

Cutaneous metastasis of cholangiocarcinoma

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Author contributions: Liu M was a major contributor in writing the manuscript; Liu BL revised it critically; Liu B, Guo L, Wang Q and Song YQ contributed to data analysis; Dong L reviewed the literature, analyzed the data, and gave final approval of the paper to be submitted; all authors read and approved the final manuscript.

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Received: September 27, 2014

Peer-review started: September 30, 2014

First decision: October 14, 2014

Revised: November 7, 2014

Accepted: December 5, 2014

Article in press: December 8, 2014

Published online: March 14, 2015

Abstract

AIM: To investigate the clinical characteristics and prognostic factors of cutaneous metastasis of cholangiocarcinoma by a retrospective analysis of published cases.

METHODS: An extensive search was conducted in the English literature within the PubMed database using the following keywords: cutaneous metastasis or skin metastasis and cholangiocarcinoma or bile duct. The data of 30 patients from 21 articles from 1978 to 2014 were analyzed. Patient data retrieved from the articles included the following: age, gender, time cutaneous metastasis occurred, number of cutaneous metastases throughout life, sites of initial cutaneous metastasis, anatomic site, pathology and differentiation of cholangiocarcinoma, and immunohistochemical results of the cutaneous metastasis. The assessment of overall survival after cutaneous metastasis (OSCM) was the primary endpoint.

RESULTS: The median age at diagnosis of cutaneous metastasis of cholangiocarcinoma was 60.0 years (range: 35-77). This metastasis showed a predilection towards males, with a male to female ratio of 3.29. In 8 cases (27.6%), skin metastasis was the first sign of cholangiocarcinoma. Additionally, 18 cases (60.0%) manifested single cutaneous metastasis, while 12 cases (40.0%) demonstrated multiple skin metastases. In 50.0% of patients, the metastasis occurred in the drainage region, while 50.0% of patients had distant cutaneous metastases. The scalp was the most frequently involved region of distant skin metastasis, occurring in 36.7% of patients. The median OSCM of cholangiocarcinoma was 4.0 mo. Patient age and cutaneous metastatic sites showed no significant relation with OSCM, while male gender and single metastasis of the skin were associated with a poorer OSCM (hazard ratio: 0.168; $P = 0.005$, and hazard ratio: 0.296; $P = 0.011$, respectively).

CONCLUSION: The prognosis of cutaneous metastasis of cholangiocarcinoma is dismal. Both male gender and single skin metastasis are associated with a poorer OSCM.

Key words: Cutaneous metastasis; Cholangiocarcinoma; Clinical characteristics; Pathological features; Prognosis

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Core tip: Skin metastasis from internal malignancy is rare, especially from cholangiocarcinoma. The clinical characteristics and prognosis of the metastases are unclear and need to be further defined. We performed a systemic analysis of 30 cases in the English literature from 1978 to 2014 to expand our understanding of this condition. To the best of our knowledge, this is the first comprehensive analysis of cutaneous metastasis of cholangiocarcinoma.

Liu M, Liu BL, Liu B, Guo L, Wang Q, Song YQ, Dong LH. Cutaneous metastasis of cholangiocarcinoma. *World J Gastroenterol* 2015; 21(10): 3066-3071 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i10/3066.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i10.3066>

INTRODUCTION

Skin metastasis is rare, involving 0.7%-9% of all cancer patients^[1]. Lung and breast cancer are the leading causes of cutaneous metastasis in males and females, respectively^[1]. The early recognition of skin metastasis of previously undiagnosed cancers is critical for timely intervention^[1,2].

Cutaneous metastases originating from cholangiocarcinoma are rarely encountered in clinical practice. To date, little is known about the clinicopathological features and prognosis of this condition, as only sporadic case reports or series are available. To obtain a full understanding of the disease, systemic reviews and analyses are required. To the best of our knowledge, our research is the first comprehensive analysis of cutaneous metastasis of cholangiocarcinoma.

MATERIALS AND METHODS

An extensive search of the English literature was performed in PubMed using the keywords "cutaneous metastasis" or "skin metastasis" and "cholangiocarcinoma" or "bile duct". Only cases with a definite pathologic diagnosis and disease course description were included. In total, 30 cases have been described in case reports or series between 1978 and 2014^[3-23].

