Original Article

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Factors Associated with Bone Scintigraphy Positivity in Cholangiocarcinoma

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Abstract:

Objective: To examine factors associated with bone scintigraphy (BS) positivity in cases with cholangiocarcinoma (CCA) to help assess appropriate utilization of BS in CCA patients.

Material and Methods: This cross-sectional study enrolled CCA patients who underwent BS for detection of bone metastasis between January 2012 and July 2020. The BS images were reviewed by two nuclear medicine physicians to assess BS positivity. Factors including tumor location, T stage, regional lymph node metastasis, other distant metastases, and serum carbohydrate antigen 19-9 (CA19-9) were evaluated. Associations between covariates and positive BS were analyzed using bivariate and multiple logistic regressions.

Results: Among 158 CCA patients, 70 (44.3%), 84 (53.2%), and 4 (2.5%) had positive, negative, and equivocal BS, respectively. Of all 70 positive cases, 50 cases (71.4%) had multiple metastatic lesions. The spine was the most common metastatic site (n=55, 78.6%). After exclusion of equivocal cases, 154 were included in the regression models. In bivariate logistic regression, the factors associated with BS positivity were intrahepatic tumor location (OR=2.18, p-value=0.039) and other distant metastasis (OR=2.08, p-value=0.028). Further analysis using multiple logistic regression showed only other distant metastasis was associated with positive BS (OR=2.66, p-value=0.008).

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Conclusion: There was a significant association between other distant metastasis and BS positivity in CCA patients. This factor should be considered as a clinical indication for requesting BS in this group of patients.

Keywords: biliary cancers, bone metastasis, bone scintigraphy, cholangiocarcinoma

Introduction

Cholangiocarcinoma (CCA), an aggressive malignancy arising from epithelial cells of the biliary tree, accounts for up to 20% of primary liver cancers[1]. The highest incidence of CCA is 85 per 100,000 reported in northeastern Thailand[2]. The metastatic pattern in CCA is to regional lymph nodes and then distant organs including the liver, lungs, peritoneum, and, occasionally, to the bone[3]. The prevalence of bone metastasis in CCA is very low, accounting for 1.5% to 2.0% of cases[4,5]. Most of these latter patients present with bone pain and neurological deficit which can affect both performance status and quality of life[6,7]. Moreover, patients with bone metastasis from CCA have an extremely poor prognosis with median overall survival of approximately four to six months[5,6]. Thus, early detection of bone metastasis can lead to early disease management which may help to improve the quality of life and prognosis of these patients.

Bone scintigraphy (BS) has good diagnostic accuracy for the detection of bone metastasis from various cancers with pooled sensitivity and specificity of 86% and 81%, respectively[8]. Bone metastasis from CCA commonly shows an increased uptake pattern on BS and involvement at the axial skeleton[4]. Currently, there are no standardized criteria for requesting BS in patients with CCA[9]. Thus, this study aimed to assess associated factors for BS positivity in CCA which could be used as indications for recommending BS in these patients.

Material and Methods

This cross-sectional study was performed in line with the principles of the Declaration of Helsinki and approved by our institution Ethics Committee for Human Research (Reference number: HE621538). From January 2012 to July 2020, patients with CCA who underwent BS were consecutively enrolled. Patients with second primary malignancy were excluded from the study. Clinical data including sex and age were obtained from the hospital database. Factors which could lead to bone metastasis were selected based on the tumor biology such as intrahepatic tumor, higher T stage, presence of regional lymph node metastasis, presence of extraskeletal metastasis, and high serum carbohydrate antigen 19-9 (CA19-9). The primary tumor location, T stage, regional lymph node metastasis, and distant metastasis were re-evaluated by a diagnostic radiologist based on computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), or positron emission tomography/computed tomography (PET/CT) findings. Another important factor, serum CA19-9 levels, was retrieved from the hospital database.

Bone scintigraphy protocol

Patients were intravenously injected with 15-20 mCi of Tc-99m methylene diphosphonate, then anterior and posterior static whole-body planar images were acquired approximately 2-4 hours later using a Vertex V60 EPIC HP dual-headed gamma camera (ADAC, CA, USA), a Genesys single headed gamma camera (ADAC, CA, USA), a Discovery NM/CT 670 imaging system (GE Healthcare, IL, USA) or Symbia Intevo 2 scanner (Siemens Healthineers, Erlangen, Germany) equipped with a low energy general purpose collimator with a 1024x1024 imaging matrix with

an energy peak set at 140 keV ±10% using continuous acquisition mode with a detector speed of 15 cm per minute. Single photon emission computed tomography/computed tomography (SPECT/CT) images were obtained in cases with inconclusive BS findings on the planar images.

