

RESEARCH COMMUNICATION

Brain Metastases from Cholangiocarcinoma: a First Case Series in Thailand

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Abstract

Background: Brain metastasis from cholangiocarcinoma (CCA) is a rare but fatal event. To the best of our knowledge, only few cases have been reported. Herein, we report the incident rate and a first case series of brain metastases from CCA. **Methods:** Between January 2006 and December 2010 5,164 patients were treated at Srinagarind hospital, Khon Kaen University; of those, 8 patients developed brain metastasis. Here we reviewed clinical data and survival times. **Results:** The incident rate of brain metastases from CCA was 0.15%. The median age of the patients was 60 years. Tumor subtypes were intrahepatic in 6 and hilar in 2 patients. All suffered from symptoms related to brain metastasis. Three patients were treated with whole-brain radiation therapy (WBRT), one of whom also underwent surgery. The median survival after the diagnosis of brain metastasis was 9.5 weeks (1-28 weeks). The longest survival observed in a patient in RPA class I with two brain lesions and received WBRT. **Conclusion:** This is a first case series of brain metastases from CCA with the incident rate of 0.15%. It is rare and associated with short survival time.

Keywords: Bile duct neoplasm - brain metastasis - cholangiocarcinoma - Thailand

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Introduction

Cholangiocarcinoma (CCA), the bile duct epithelium neoplasm, has varied incidence and risk factors upon the region of the world (Jemal et al., 2011). The highest incidence is reported from the Northeastern part of Thailand (Sripa et al., 2008). The major risk factor for CCA in the mentioned area is *Opisthorchis viverrini* infection, while *Clonorchis sinensis* is associated with CCA in Korea and China (Shin et al., 2010; Tao et al., 2010; Kamsa-ard et al., 2011). Other risk factors for CCA in the Western countries are hepatitis B virus, hepatitis C infection, obesity, chronic non-alcoholic liver disease, and cirrhosis (Shaib et al., 2004; Welzel et al., 2007).

Common presenting symptoms for CCA include jaundice, dyspepsia, and palpable abdominal mass. The symptoms of CCA depend on location of the tumor mass whether it is at intrahepatic, hilar or extrahepatic area. Surgical intervention plays a major role in treatment of early stage CCA with a promising result (Li et al., 2009; Nanashima et al., 2012) However, most patients are advanced at the time of diagnosis and not appropriate for curative surgical treatment. The prognosis of advanced CCA is extremely poor. Palliative surgical bypass showed slightly improved survival rate compared to percutaneous transhepatic biliary drainage (Wongkonkitsin et al., 2006).

Palliative chemotherapy does not show significant benefit since the survival rate remained low (Thongprasert, 2005; Eckman et al., 2011).

The common metastatic sites of CCA are regional lymph nodes and adjacent organs. Distant metastasis of CCA is uncommon. The previous reported distant metastatic sites of CCA are bone, muscle, and thyroid gland (Kidambi et al., 2011; Li et al., 2011; Park et al., 2012). Brain metastasis from CCA is extremely rare with a few case reports (Gudesblatt et al., 1984; Shuangshoti et al., 1989; Okamura et al., 2008; Mimatsu et al., 2011; William et al., 2011). Here, we reported a series of brain metastatic CCA in our institution with the aim to provide useful information on this rare condition.

Materials and Methods

We retrospectively reviewed all medical records of CCA patients with brain metastasis treated at Srinagarind hospital, Khon Kaen University between January 1, 2006 and December 31, 2010. Our hospital is the referral center for CCA in the Northeastern part of Thailand. The demographic data, clinical characteristics, the recursive partitioning analysis (RPA) class, pathological report, radiological imaging, and treatment method were recorded. The Statistical Package for the Social Sciences,

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Table 1. Clinical Characteristics of 8 Patients with Brain Metastases from Cholangiocarcinoma