The data that were retrieved included the following: age, gender, time cutaneous metastasis occurred, number of cutaneous metastases throughout life, sites of initial cutaneous metastasis, anatomic site, pathology and differentiation of cholangiocarcinoma, and immunohistochemical results of the cutaneous metastasis. The primary aim was to determine overall survival after cutaneous metastasis (OSCM), defined as the period from diagnosis of cutaneous metastasis to death or latest follow-up. The evaluation of OSCM

will help to clarify the value of cutaneous metastasis in predicting the survival outcome in cholangiocarcinoma patients.

The Kaplan-Meier method was used to generate the cumulative survival curve, and the log-rank (Mantel-Cox) test was used to compare survival differences. We used SPSS version 17.10 (SPSS, Inc., Chicago, IL, United States) for data analysis, and $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and pathological features

As shown in Table 1, the median age at diagnosis of cutaneous metastasis of cholangiocarcinoma was 60.0 years (range: 35-77). This metastasis affected more males, with a male to female ratio of 3.29. Skin metastasis was the first sign of cholangiocarcinoma in 8 cases (27.6%). For those with a definite diagnosis of cholangiocarcinoma, the mean time for cutaneous metastasis development was 14.51 mo.

In total, 18 cases (60.0%) manifested single cutaneous metastasis, while 12 cases (40.0%) demonstrated multiple skin metastases. In 50.0% of patients, the metastasis occurred in the drainage region, namely the percutaneous biliary drainage or catheterization site, while 50.0% of patients had distant cutaneous metastasis. The scalp was the most frequently involved region of distant skin metastasis, occurring in 36.7% of all patients.

The cutaneous metastases presented as nodules, papules, erythema and lesions with or without ulcers, which were sized between 0.3 cm and 4 cm. Figure 1 shows a metastatic nodule and erythema in the scalp and along the drainage tube, respectively. The size of skin metastases had no association with OSCM.

In total, 24 cases had explicit descriptions of the anatomic site of cholangiocarcinoma, of which 4 cases were extrahepatic, 10 cases were hilar, and 10 cases were intrahepatic. With respect to the pathology of cholangiocarcinoma, 26 cases had clear documentation, of which 25 cases were adenocarcinoma and one case was small cell cholangiocarcinoma. Additionally, 17 cases had information on the differentiation of the primary tumor. The well, well-to-moderate, moderate-to-poor, poor, and undifferentiated types comprised 6, 2, 1, 7, and 1 cases, respectively. Only 9 cases had detailed immunohistochemical analysis of the cutaneous metastasis (Table 2).

When cutaneous metastasis (or metastases) occurred, 8/24 patients underwent surgery, including to the skin lesion, while 16/24 did not. Chemotherapy was performed in 8/23 patients, while 15/23 patients did not undergo chemotherapy. Only 4/23 patients received local radiotherapy to the skin metastasis, while 19/23 did not. However, the response to chemotherapy or radiotherapy was poor.

Table 1 Clinical features of patients with cutaneous metastasis of cholangiocarcinoma

Age (n = 30)	n (%)
Median at diagnosis (yr) 60.0	
Range (yr) 35-77	
30-40	2 (6.7)
41-50	6 (20.0)
51-59	6 (20.0)
60-70	9 (30.0)
> 70	7 (23.3)
Sex (n = 30)	
Male	23 (76.7)
Female	7 (23.3)
Cutaneous metastasis occurrence (n = 30)	
Before diagnosis of cholangiocarcinoma	8 (26.7)
After diagnosis of cholangiocarcinoma	21 (70.0)
Not available	1 (3.3)
Number of cutaneous metastasis throughout life (n = 30)	
Single	18 (60.0)
Multiple	12 (40.0)
Sites of initial cutaneous metastasis (n = 30)	
Drainage site	15 (50.0)
Distant site	15 (50.0)
Scalp ¹	11 (36.7)
Head ²	2 (6.7)
Shoulder	1 (3.3)
Trunk	1 (3.3)

¹Including a case with initial skin metastasis of scalp and head and two cases with initial skin metastasis of scalp and trunk; ²Including a case with the initial skin metastasis on the head, face, and trunk.