Bone scintigraphy interpretation

BS images were independently reviewed by two experienced nuclear medicine physicians who were blinded to the clinical information. The BS results were classified into positive, negative, and equivocal for bone metastasis. The definition of positive for bone metastasis was focally increased or decreased radiotracer uptake at any skeletal site or a superscan without suspected other etiologies. Any discrepant readings were resolved by a consensus between two readers. Positive results were further clarified regarding numbers and locations of metastatic diseases.

Statistical analysis

The categorical data are presented as numbers and percentages. The continuous data are presented as mean ± standard deviation (S.D.) or median (interquartile range). Bivariate logistic regression and multiple logistic regression were used to test associations between the variables (primary tumor location, T stage, regional lymph node metastasis, distant metastasis, CA19-9) and positive BS. Cohen's kappa was used to evaluate interobserver reliability between the two BS readers. A 95% confidence interval (95% CI) was calculated where appropriate. All statistical methods were two-sided, and a p-value <0.050 was considered statistically significant. Statistical analysis was carried out using STATA 10.1 (StataCorp LP, College Station, TX, USA).

Results

A total of 164 patients met the inclusion criteria. Six patients were excluded due to coexisting malignancies (colorectal cancer, gastric cancer, lung cancer, gallbladder cancer, and lymphoma). Thus, the BSs of 158 patients who were sent for staging (n=119, 75.3%) or surveillance (n=39, 24.7%) were reviewed. The interobserver reliability of the two BS readers was almost perfect (Cohen's kappa =0.91). There were 70, 84, and 4 patients with positive, negative, and equivocal BS, respectively. The mean ages of the 154 patients with unequivocal BS was 60.2 years. Most of them were male (n=105, 68.2%). More than half of the patients had intrahepatic CCA (n=92, 59.7%) or regional lymph node metastasis (n=94, 61.0%). Eighty-four patients (54.5%) had other distant metastases, namely distant lymph nodes (n=58), lung (n=32), brain (n=1), adrenal gland (n=1), gallbladder (n=1), and peritoneum (n=1). A comparison of the demographic data in patients with positive and negative BS is shown in Table 1. There was a significant difference between numbers of patients with other distant metastasis (p-value=0.027). However, there were no significant differences between mean ages, sex, primary tumor location, T stage, distant metastasis, or serum CA19-9 levels between the two groups.

Results of bone scintigraphy

Among the 70 patients with a positive BS, 50 patients (71.4%) had multiple bone metastases. The three most common metastatic sites were spine (n=55, 78.6%), rib (n=29, 41.4%), and pelvis (n=26, 37.1%). Spinal metastasis was most commonly found at the thoracic level (n=52, 74.3%) followed by the lumbar, cervical, and sacral levels. Metastasis to long bones was most commonly seen at the femur (n=13, 18.6%) or humerus (n=11, 15.7%). Distal appendicular bone lesions were very rare. There were only two patients with tibial metastasis and two with forearm metastasis. The details regarding BS findings are shown in Table 2.

Table 1 Characteristics of the study cohort

Characteristic	Patients with positive BS (n=70)		Patients with negative BS (n=84)		p-value	Total (n=154) (%)
	Number	Percentage	Number	Percentage		
Age (years)						
Mean±S.D.	60.4±9.8	–	60.1±10.8	–	0.853	60.2±10.3
Gender					0.430	
Male	50	71.4	55	65.5		105 (68.2)
Female	20	28.6	29	34.5		49 (31.8)
Tumor location					0.107	
Extrahepatic	15	21.4	30	35.7		45 (29.2)
Intrahepatic	48	68.6	44	52.4		92 (59.7)
Mixed type	7	10.0	10	11.9		17 (11.1)
T stage					0.596	
T1–T2	38	54.3	42	50.0		80 (51.9)
T3–T4	32	45.7	42	50.0		74 (48.1)
Regional lymph nod metastasis					0.057	
Absence	33	47.1	27	32.1		60 (39.0)
Presence	37	52.9	57	67.9		94 (61.0)
Other distant metastasis					0.027	
Absence	25	35.7	45	53.6		70 (45.5)
Presence	45	64.3	39	46.4		84 (54.5)
Serum CA19-9*					0.594	
<103 U/mL	29	46.8	37	51.4		66 (49.3)
≥103 U/mL	33	53.2	35	48.6		68 (50.7)

