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Clinical commentary

Cholangiocarcinoma with spinal metastasis: Single center survival analysis

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ABSTRACT

The aim of this study was to perform a survival analysis of Cholangiocarcinoma (CCA) with spinal metastases. 55 cases of CCA with spinal metastases were retrospectively reviewed. We recorded age, sex, Kanofsky performance score, Frankel scale, number and region of affected vertebrae, presence of appendicular bone metastases, treatment received, and survival time; then performed a survival analysis. Overall median survival was 4 months (95%CI, 2.89–5.11). Frankel A had the poorest survival (2 months—95%CI, 1.15–2.85) compared to Frankel C and D ($P = 0.004$ and <0.001, respectively). One-level spinal metastasis had the longest survival (8 months—95%CI, 5.98–10.02) compared to two-level and more than two-level involvement ($P = 0.036$ and 0.001, respectively). The higher Kanofsky score had the longer survival (11 months—95%CI, 9.61–12.39) compared with the low and moderate score groups ($P < 0.001$ and 0.012, respectively). Radiation therapy had a survival of 6 months (95%CI, 3.41–8.59), significantly longer than the 3 months for palliative spine surgery and 2 months for palliative treatment alone. CCA resection and palliative spine surgery—when performed together and/or combined with other adjuvant treatment(s)—had a survival time of longer than 9 months. In conclusion, CCA with spinal metastases had a poor median survival. A single level of affected spine, a Frankel scale of C or better, a moderate to high Kanofsky score, and radiation therapy were associated with significantly longer median survival. CCA resection and spinal surgery may play an important role in prolonging survival when used in conjunction with other adjuvant treatment modalities.

1. Introduction

Cholangiocarcinoma (CCA) is an epithelial cell malignancy arising from various locations within the biliary tree, presenting the marker for cholangiocyte differentiation [1]. CCA tends to progress locally and regionally by spreading through the lymphatic system with metastases through the venous and lymphatic systems [2–5]. The incidence of CCA varies worldwide and the highest incidence is in Khon Kaen province, Thailand, where the incidence is 44.3 and 17.6 per 100,000 males and females, respectively [6]. A definite diagnosis of CCA is based on pathological examination; however, in general practice, diagnosis of CCA is usually based on clinical signs and symptoms with corroborative radiographic imaging (CT and MRI) [6].

The spine is the most commonly affected musculoskeletal metastasis [2,7,8], while the most commonly identified primary sites of metastases are the lungs, breasts, prostate, kidneys, and the hematopoietic system [2,3,9]. We recently reported that CCA was the second most common primary site metastasizing to the spine [2].

In a recent review of CCA with spinal metastases, Goodwin et al. [2] identified 16 CCA patients with spinal metastases. Most of the patients had multiple levels of spinal metastases at diagnosis. The median survival time was very poor (1.5 months after diagnosis) of the primary and/or spinal metastases. This is poorer than the median survival time of 4 months for primary CCA regardless of any treatment interventions [2,10–12].

Our institute—Khon Kaen University Hospital—is a tertiary hospital and referral center centrally located in northeastern Thailand. This region is endemic for CCA. For example, our hospital had 661 new CCA patients diagnosed between 2008 and 2009 [6,13]. Notwithstanding, survival analysis of CCA patients with spinal metastases is not well understood due to the relatively small number of patients.

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The aim of this study was (a) to investigate median survival time of CCA patients with spinal metastases and (b) to compare survival outcomes between the various treatment modalities employed at Srinagarind Hospital for spinal metastasis.

2. Methods

2.1. Study design

Single center, retrospective study.

2.2. Selection of patients and grouping

We retrospectively reviewed 176 patients with a diagnosis of spinal metastases of CCA who received treatment in the Department of Orthopaedics between January 1993 and December 2013. The inclusion criteria were: (a) a diagnosis of CCA by clinical and imaging study with or without tissue diagnosis either from (i) an incisional or excisional biopsy at the primary tumor site or (ii) biopsy from the metastases site; (b) clear metastatic spinal lesions diagnosed by MRI imaging; and, (c) an identified survival time period. Accordingly, only 55 CCA patients with spinal metastases fulfilled the inclusion criteria and were included.

We recorded patient age, sex, Kanofsky performance score [14], Frankel scale for neurological status [15], number and region of affected vertebrae, presence of appendicular bone metastases, treatment, and survival. We also grouped the patients by the treatment received, which included chemotherapy, radiation at affected spinal levels, palliative care (symptomatic treatment and pain management), and surgery (type including at the primary site and palliative spinal surgery at the regions affected by metastases. The Kanofsky score was divided into three groups: high (score of 80–100), moderate (score of 50–70), and low (score of 10–40).