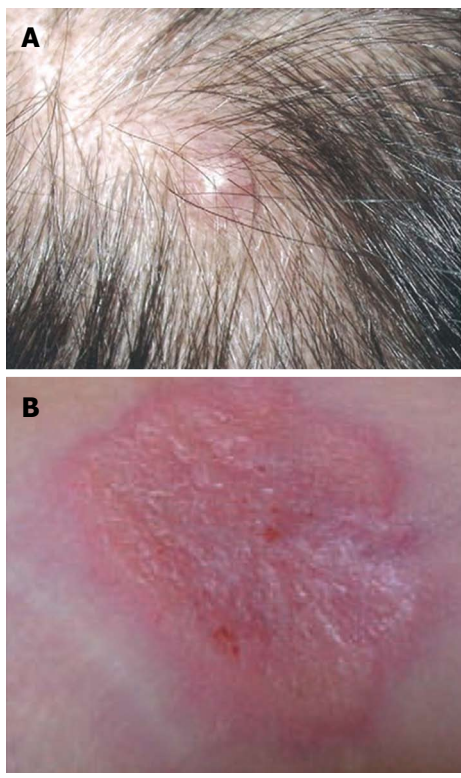


Figure 1 Typical manifestations of skin metastasis of cholangiocarcinoma. A: A metastatic nodule in the scalp^[11]; B: Erythema along the catheter tract^[8].

Table 2 Immunohistochemical analysis of cutaneous metastasis in 9 cases

Case number	Immunohistochemistry results
1	CK7+, CEA-, CK20-
2	CK7+, CK19+
3	CK19+, CEA+
4	CK7+, CK8/18/19+, CEA+, CK20-
5	CK7+, CAM5.2+, AE1/3+, CK20-
6	CK7+, CK20+, CA199 (focally+), TTF1-
7	CK7+, CK19+
8	CK7 (strongly+), CK20 (weakly+)
9	CK7+, CK20+, p53+

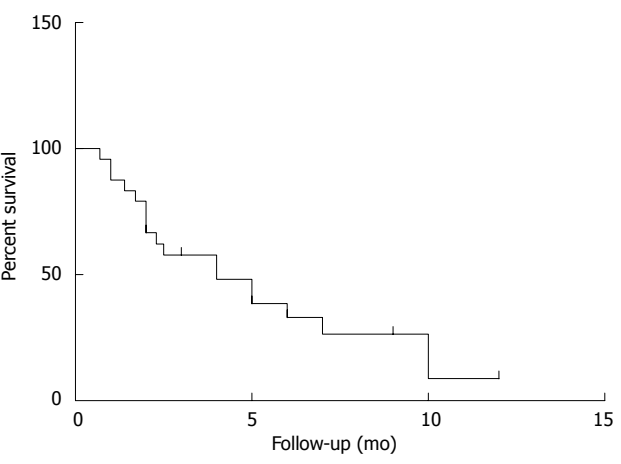


Figure 2 Overall survival after cutaneous metastasis of cholangiocarcinoma (n = 24). The median OSCM of cholangiocarcinoma was only 4.0 mo. OSCM: Overall survival after cutaneous metastasis.

Prognostic factors of overall survival

As shown in Figure 2, the median OSCM of cholangiocarcinoma was only 4.0 mo (n = 24). When cutaneous metastasis occurred, 12/13 patients had concurrent metastasis of other sites, such as the bone, lung, brain, and lymph nodes. In 17 cases, there was no description of concurrent metastasis in other sites.

As shown in Figure 3A and B, male gender and single metastasis were associated with a poorer OSCM (male vs female, 2.4 mo vs 10 mo; hazard ratio (HR) = 0.168; 95% confidence interval (CI): 0.058-0.490; P = 0.005; single metastasis vs multiple metastases: 2.3 mo vs 7 mo; HR = 0.296; 95%CI: 0.104-0.842; P = 0.011).

As shown in Figure 3C and D, age and cutaneous metastatic sites showed no significant relationship with OSCM (≥ 60 years vs < 60 years, 4 mo vs 6 mo: HR = 1.203; 95%CI: 0.448-3.231; P = 0.878; drainage vs distant, 2.15 mo vs 5.5 mo: HR = 1.638; 95%CI: 0.542-4.956; P = 0.223).

