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Natural History and Prognostic Factors of Cholangiocarcinoma With Spinal Metastasis

A 10-Year Single Center Study

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Study Design: This is a retrospective analysis.

Objective: The aim of this study was to determine the epidemiology, survival, and prognostic factors for cholangiocarcinoma (CCA) with spinal metastasis.

Summary of Background Data: CCA is an epithelial cell malignancy of the bile duct, and a frequent site for its metastasis is the spine. Many areas of Asia are endemic for CCAs. To date, there is limited data on the epidemiology, natural history, and prognostic factors of CCA with spinal metastasis, which is crucial for better management and treatment of the disease.

Materials and Methods: Patients diagnosed with CCA were recruited to our study, in order to identify cases with spinal metastasis. The survival rate was estimated by the Kaplan-Meier method. The univariate and multivariate analyses of tumor-specific and spinal metastatic factors were performed to identify the independent factors that affect survival.

Results: From 2006 to 2015, 4585 CCA patients were identified and 182 of these patients had spinal metastasis. The overall median survival of patients with spinal metastasis was 88 days. Serum carcinoembryonic antigen <5 ng/mL, carbohydrate antigen 19-9 <39 U/mL, albumin ≥ 3.5 g/L, and Frankel score D–E were found to be independent factors that resulted in better survival in a multivariate Cox regression analysis. CCA resection or spinal surgery did not prolong the survival of patients with spinal metastasis.

Conclusion: Spinal surgery should be considered for CCA patients with spinal metastasis, who have a favorable prognosis, and are likely to live long enough to benefit from surgery. The aim is to palliate the symptoms and not as much to improve the survival.

Key Words: cholangiocarcinoma, spinal metastasis, survival analysis, prognostic factors, spine, surgery

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Cholangiocarcinoma (CCA) is a neoplasm of the hepatic bile duct epithelium. CCA is considered a rare tumor comprising only 3% of all gastrointestinal tumors; however, in Northeastern Thailand and many areas of southeastern Asia, a high prevalence of CCA has been noted due to the consumption of raw fish leading to liver fluke infection including *Opisthorchis viverrini* or *Clonorchis sinensis* infection,[1,2] which has been shown to increase the risk of CCA. Moreover, high incidence of hepatitis B infection appears to be yet another driving factor for the higher prevalence of CCA in Asian population.[3] CCA was found to be the third most common cancer accounting for 15.5% (4585/29,447) of cases treated at the Chiang Mai University Hospital which is a tertiary center for cancer patients in the Northern part of Thailand, an endemic area for CCA.[4] Diagnosis is usually based on clinical signs and symptoms with confirmation using computed tomography (CT) scan, magnetic resonance imaging (MRI) or fluorodeoxyglucose positron emission tomography scan.[5] Even though CCA is not considered to be highly osteophilic, the spine remains the most common site for metastasis, and it is reasonable to assume that the prevalence and incidence of CCA with spinal metastasis may be high in areas endemic for CCA. It is, therefore, important to know the magnitude of the disease, its epidemiology, and natural history, all of which are crucial for developing optimal management guidelines.

Treatment options for spinal metastases are radiation, chemotherapy, and surgery; however, the risks and benefits of the surgery should be properly weighed. Thus, survival prognostication is key to selecting patients who can be expected to survive long enough to benefit from surgery. In this study, 4585 CCA patients were recruited to identify spinal metastasis patients in order to assess the magnitude of the disease. Clinical parameters of these patients were used to characterize the natural history and determine the prognostic factors for spinal metastatic CCA.

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MATERIALS AND METHODS

Study Design, Patient Selection, and Data Collection

This is a retrospective cohort that recruited all CCA patients diagnosed by at least CT at the Chiang Mai University Hospital since 2006 through 2015. All patient information was obtained from the Chiang Mai Cancer Registry. From all the recruited patients, cases of CCA with spinal metastases were identified. Spinal metastasis was diagnosed by one or more of the following modalities: pathologic report of a spinal biopsy, MRI, CT scan, or a nuclear bone scan. Patient data for the primary tumor and the spinal metastasis including demographic characteristics and clinical data were collected and recorded at the time of spinal metastasis diagnosis. We recorded sex, age, type of CCA, treatment of primary CCA, serum carcinoembryonic antigen (CEA), serum carbohydrate antigen 19-9 (CA19-9), serum albumin, total bilirubin, visceral metastasis, presentation of skeletal-related events (SREs), number of spinal metastasis, presentation of spinal metastasis, location of spinal involvement, treatment of spinal metastasis, Frankel scale, Karnofsky performance status (KPS), and the number of nonspinal bone metastasis. Numbers of all spinal metastasis patients treated in our hospital during this period were also collected to determine the percentage of CCA with spinal metastases among all spinal metastases.