BS=bone scintigraphy, S.D.=standard deviation, CA19-9=carbohydrate antigen 19-9

*Serum CA19-9 levels were available in 134 patients

Table 2 Bone scintigraphy findings

Characteristic	Number	Percentage
Indication		
All	158	100.0
Staging	119	75.3
Surveillance	39	24.7
Result		
Positive	70	44.3
Negative	84	53.2
Equivocal	4	2.5
Focality		
Positive bone scintigraphy	70	100.0
Single	20	28.6
Multiple	50	71.4

Table 2 (continued)

Characteristic	Number	Percentage
Metastatic site		
Skull	13	18.3
Spine	55	78.6
Cervical	16	22.9
Thoracic	52	74.3
Lumbar	26	37.1
Sacral	13	18.6
Pelvis	26	37.1
Rib	29	41.4
Sternum	9	12.9
Humerus	11	15.7
Femur	13	18.6
Scapula	10	14.3
Clavicle	7	10.0
Forearm	2	2.9
Tibia	2	2.9
Coccyx	1	1.4

A SPECT/CT was done in 33 patients. The SPECT/CT detected one osteolytic metastasis at the T12 spine which was not seen on the planar images. The SPECT/CT also helped to confirm the diagnoses of positive and negative planar BS in 16 and 15 patients, respectively. However, there was still one patient who had an equivocal BS despite undergoing an additional SPECT/CT.

There was only one patient with positive BS who had histologically confirmed metastatic disease. The details are in Figure 1.