DISCUSSION

Cholangiocarcinoma is a rare neoplasm originating

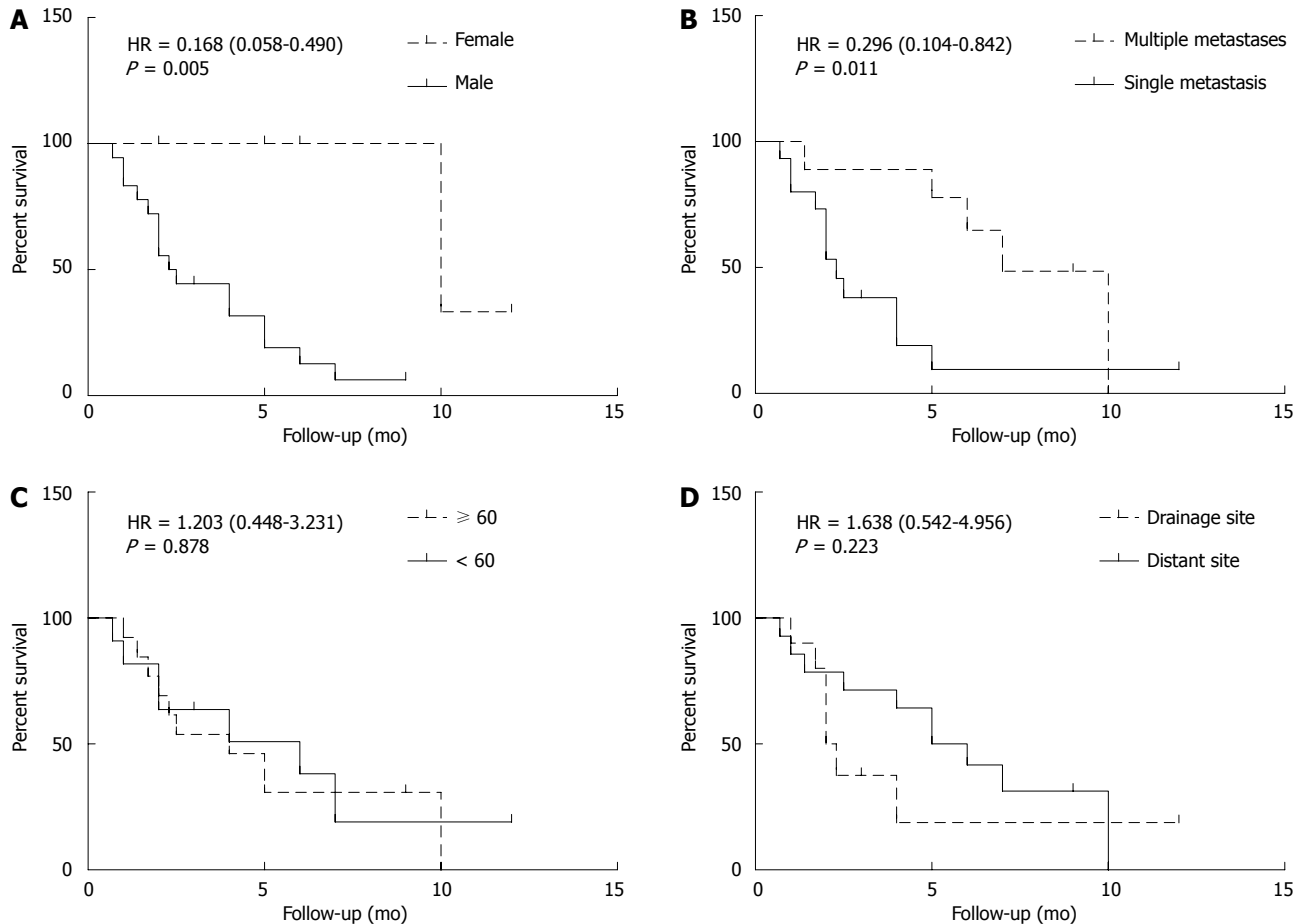


Figure 3 Prognostic factors of overall survival after cutaneous metastasis. A: Male gender was associated with a poorer OSCM (HR = 0.168; 95%CI: 0.058-0.490; $P = 0.005$); B: Single metastasis was associated with a poorer OSCM (HR = 0.296; 95%CI: 0.104-0.842; $P = 0.011$); C: Age showed no significant association with OSCM; D: Cutaneous metastatic site had no significant association with OSCM. HR: Hazard ratio; CI: Confidence interval.

from the epithelial cells of the bile duct, and it accounts for less than 2%^[23] of all cancers. Cholangiocarcinoma is typically defined according to the anatomic site, as intrahepatic, hilar, or extrahepatic cholangiocarcinoma^[24]. Unfortunately, cholangiocarcinoma has a very poor prognosis, with the majority of patients losing the opportunity for radical surgery. Cholangiocarcinoma is prone to metastasize to the lung, liver, peritoneum, and retroperitoneal lymph nodes, while cutaneous metastasis is uncommon^[23]. Currently, cutaneous metastasis has only been described in sporadic case reports or series. No systematic research has been initiated to elucidate the clinicopathological features, prognosis and overall survival related to cutaneous metastasis, and we are the first group to analyze and summarize the characteristics of skin metastasis of cholangiocarcinoma.