No.	Age	Sex	KPS	RPA	Type	Staging	Operation	Symptoms	No. of brain metastasis	Treatment	Survival time (weeks)
1	77	M	<70	3	hilar	4	None	Weakness	1	None	8
2	61	M	<70	3	intrahepatic	4	Segmentectomy+cholecystectomy	Alteration ^a	≥4	WBRT	12
3	55	F	<70	3	intrahepatic	4	Left hepatectomy	Weakness	1	WBRT+surgery	8
4	54	F	<70	3	intrahepatic	4	None	Headache	≥4	None	11
5	46	F	≥70	1	intrahepatic	4	Left hepatectomy+cholecystectomy	Headache	2	WBRT	28
6	60	M	<70	3	hilar	3	PTBD	Alteration ^a	1	None	1
7	60	F	≥70	1	intrahepatic	4	Rt hepatectomy+cholecystectomy	Weakness	1	None	13
8	72	F	<70	3	intrahepatic	4	None	Alteration ^a	1	None	8

*KPS, Karnofsky performance status; RPA, recursive partitioning analysis; PTBD, percutaneous transhepatic biliary drainage; WBRT, whole-brain radiation therapy; ^aAlteration of conscious

Version 17.0 was used to analyze the data. The study was approved by Ethic Committee of Medicine Faculty, Khon Kaen University under the respect of Helsinki Declaration.

Results

There were 5,164 CCA patients during the study period. Of those, eight patients (0.15%) had brain metastasis. The clinical characteristics of patients were summarized in Table 1. The median age of patients at the time of diagnosis of CCA was 60 years (46-77). Six out of eight patients were female. Six patients were RPA class 3 and the other two patients were in RPA class I. Median CA 19-9 level at the time of the diagnosis of brain diagnosis was 13.6 U/ml (0.6-1000).

Six patients were intrahepatic CCA, whereas two patients were perihilar CCA. Four patients underwent radical surgery, while the rest had advanced CCA that were beyond to operate. Two patients had brain metastasis at the time of first presentation.

All brain metastatic CCA had any of these neurological symptoms including weakness, alteration of consciousness, or headache. Five patients had a single brain lesion, one patient had two brain lesions, and the other two patients had more than four brain lesions. Most of the brain lesions were located in frontal and occipital lobes.

Only one patient underwent craniotomy and tumor removal with whole brain radiotherapy (WBRT). The other two patients had WBRT, while other five patients were treated with dexamethasone only. The median time from diagnosis of primary tumor to brain metastasis was 8 months (0-96) and median survival time after brain metastasis was 9.5 weeks (1-28). The longest median survival time was 28 weeks (patient no. 5 in Table 1). She had two brain lesions and was in RPA class I. She was diagnosed with intrahepatic CCA stage IV, underwent left hepatectomy and cholecystectomy and brain metastasis was treated with WBRT.

Discussion

Srinagarind hospital, a university hospital of Khon Kaen University, is a referral hospital located in the center of the Northeastern part of Thailand or the endemic area of CCA. Our hospital is named as the center for CCA center of Thailand. The brain metastasis of CCA in our series is 0.15% which may be underestimated because

brain imaging is not routinely done in all CCA patients. Occult brain metastasis may be missed. Though, what is known from our study is that if CCA patients have any neurological symptoms such as headache, motor weakness, or alteration of consciousness, brain metastasis should be considered.

We would like to purpose why CCA has low rate of brain metastasis. First, CCA patients always firstly present with advanced disease. Once diagnosed, the survival rate is short (William et al., 2011). Cancer with better survival time or good response to treatment may have more brain metastasis (Eichler et al., 2007). Second, CCA is not a highly vascularized tumor. Hematogenous metastasis may not frequently occur. Lastly, brain computed tomography is not routinely done in our hospital.

Risk factors for brain metastasis could not be concluded due to small sample size. But, CCA patients with RPA class III have high likelihood to have brain metastasis as previously reported (Jiang et al., 2011; Craighead et al., 2012). Even though it is difficult to draw a conclusion about site of CCA and brain metastasis, note that no patient with extrahepatic CCA had brain metastasis.

The outcome of CCA with brain metastasis is poor comparing to other primary cancer metastasize to brain (Sen et al., 1998; Niwinska et al., 2010; Jung et al., 2011). Only three patients received definite treatment, while the others had only palliative treatment. Most patients denied surgical treatment or WBRT due to negative belief with these modalities of treatment. However, the outcome was slightly better than those with hepatocellular carcinoma with brain metastasis (Choi et al., 2009).

In conclusion, this is a first case series of brain metastases from CCA. Brain metastasis in CCA is rare and has short survival time.

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