STATISTICAL ANALYSIS

Median Survival Time and Overall Survival Rate

Time-to-event analysis was performed using the Kaplan-Meier curve to determine the median survival time and the overall survival rate of CCA patients after spinal metastases.

Identification of Prognostic Factors

Univariate and multivariate Cox regression analyses were used to evaluate the influence of each of the demographic and clinical parameters on survival. Factors with P-value ≤ 0.2 from a univariate analysis were submitted to a multivariate Cox regression analysis. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using the Stata Statistical software version 12 (StataCorp, LP, College Station, TX).

Development of a Prognostic Score

The hazard ratios from the factor that independently affected the survival were rounded off to the nearest and divided off to the smallest integer. The patients were divided into groups according to number of prognostic factors affecting the survival. Median overall survival in each group was determined.

RESULTS

Demographic Data for CCA With Spinal Metastases

A total of 4585 CCA patients were identified, of which 182 (4%) had spinal metastases accounted for 15.3% of all 1190 spinal metastasis patients treated in our hospital. Of those 182 CCA with spinal metastasis patients, 154 of them (82.8%) were initially diagnosed with CCA based on clinical symptoms such as jaundice, hepatomegaly, palpable gall bladder, and/or liver mass and were confirmed by imaging using CT and/ or MRI. Only 28 cases (18.2%) were confirmed by pathologic analysis. The median age of the patients was 57 (range: 37–85) years, and 112 (61.5%) of them were male. Fifty-two (28.5%) patients had a history of CCA before the diagnosis of spinal metastasis and the median time from the diagnosis of primary CCA to spinal metastasis was 197 days (range: 2–259 d). The remaining 130 (71.5%) patients presented with signs and symptoms of spinal metastasis, and CCA was diagnosed after the working up the case. The most common SRE was neural compression (54.6%) followed by pain (31.2%) and pathologic fracture (14.2%). Two or more levels of spinal metastases were seen in 128 patients (70.4%). The areas of the affected spine included: combined region of affected spine (51%), thoracic (23.7%), lumbar (19.8%), and cervical (5.5%). For the treatment of primary CCA 12 patients (6.6%) received CCA resection surgery before the diagnosis of spinal metastasis, 12 patients (6.6%) received percutaneous biliary drainage, and 158 patients (86.6%) received palliative treatment. For the treatment of spinal metastasis, 3 patients (1.6%) received palliative spinal surgery combined with postoperative external beam radiation (EBRT), 9 patients (5%) received palliative spine surgery alone, 54 patients (29.7%) received EBRT alone, and 116 patients (63.7%) received palliative treatment. The demographic and clinical data of the CCA with spinal metastases patients are summarized in Table 1.

Survival Rate of CCA Patients With and Without Spinal Metastases

The overall median survival of CCA patients was 121 days (range: 1–3059 d). Of the patients with spinal metastasis, 180 of them died, while 2 patients were alive as of December 2015 and the overall median survival was 88 days (range: 1–1921 d) (Fig. 1). The overall survival rates for CCA with spinal metastases at 3, 6, 9, 12, and 24 months were 83%, 49%, 31%, 17%, 10%, and 3%, respectively. When categorized based on the treatment of the primary CCA, the median survival for patients who underwent tumor resection, percutaneous biliary drainage and palliative treatment was 112 (range: 32–473 d), 149 (range: 5–625 d), and 65 days (range: 1–1921 d), respectively. Patients who underwent palliative spine surgery for spinal metastasis had a median survival of 136 days (range: 16–356 d). Patients who received EBRT alone treatments had a median survival of 112 days (range: 7–655 d) whereas patients who received palliative treatment had a median survival of 102 days (range: 1–1921 d).