2.3. Statistical analysis

The survival analysis was estimated and plotted by the Kaplan–Meier method. The log-rank test was used to compare the survival curves. Bonferroni's correction was used to correct the *p*-values when curves for more than two groups were compared. All statistical tests were two-sided with a significance level of 0.0125 for Frankle scale, and 0.0167 for number of affected spinal level, Kanofsky score, and treatment received group. All statistical analyses were performed using SPSS 23.0 software (SPSS, Chicago, IL, USA).

3. Results

The demographic data are presented in Table 1. CCA with spinal metastases occurred predominately in males (61.8%). Most had incomplete cord lesions and more than two-thirds had two or more than two levels spinal metastases. The most commonly affected region was the thoracic spine followed by the lumbar spine. The mean Kanofsky functional score was intermediate (50.18 ± 22.65). One-third (29.1%) presented with associated appendicular bone metastases. Only 4 patients received CCA resection surgery and 10 received palliative spinal surgery by posterior decompression and instrumentation.

Two-thirds (61.8%) of patients were diagnosed with CCA by clinical signs and symptoms (viz., obstructive jaundice, hepatomegaly, palpable gall bladder, liver mass, and corroborated by a radiographic diagnosis by a radiologist using CT and/or MRI imaging. Only 21 patients had a diagnosis of CCA confirmed by a pathology report. All of the patients in the current study died; overall median survival was 4 months (95%CI, 2.89–5.11) (range, 1 month to 54 months) (Table 2).

Table 1
Patients demographic data.

Demographic data	
Age (Mean ± SD)	58.98 ± 8.48
Gender	
Male	34 (61.8%)
Female	21
Kanofsky performance score (Mean ± SD)	50.18 ± 22.65
Low	18 (32.7%)
Moderate	29 (52.7%)
High	8 (14.6%)
Neurological involvement (Frankel Scale)	
A (Complete paraplegia)	4 (7.3%)
B	17 (30.9%)
C	26 (47.3%)
D	7 (12.7%)
E (Normal)	1 (1.8%)
Number of spinal metastases	
1 level	17 (30.9%)
2 levels	17 (30.9%)
More than 2 levels	21 (38.2%)
Affected spinal region	
Cervical	14
Thoracic	36
Lumbar	23
Sacral	2
Appendicular skeletal metastases	
Present	16 (29.1%)
Diagnosis	
Clinical and imaging diagnosis	34 (61.8%)
Pathological diagnosis	21
At primary site	10
At appendicular skeletal metastasis site	2
Core needle biopsy at affected vertebrae	12
Treatment	
CCA resection surgeries	4
Palliative spine surgery	10
Chemotherapy	6
Radiation therapy at spine	16
Palliative treatment	28
PTBD	2

CCA is Cholangiocarcinoma, PTBD is Percutaneous Biliary Drainage.

The respective Frankel A, B, C, D, and E median survival time was 2 months (95%CI, 1.15–2.85), 3 months (95%CI, 1.71–4.29), 5 months (95%CI, 3.59–6.41), 11 months (95%CI, 9.72–12.28), and 54 months. The Log-rank test showed a significant difference in median survival between the Frankel scales: A and C ($P = 0.004$); A and D ($P < 0.001$); B and C ($P = 0.001$); and, B and D ($P < 0.001$) (Table 3). The Kaplan–Meier plot is presented as Fig. 1A.

Fig. 1B shows the Kaplan–Meier plot according to the number of affected spinal levels. One-level involvement had a median survival of 8 months (95%CI, 5.98–10.02), while two-level involvement was 4 months (95%CI, 2.07–5.93), and more than two was 3 months (95%CI, 2.19–3.81). The difference in median survival between one-level and more than two levels ($P = 0.001$) was statistically significant, while the difference between one-level and two-level and two-level and more than two levels were not ($P = 0.036$ and 0.247, respectively) (Table 3). The presence of appendicular skeletal metastases had a median survival of 3 months (95%CI, 1.74–4.27), whereas the absence of metastases had a median survival of 5 months (95%CI, 2.56–7.44). The presence or absence of associated appendicular skeletal metastases was associated with a significantly different median survival ($P = 0.001$) (Fig. 2A).

A low Kanofsky functional score had a median survival of 3 months (95%CI, 2.02–3.98), while for a moderate score it was 4 months (95%CI, 2.95–5.05), and a high score was 11 months