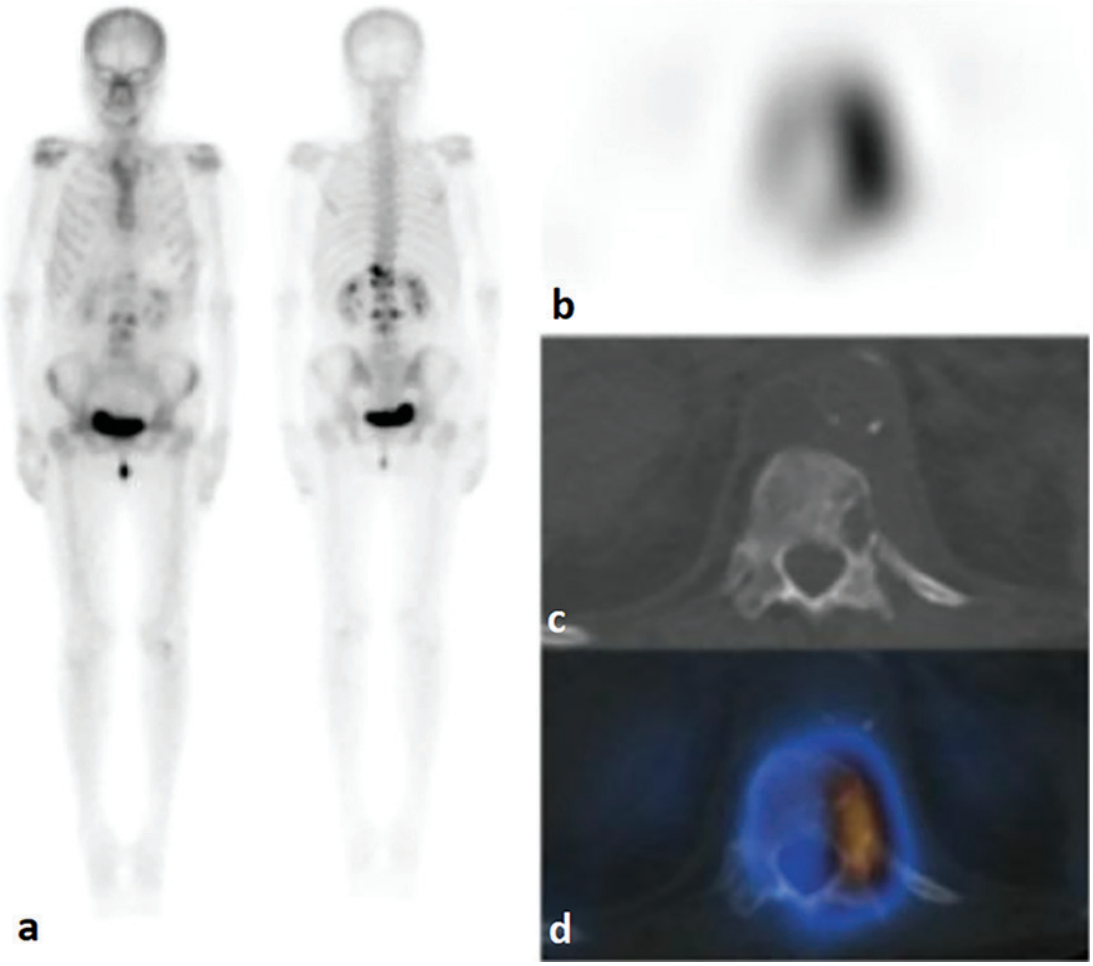

Figure 1 Images from the case of a 69-year-old female with extrahepatic cholangiocarcinoma with regional lymph node and lung metastases. Planar bone scintigraphy (a) shows increased radiotracer uptake at the T12 and L1-L4 vertebrae. The add-on SPECT/CT (b, c, d) reveals increased uptake with an osteolytic lesion at the left pedicle of the T12 vertebra. The pathological findings from a transpedicular biopsy taken at the T12 vertebra confirmed metastatic cholangiocarcinoma.

Factors associated with bone scintigraphy positivity

Associations between primary tumor location, T stage, regional lymph node metastasis, distant metastasis and BS positivity were analyzed in 154 patients with unequivocal BS. There were two factors, intrahepatic CCA and other distant metastasis, which showed significant associations with positive BS in the bivariate logistic regression with p-values of 0.039 and 0.028, respectively. However, only other distant metastasis showed a significant association with positive BS in multiple logistic regression (adjusted odds ratio=2.66, 95% CI: 1.29-5.48, p-value=0.008) as shown in Table 3. Additionally, the multiple logistic regression analysis of 134 patients after adding serum CA 19-9 as a covariate still showed a significant association between other distant metastasis and positive BS (adjusted odds ratio=2.67, 95% CI: 1.22-5.87, p-value=0.014) while tumor location, T stage, and serum CA 19-9 levels were not significantly associated with positive BS as shown in Table 4.

Discussion

To the best of our knowledge, this is the first study which aimed to find associated factors for positive BS in a large number of CCA patients. The proportion of patients with positive BS in our study was very high which represented the high number of patients with bone metastasis. However, earlier studies reported much lower figures. One study which included 13,190 CCA patients found only 199 (1.5%) with bone metastasis[4] while another study found 4 (2.0%) of 200 extrahepatic CCA patients with bone metastasis detected by PET/CT, CT, or plain radiograph[5]. The high prevalence of bone metastasis in our cohort could be explained by patient selection for BS. Referral physicians tend to request BS in patients with a high possibility of bone metastasis and this is a likely reason we had a much higher number of BS positive patients.

Table 3 Associated factors of bone scintigraphy positivity in 154 patients

Factor	Bivariate logistic regression		Multiple logistic regression	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Tumor location				
Extrahepatic	1.00	-	1.00	-
Intrahepatic	2.18 (1.04-4.58)	0.039	1.95 (0.87-4.40)	0.106
Mixed type	1.40 (0.44-4.41)	0.566	1.13 (0.34-3.75)	0.838
T stage				
T1-T2	1.00	-	1.00	-
T3-T4	0.84 (0.45-1.59)	0.596	1.27 (0.59-2.75)	0.541
Regional lymph node metastasis				
Absence	1.00	-	1.00	-
Presence	0.53 (0.28-1.02)	0.059	0.40 (0.19-0.86)	0.018
Other distant metastasis				
Absence	1.00	-	1.00	-
Presence	2.08 (1.08-3.98)	0.028	2.66 (1.29-5.48)	0.008