The Prognostics Factors for CCA With Spinal Metastases

According to a univariate analysis, patients who had serum CEA ≥ 5 ng/mL and albumin <3.5 g/L, had a worse survival than those who did not with a P-value of 0.06 and <0.01, respectively. Among the other possible prognostic factors, a Frankel score of A–C had a worse survival

TABLE 1. Demographic Data, Clinical Parameters, and Treatment Modalities

Clinical Characteristics	Frequency	Percentage
Age (y)		
Mean ± SD	57 ± 9	
Median (range)	57 (37–85)	
Sex		
Male	112	61.5
Female	70	38.5
Subtype		
Intrahepatic	177	97.2
Extrahepatic	5	2.8
Treatment of primary CCA		
CCA resection surgeries	12	6.6
CCA palliative surgery (PTBD)	12	6.6
Palliative treatment	158	86.8
Serum CEA level (ng/mL)		
< 5	61	40.6
≥ 5	89	59.4
Serum CA19-9 (U/mL)		
< 39	43	28.3
≥ 39	109	71.7
Serum albumin (g/L)		
< 3.5	91	54.5
≥ 3.5	76	45.5
Total bilirubin (mg/dL)		
< 1.2	131	78.4
≥ 1.2	36	21.6
Visceral metastases		
No	111	61.3
Yes	70	38.7
Presentation of SREs		
Incidental finding	63	34.6
Pain	37	20.3
Pathologic Fracture	17	9.3
Cord compression	65	35.7
Number of spinal metastases		
Solitary	54	29.8
2	47	25.9
Multiple	81	44.5
Presentation of spinal metastasis		
Subsequent	52	28.5
Concomitant	130	71.5
Location of spine involvement		
Cervical	10	5.5
Thoracic	43	23.7
Lumbar	36	19.8
Combine	93	51
Treatment of spinal metastases		
Palliative spine surgery+postop EBRT	3	1.6
Palliative spine surgery alone	9	5
EBRT alone	54	29.7
Palliative treatment	116	63.7
Neurological involvement (Frankel scale)		
A (complete paraplegia)	11	6
B	1	0.5
C	23	12.7
D	35	19.3
E (normal)	111	61.5
General condition (KPS)		
Good (80–100)	54	30.5
Moderate (50–70)	110	62.2
Poor (0–40)	13	7.3
No. nonspinal bone metastases		
None	127	70
Solitary	30	17
2	15	8.2
Multiple	10	4.8

CA19-9 indicates carbohydrate antigen 19-9; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; EBRT, external beam radiation; KPS, Kanofsky performance status; PTBD, percutaneous biliary drainage; SREs, skeletal-related events.

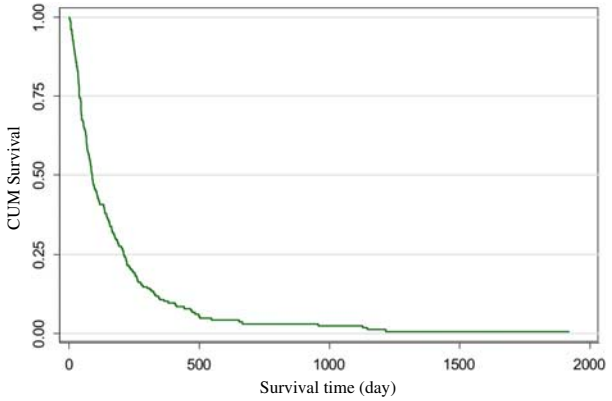

FIGURE 1. Kaplan-Meier plot of overall median survival of cholangiocarcinoma with spinal metastasis. full color online

compared with a Frankel score of D–E ($P = 0.08$). A moderate to poor KPS also resulted in poor survival compared with a good KPS with $P = 0.02$ and 0.01, respectively. According to a multivariate analysis, serum CEA, CA19-9, albumin level, and Frankel score A–C were found to affect the survival independently. Treatment approaches of both primary tumor and spinal metastasis did not influence the survival. Details of the analysis are listed in Table 2. A Kaplan-Meier plot of these factors is shown in Figure 2.

