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Clinical Study

Malignant peripheral nerve sheath tumors of the spine: A SEER database analysis

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ABSTRACT

Peripheral nerve sheath tumors are uncommon neoplasms that can affect any area of the body. Spinal lesions, especially those that are malignant, pose difficult management challenges, and data regarding these lesions are limited by the disease rarity. This study provides a population-based analysis using the Surveillance, Epidemiology, and End Results (SEER) database, focusing on patient characteristics and treatments. Surgery is associated with improved survival, whereas radiation therapy is associated with decreased survival in this cohort with malignant peripheral nerve sheath tumor in the spine.

1. Introduction

Peripheral nerve sheath tumors (PNST) are rare neoplasms that may arise from peripheral nerves, nerve sheaths, or sympathetic ganglia and are often benign. PNSTs are more common than malignant peripheral nerve sheath tumors (MPNST) and often have favorable prognoses [1]. In contrast, MPNST often have poor prognoses with high rates of recurrence and metastasis with reported 5 year survival rates that range from 16% to 52% [2–5]. MPNST include malignant schwannoma, neurogenic sarcoma, and neurofibrosarcoma and account for 5–10% of all soft tissue tumors [6,7]. While the incidence in the general population stands at around 0.001%, the incidence in patients with neurofibromatosis type 1 (NF1) is 5% [4,6,8]. There is a clear association between MPNST and NF1; 50–60% of MPNST occur in patients with NF1 [1,2,9].

MPNST in the spine are rare, with an annual incidence of 0.3 to 0.4 per 100,000 [6]. Surgical resection remains the most effective treatment for MPNST, but since MPNST in the spinal region have only been documented as isolated reports or small case series, outcomes in this population remain unclear [7,10–19]. Additionally, surgery is indicated in many cases as clinical symptoms and radiographic imaging alone are insufficient for accurate diagnosis of MPNST. The spinal location poses challenging treatment constraints; MPNST occurring in a limb may even involve amputation.

Management of MPNST remains somewhat controversial. Most have agreed on the benefits of maximal tumor resection in contributing to favorable outcomes and long-term survival but have yet to reach a consensus regarding the benefits of post-operative radiation [7]. Some continue to advocate the use of post-operative radiation despite obtainment of clear surgical margins and the radioresistant characteristics of MPNST [4,9,20]. Despite reports showing radiation to be of only limited value, it is still being used routinely [21]. It has also been suggested that exposure to ionizing radiation can lead to the development of MPNST [11,22].

The present study examined the clinical features and treatment outcomes of MPNST in the spine. This analysis of the Surveillance, Epidemiology, and End Results (SEER) database (1973–2008) evaluated the impact of demographic and treatment factors on survival. The survival of patients with benign and malignant PNST was assessed based on (1) tumor grade, (2) the extent of surgical resection, and (3) the use of radiation alone or in combination with surgery.

2. Methods

2.1. Study population

Data for this analysis were obtained from the SEER program (1973–2008) of the USA National Cancer Institute. This cancer

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registry includes data from 17 geographic areas in the USA and represents approximately 26% of the USA population. For the purposes of the present analysis, cases from Louisiana were not utilized as suggested by SEER due to non-continuous reporting of data due to the impact of Hurricanes Katrina and Rita in the Gulf Coast region. Site and histology codes of The International Classification of Disease for Oncology (ICD-O-3) were used to identify cases. Subjects classified as having histopathologically confirmed neurofibrosarcoma (ICD-O-3: 9540) or neurilemmoma (ICD-O-3: 9560) located in the spine (primary site code for spinal cord C72.0; cauda equina C72.1; spinal meninges C70.1) were included in this study. Because benign tumors have only been consistently included in SEER since 2004, our analysis of non-malignant neurofibroma and neurilemmoma covered the period from 2004–2008. We included only individuals for whom MPNST were their only or first primary tumor. Subsequent tumors, recurrences, and cases diagnosed at autopsy were not considered for this analysis. SEER data are publicly available and therefore exempt review status was received from our Institutional Review Board.