OR=odds ratio, 95% CI=95% confidence interval

Table 4 Associated factors of bone scintigraphy positivity in 134 patients

Factor	Bivariate logistic regression		Multiple logistic regression	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Tumor location				
Extrahepatic	1.00	–	1.00	–
Intrahepatic	2.18 (1.04–4.58)	0.039	2.20 (0.90–5.38)	0.084
Mixed type	1.40 (0.44–4.41)	0.566	1.02 (0.25–4.22)	0.980
T stage				
T1–T2	1.00	–	1.00	–
T3–T4	0.84 (0.45–1.59)	0.596	2.02 (0.85–4.80)	0.113
Regional lymph node metastasis				
Absence	1.00	–	1.00	–
Presence	0.53 (0.28–1.02)	0.059	0.34 (0.15–0.80)	0.013
Other distant metastasis				
Absence	1.00	–	1.00	–
Presence	2.08 (1.08–3.98)	0.028	2.67 (1.22–5.87)	0.014
Serum CA19-9				
<103 U/mL	1.00	–	1.00	–
≥103 U/mL	1.20 (0.61–2.37)	0.594	1.20 (0.58–2.51)	0.624

OR=odds ratio, 95% CI=95% confidence interval, CA19-9=carbohydrate antigen 19-9

Regarding positive BS findings, 71.4% of the patients had two or more metastatic lesions. Most of the lesions involved the axial skeleton including the spine and ribs which was similar to a previous study which found 169 (84.9%) and 80 (40.2%) of 199 patients with spinal and rib metastasis, respectively[4]. This distribution is related to hematopoietically active red bone marrow which is frequently localized in the axial bones[10]. The most commonly affected spine in our study was the thoracic spine. This finding corresponds to a previous study which found about two-thirds of 55 CCA patients (n=36, 65.5%) had thoracic spine metastasis[6]. This spinal level is most prone to hematogenous spread as it contains the highest volume of bone marrow per vertebrae[11]. Long bone metastases are rare and frequently found at the humerus and femur. Previous studies have also reported long bone metastases from CCA at the proximal humerus, distal femur, and distal fibula, with all patients presenting with bone pain. Appropriate pain control, bisphosphonate, and local treatment can reduce pain and improve the quality of life of these patients[12–14].

We found that the SPECT/CT could identify osteolytic metastasis in one patient with negative planar BS, while SPECT/CT in 31 other patients helped to confirm the diagnosis of planar BS. Another previous study found that most of the metastatic lesions from CCA had mixed osteolytic and osteoblastic patterns on the CT images (40.8%) and increased uptake on planar BS (93.6%)[4], while another study found lytic lesions were the most common metastatic type, accounting for 57.5% of the patients.[15] Thus, the benefit of add-on SPECT/CT is still unclear and needs to be further investigated.

Regarding predictive factors for BS positivity in CCA patients, the presence of a distant metastasis was the only independent predictor with an adjusted odds ratio of 2.66. This finding concurs with a previous study which found that bone metastasis was synchronous with visceral metastases

in 48 of 137 cases (35.0%) of patients with biliary cancers. Furthermore, bone metastasis was subsequently seen in 82 patients (60.0%) who had visceral disease[15]. This finding can be explained by hematogenous spread which is the common route of metastasis to bone or other visceral organs[16]. Surprisingly, we found that absence of regional lymph metastasis was associated with positive BS in multivariable analysis. This is in discordance with tumor biology and a previous study which found a significant association between lymph node and bone metastases (p-value<0.005) in patients with extrahepatic CCA[5]. Thus, this finding could have occurred by chance. The covariates of tumor location, higher T stage, and serum CA 19-9 levels were not associated with BS positivity in our study. Additionally, a previous study also found that there was no significant association between bone metastasis and pathological factors such as histological type, vascular invasion, lymphatic invasion, and perineural invasion[5].

There are some limitations in our study. Firstly, almost all of the positive BS cases were not histologically confirmed as bone metastases. Thus, we do not know what the false positive rate was. Secondly, because of the retrospective design, selection bias was possible. BSs were requested in patients who were already suspicious for bone metastasis, which resulted in a high number of patients with BS positivity.

Conclusion

In conclusion, this study found a significant association between other distant metastasis and BS positivity in CCA patients. This factor should be considered one of the clinical indications for requesting BS in this group of patients.

Conflict of interest

The authors declare that they have no conflicts of interest.

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