Prognostic Score

Patients could be divided into 5 groups according to number of prognostic factors affecting the survival from 0 to 4. Median overall survival of each patient group is

TABLE 2. Prognostic Values of Clinical Parameters According to Univariate and Multivariate Cox Regression Analysis

	Univariate Analysis			Multivariate Analysis		
Variables	HR	95% CI	P*	HR	95% CI	P†
Serum CEA level (ng/mL)						
< 5	1			1		
≥ 5	1.53	0.99–2.36	0.06	2.4	1.19–4.80	0.02
Serum CA19-9 (U/mL)						
< 39	1			1		
≥ 39	1.33	0.92–1.91	0.13	2.15	1.01–4.54	0.05
Serum albumin (g/L)						
≥ 3.5	1			1		
< 3.5	1.82	1.33–2.50	< 0.01	2.4	1.34–4.28	0.03
Visceral metastases						
No						
Yes	1.20	0.89–1.63	0.20	1.44	0.79–2.62	0.20
Frankel score						
D–E	1			1		
A–C	1.4	0.96–2.03	0.08	2.17	0.99–4.57	0.05
General condition (KPS)						
Good (80–100)	1			1		
Moderate (50–70)	1.71	1.22–2.40	0.02	1.17	0.57–2.53	0.66
Poor (0–40)	2.79	1.50–5.18	0.01	0.93	0.20–4.31	0.91

CA19-9 indicates carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; KPS, Kanofsky performance status; SREs, skeletal related events.

*P-value ≤ 0.2 for multivariate analysis.

†P-value < 0.05 were considered statistically significant.

