagnosed with non-hepatocellular carcinoma metastasis to the spinal column according to the known literature. The overall objectives of this study are to answer the following clinical questions. (1) What is the post-diagnosis and post-operative survival for patients diagnosed with metastatic non-hepatocellular carcinoma of the spine? (2) Are there any known variables in the literature that may help to determine which patients will perform better or worse with surgery?

2. Methods

2.1. Electronic literature search

A systematic review of the literature was performed using PubMed, Embase, CINAHL, Cochrane Library and Web of Science search engines. A summary of search strings, as well as inclusion and exclusion criteria are provided in Figure 1. Once all eligible articles were identified for further analysis, we also reviewed each article's bibliography to identify further studies for inclusion. All searches were limited to human patients and no other limitations were placed on the searches unless otherwise specified. The PRISMA registration number for this study is CRD42015024381.

2.2. Data extraction

The following data were extracted from the eligible articles: patient demographics including age and sex, patient presentation (pain, ambulatory dysfunction, weakness, paralysis, paresthesias), treatment for primary tumor and spinal metastasis (surgical resection, laminectomy, chemotherapy, radiotherapy, kyphoplasty, vertebroplasty, percutaneous cryoablation, radiofrequency ablation and cementoplasty), time to spinal metastasis, patient survival (including survival after diagnosis of primary tumor and spinal metastasis, survival after treatment of primary tumor and spinal metastasis) as well as overall patient outcomes.

2.3. Study eligibility and quality assessment

All potentially eligible studies were determined by two reviewers (C.B. and N.A.B.). A third reviewer (C.R.G.) also reviewed the articles and served to resolve discrepancies. Data were extracted by two reviewers (C.B. and N.A.B.) and were verified independently by a third reviewer (C.R.G.). We excluded papers with primary spine tumors, metastasis not of liver origin, hepatocellular metastases, or metastasis not to the bony spine. Articles were also excluded if they reported only on combined outcomes from several neoplasms and did not delineate the clinical characteristics specific to the non-hepatocellular carcinoma, were not relevant to the review (that is, subject matter did not deal with non-hepatocellular carcinoma or metastasis) or were not in English. We were unable to obtain full texts for two articles.

2.4. Statistical analysis

All survival statistics and Kaplan–Meier curves were calculated using GraphPad Prism 5.0 (GraphPad; La Jolla, CA, USA). Patients with unknown follow-up or survival times were not included in the analyses.

3. Results

3.1. Study selection

We identified 178 non-duplicate articles on our initial screen using the search criteria and search engines specified. Nineteen articles ultimately met the inclusion and exclusion criteria and were included in this review (16 cholangiocarcinoma [6–8,13,15–26], two angiosarcoma [10,27] and one hemangiosarcoma [28]). All included articles were at a class of evidence of IV, with either case

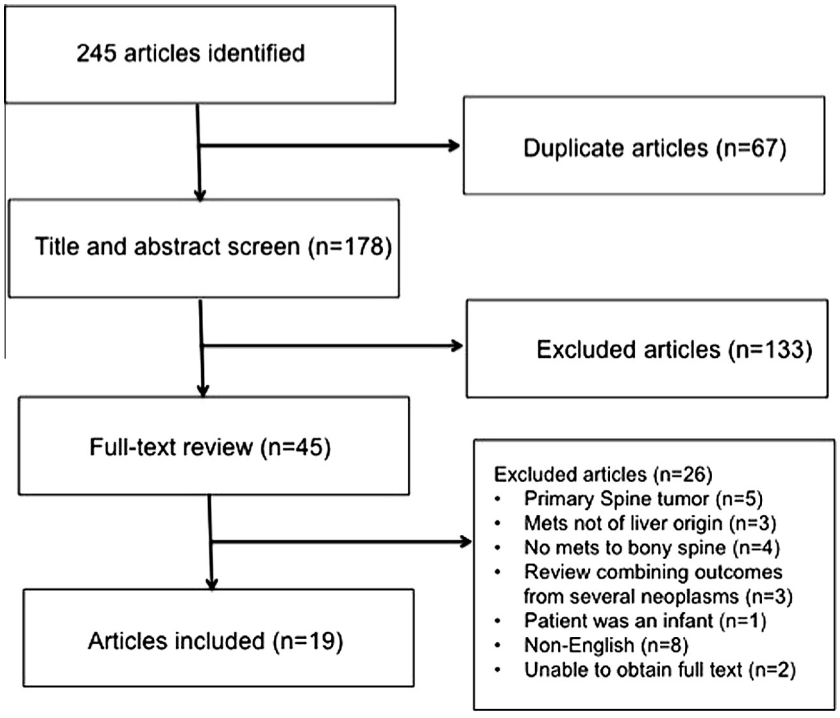

Fig. 1. Flowchart detailing article selection for this literature review. Mets = metastasis.