2.2. Surgical procedure data

In the SEER program, surgical procedure codes are extracted by trained coders according to established guidelines in medical records review in order to determine the extent of resection. The variable containing surgery codes for the patients diagnosed between 1998 and 2007 was named "RX Summ-Surg Prim Site (1998+)" and was based on the American College of Surgeons Commission on Cancer's Facility Oncology Registry Data Standards [23]. Field codes for patients diagnosed between 1983 and 1997 were included in the "Site Specific surgery (1983–1997)" variable. Any patients diagnosed prior to 1983 were coded using a non-specific scheme (yes/no/unknown). In order to create a new variable for analysis that included patients from all time periods, we recoded the surgical procedures for all years into six previously established procedures [24]. Briefly, these categories included: no surgery (pre-1998 codes 00, 01, 03, 04, 07; for 1998+, code 00); biopsy (biopsy, pre-1998 code 02; for 1998+, code 20); partial resection (pre-1998 codes 20, 40; for 1998+, code 40); gross total resection (pre-1998 codes 30, 50, 60; for 1998+, code 55); surgery not otherwise specified (pre-1998 codes 10, 90; for 1998+, codes 10, 90), and surgery status unknown (pre-1998 codes 05, 06, 09, 80; for 1998+, code 99) [25,26].

2.3. Covariates

Sex, age or categorical age at diagnosis (<18, 18–29, 30–39, 40–49, 50–64 and 65+ years), type of surgical (no surgery/biopsy/partial resection/gross total resection/surgery not otherwise specified/unknown), and radiation therapy were evaluated in this analysis. Detailed patient and treatment related factors such as chemotherapeutic regimens, radiotherapy technique, and comorbid conditions were unaccounted for in SEER and were therefore not evaluated in the present analysis.

2.4. Statistical analysis

Descriptive analyses were conducted to evaluate the distribution of patient and tumor related characteristics. The Kaplan-Meier method was used to estimate overall survival as well as 1, 2, 5, and 10 year survival. The association of variables with survival was quantified using hazard ratios (HR) estimated from Cox proportional hazards models. Univariate Cox proportional hazards models were used to calculate HR and 95% confidence intervals (CI) in order to estimate the influence of each variable of interest on the hazard function. Additionally, multivariate Cox proportional hazards models were conducted to estimate the hazard function utilizing variables identified for analysis based on *a priori* assumptions of associations with survival. The statistical analyses were carried out using STATA version 12 (Stata Corporation, College Station, TX, USA). p values of <0.05 were defined as statistically significant.

3. Results

3.1. Patient population

The SEER database was analyzed from 1973–2008 for all patients diagnosed with spine tumors. Of 5076 tumors in the spinal location, there were 690 patients over 18 years of age with primary PNST pathology. The mean age at diagnosis was 50 years with more patients in the higher age group. Fifty-four percent of patients were male. A majority (80%) of the patients were white (Table 1). Of the 690 patients, 626 had benign PNST of the spine and 64 had MPNST of the spine. Sex, age, and race were similar between the malignant and non-malignant groups.

Of patients with MPNST, 76% underwent surgical intervention with 20% having partial resection, 39% having gross total resection, and 27% with an unspecified surgical procedure. In the 14% of patients who did not have surgical resection 11% had a biopsy and 3% had no surgical treatment. Considering the combination of radiation and surgery together, 3% of MPNST patients only had radiation, 58% only had surgery, and 39% had both radiation and surgery.

3.2. Univariate and multivariate analyses

A univariate analysis and a multivariate analysis of patients with MPNST using Cox proportional hazards models revealed radiation therapy and surgical treatment to be significantly associated with survival at 1, 2, 5, and 10 years. As analysis results did not differ substantively in univariate and multivariate models, multivariate analysis results are shown (Table 2). No demographic factors such as sex, age at diagnosis, race, or period of diagnosis were shown to have impact on mortality with MPNST of the spine. To be able to study the effect of extent of surgical resection, those with "surgery not otherwise specified" were excluded from this model. When compared to the reference category of surgical biopsy, the association between partial resection and increased mortality was found to trend toward significance at 1 year after diagnosis (HR 9.16, 95%CI 0.92–90.30, $p = 0.06$) and remained similarly trending toward significance at 5 years after diagnosis. The CI is notably large.

3.3. Outcome and survival

As expected, individuals with MPNST had a significantly higher mortality according to log-rank analysis ($p < 0.001$) than those with the corresponding benign tumor. One, 2, 5, and 10 year survival for adults with primary MPNST was 70%, 65%, 63%, and 52%, respectively (Fig. 1). Survival in those with benign tumors was higher, at 98%, 96%, and 93% at 1, 2, and 5 years, respectively. Patients with MPNST who underwent radiation treatment were also found to have significantly higher mortality ($p < 0.0001$) than those who did not. One, 2, 5, and 10 year survival rates for radiated patients were 35%, 35%, 29%, and 18% respectively, compared to 88%, 80%, 80%, and 71% for those without radiation treatment (Fig. 2). There was also a significant survival difference found by log-rank analysis ($p = 0.003$) when comparing survival with extent of surgical resection at all time points; there was a higher survival rate in patients who had gross total resection *versus* partial