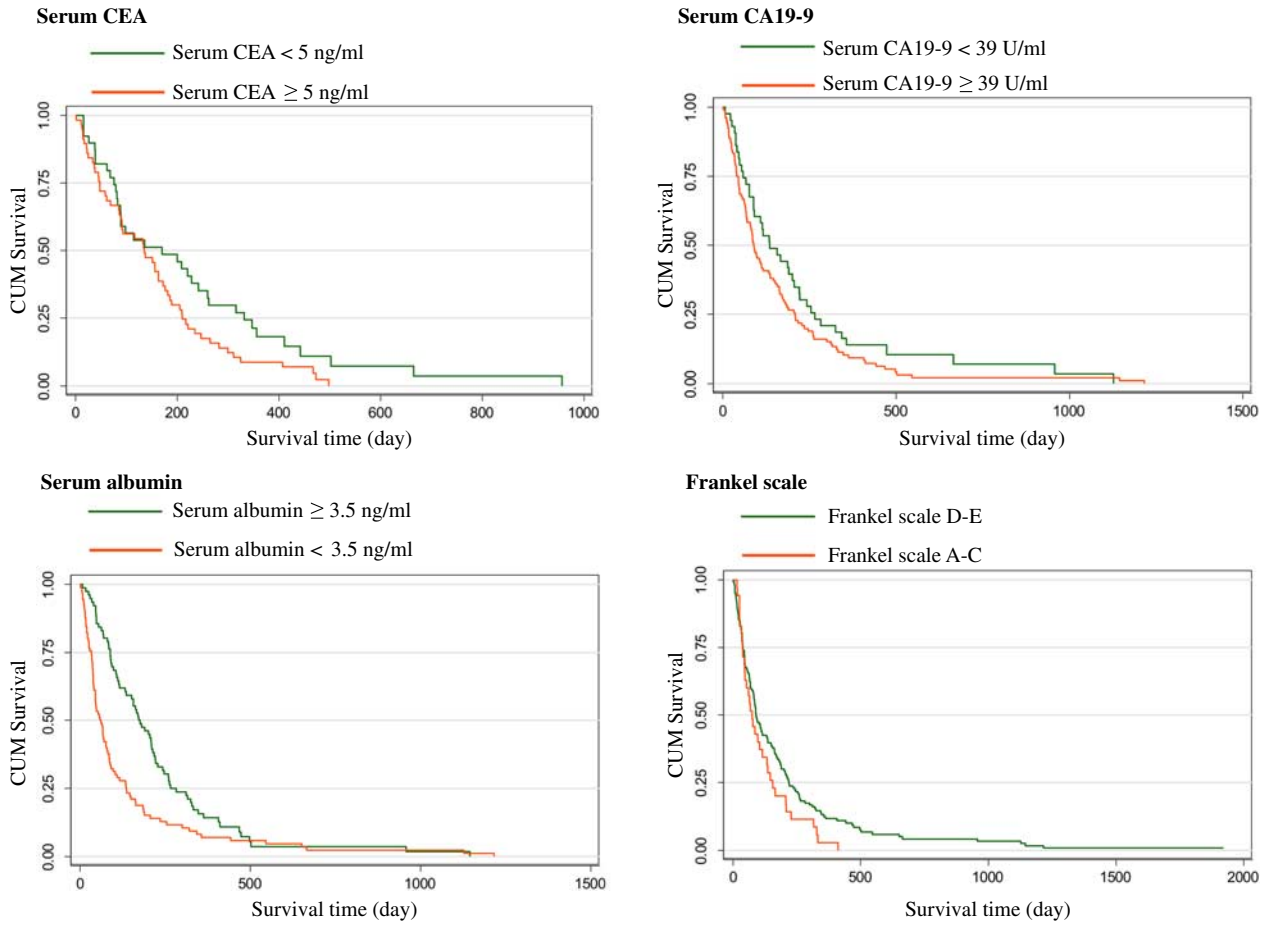

FIGURE 2. Kaplan-Meier plot of independent prognostic factors of cholangiocarcinoma with spinal metastasis. CEA indicates carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; KPS, Karnofsky performance status; SREs, skeletal-related events. full color online

listed in Table 3. Kaplan-Meier plot of each patient group is plot in Figure 3.

DISCUSSION

Although CCA is considered as a rare cancer in the western countries, its prevalence in some parts of Asia, including, Thailand is high. Most patients present with an unresectable disease at the time of diagnosis, and thus have a poor prognosis with 3–6 months of median survival.[6] Even though CCA is not considered to be an osteophilic cancer, a significant number of CCA patients experience spinal metastases. Thus, CCA with spinal metastases should be considered a significant orthopedic problem in the high prevalence areas. This study is the first study to recruit CCA patients to evaluate the prevalence and incidence of spinal metastasis among them. We found that 4% of the CCA patients developed spinal metastases. However, this number may not be accurate because looking for skeletal and spinal metastases at the time of the initial CCA diagnosis as well as follow-ups is not a routine procedure. Therefore, some patients with occult spinal metastasis could have died before it became symptomatic, given the median survival for CCA patients (121 d) is shorter than the median time from the diagnosis of the primary CCA to the diagnosis of spinal metastasis (197 d). Our study showed that of the average 119 cases of spinal metastasis per year treated at our hospital, an average of 18 (15%) were CCA patients with spinal metastasis. However, the incidence could be much higher due to the aforementioned reason. Thus, CCA should be a differential diagnosis in cases with spinal metastasis and work up of CCA should be a routine in patients with spinal metastasis, especially in the high prevalence areas. More than half of the patients presented with neural compression and neurological deficits. Therefore, routine

TABLE 3. Median Survival Time in Each Group of Cholangiocarcinoma With Spinal Metastasis Patients According to Number of Prognostic Factors Affecting the Survival

No. Prognostic Factors	Median Survival (d)
0	242
1	254
2	98
3	61
4	25

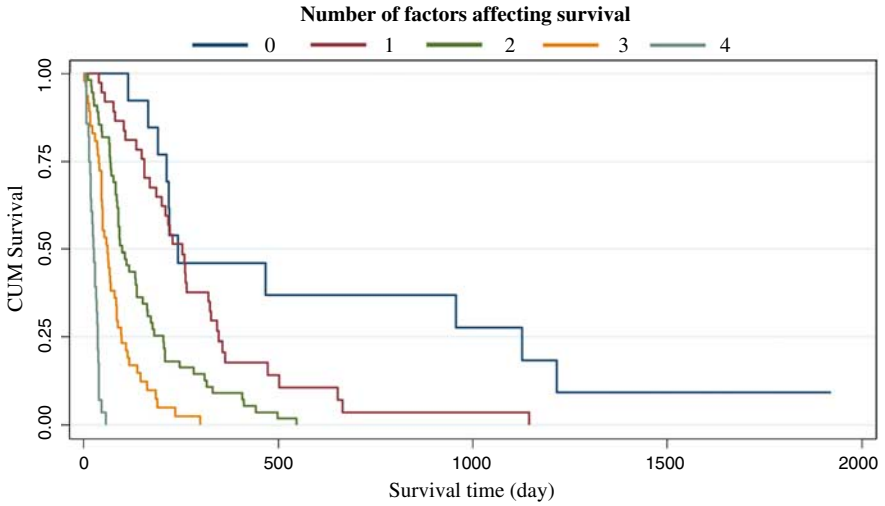

FIGURE 3. Kaplan-Meier plot of median overall survival of patient groups according to number of factors affecting survival. full color online

imaging of the spinal column should be done for patients with a history of CCA, to enable an early detection of spinal metastasis and prevention of the sequelae of neural cord compression.