Interestingly, in 27.6% (8/29) of cases, skin metastasis was the first sign of cholangiocarcinoma, suggesting that bile duct examination should be performed for cutaneous metastasis of unknown origin. The confirmation of primary malignancy was the prerequisite of rational treatment. In our research, skin metastasis of cholangiocarcinoma

could be further divided into two subtypes, involving the site of percutaneous biliary drainage (PTBD) or distant regions, which have different tumor behavior. The former showed seeding of the tumor along the catheter tract, while the latter was associated with distant dissemination. However, skin metastasis of the drainage site composed half of all the cutaneous metastasis in cholangiocarcinoma, suggesting that more attention should be paid to this complication of PTBD. Hepatocellular carcinoma has also been related to cutaneous metastasis in the biopsy site. When addressing scalp metastasis of unknown origin, we should keep the possibility of bile duct-derived carcinoma in mind, as our data showed that the scalp was the most frequently involved site of distant skin metastasis in cholangiocarcinoma. This hematogenous dissemination likely resulted from the intracranial venous sinuses, which communicated with valveless vertebral venous plexus. Additionally, the abdominal and pelvic venous blood enters into the vertebral venous plexus^[11].

Skin metastasis of cholangiocarcinoma usually indicates a poor prognosis, with a median OSCM of 4 mo. In our analysis, the longest OSCM was 12 mo, while the shortest was only 21 d. In univariate

analysis, female gender showed an OSCM advantage over male gender (10 mo vs 2.4 mo). However, the number of female cases with OSCM data was small (only 6), and more cases should be recruited in the future to confirm this trend. Surprisingly, the group with multiple skin metastases was superior to the group with a single metastasis with respect to OSCM. Among the 18 patients with a single cutaneous metastasis, 12 cases (66.7%) had a lesion at the drainage site. Patients who required PTBD usually had more advanced primary tumors and, thus, were more likely to have a single skin metastasis. As more advanced primary tumors were usually associated with a shorter overall survival, this phenomenon partly accounts for the unexpected observation that patients with a single skin metastasis had a shorter survival than those with multiple metastases.

Skin metastasis of cholangiocarcinoma is rather rare compared with lung cancer or breast cancer. Over a span of nearly 50 years (from 1978 to 2014), only 30 cases could be found in the English language literature. Only published cases with a description of disease course could be included, and the characteristics of unpublished cases may not be representative. Despite the limitation in case numbers, we have helped to expand the understanding of this unique entity. With new reports of such cases in the future, more consensus will be achieved.

In conclusion, the prognosis of cholangiocarcinoma with cutaneous metastasis is dismal. The scalp is the most frequently involved site of distant skin metastasis. Male gender and single metastasis are associated with a relatively poorer OSCM.

COMMENTS

Case characteristics

We investigated the clinical characteristics and prognostic factors of cutaneous metastasis of cholangiocarcinoma by retrospective analysis of 30 cases from 21 published articles from 1978 to 2014.

Clinical diagnosis

Cutaneous metastasis of cholangiocarcinoma.

Differential diagnosis

Cutaneous metastasis of other origins.

Imaging diagnosis

Computed tomography or magnetic resonance imaging of related sites demonstrated the lesions of cutaneous metastasis.

Pathological diagnosis

Pathologic examination showed metastatic carcinoma consistent with cholangiocarcinoma.

Treatment

Patients underwent surgery or radiotherapy to the local cutaneous metastasis or chemotherapy or none of these strategies.

Related reports

To the best of our knowledge, this is the first comprehensive analysis of cutaneous metastasis of cholangiocarcinoma.

Term explanation

The overall survival after cutaneous metastasis, defined as the period from diagnosis of cutaneous metastasis to death or latest follow-up, will help to clarify the value of cutaneous metastasis for predicting survival outcome in

cholangiocarcinoma patients.

Experiences and lessons

The prognosis of cutaneous metastasis of cholangiocarcinoma is very poor, and both male gender and single metastasis are associated with worse overall survival after cutaneous metastasis.

Peer-review

This is a comprehensive, detailed analysis with interesting findings, as it is the first combined analysis of clinical data and survival of many cases of cutaneous metastasis of cholangiocarcinoma, which is an extremely rare manifestation of this disease.

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P- Reviewer: Kawakami H, Mott JL, Rerknimitr R, Tanaka T, Vasilieva LE

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ISSN 1007-9327