Median overall survival of CCA patients with spinal metastasis recruited in this study was 88 days which was a month shorter than that reported in a previous study from the Khon Kean University, Thailand, which is an area endemic for CCA.[7] However, another systematic review combining 16 cases of CCA, 2 cases of angiosarcoma, and a case of hemangiosarcoma, reported a median overall survival of 1.5 months.[8] Most of the articles included in the latter study are from low prevalence areas of Opisthorchis viverrini infection. The different causes of the disease may, therefore, explain the difference in survival. When we compared the median overall survival to other metastatic tumors to the spine including lung cancer (11.3 mo),[9] breast cancer (21.7 mo),[10] renal cancer (11.3 mo),[11] hormone naïve prostate cancer (58.3 mo),[12] hormone refractory prostate cancer (5 mo),[12] thyroid cancer (15.4 mo),[13] and hepatocellular carcinoma (8.7 mo),[14] CCA with spinal metastasis patients has much shorter survival (3 mo). CCA with spinal metastasis have poor survival because many CCA patients are asymptomatic until the disease is advanced so most of the patients present with unresectable stage III or stage IV disease.[15] This study also demonstrated the same result that most of the patients (71.5%) presented with signs and symptoms of spinal metastasis and the CCA was diagnosed after the working up the case. Moreover, adjuvant therapy for CCA is considered to have poor sensitivity. Chemotherapy have been shown to slightly prolong the survival time[5] while additional studies regarding stereotactic body radiotherapy and targeted treatments are warranted.[16]

Most of the factors reported to affect the survival in CCA, such as levels of serum CEA, CA19-9, and albumin are all tumor-specific[17–19] while the Frankel score is the only factor related to spinal metastasis. These results were consistent with a meta-analysis that demonstrated that tumor-specific factors affected survival prognostication in spinal metastasis.[20] The study from the Khon Kean University[7] included only cases with spinal metastasis, and so they did not consider the tumor-specific factors. Therefore, the conclusion that a resectable primary CCA, single level spinal metastasis, a Frankel score better than C, and a moderate KPS were all favorable prognostic factors, that justified CCA resection combined with spinal surgery, may not be true because these patients may have carried other favorable tumor-specific factors too that could have influenced the decision for surgery. In contrast to the aforementioned study, CCA resection or spinal surgery did not improve the overall survival, and had no prognostic role in this study; moreover, CCA resection is not indicated in disseminated CCA.[5] On the basis of our findings, we recommended palliative spinal surgery for patients with favorable prognostic factors such as serum CEA <5 ng/mL, serum CA19-9 <39 U/mL, serum albumin ≥3.5 mg/mL, and a Frankel score better than C, who may survive long enough to benefit from surgery. Spinal surgery in CCA patients with spinal metastasis aims to reverse the neurological deficit, decrease pain, and improve ambulatory status but not to improve survival. However, further studies are needed to evaluate the efficacy of surgery in spinal metastatic CCA.

This study has some limitations, such as (a) being a retrospective study, some data could have been missing and (b) being a single center study, it may not represent the general population. However, this is the first and the largest study to evaluate the survival and prognostic factors of CCA with spinal that included both tumor-specific and spinal metastatic–related factors that possibly affect survival. This study also provided an insight into the magnitude of the disease, its natural history, survival, and prognostic factors that can help improve the management of CCA with spinal metastasis.

CONCLUSIONS

CCA with spinal metastasis patients has a short survival. Palliative spine surgery should be considered in

patients who are likely to live long enough to benefit from the surgery; however, the decision about the treatment is complex. Beside clinical judgement on a case by case basis of multidisciplinary team, the information obtained by the score may be used as an additional support when making decision. The aim of the surgery is to palliate the symptoms and not as much to improve the survival.

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