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J Hepatobiliary Pancreat Sci (2012) 19:536–542
DOI 10.1007/s00534-012-0521-y

GUIDELINE

Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

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Published online: 21 June 2012

Abstract
Background IgG4-sclerosing cholangitis (IgG4-SC) patients have an increased level of serum IgG4, dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall, and a good response to steroid therapy. However, it is not easy to distinguish IgG4-SC from primary sclerosing cholangitis, pancreatic cancer, and cholangiocarcinoma on the basis of cholangiographic findings alone because various cholangiographic features of IgG4-SC are similar to those of the above progressive or malignant diseases.
Methods The Research Committee of IgG4-related Diseases and the Research Committee of Intractable Diseases of Liver and Biliary Tract in association with the Ministry of Health, Labor and Welfare, Japan and the Japan Biliary

This article is a secondary publication based on a study first reported in the JBA (Journal of Japan Biliary Association), 2012;26:59–63.

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Association have set up a working group consisting of researchers specializing in IgG4-SC, and established the new clinical diagnostic criteria of IgG4-SC 2012.

Results The diagnosis of IgG4-SC is based on the combination of the following 4 criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentrations, (3) the coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. Furthermore, the effectiveness of steroid therapy is an optional extra diagnostic criterion to confirm accurate diagnosis of IgG4-SC.

Conclusion These diagnostic criteria for IgG4-SC are useful in practice for general physicians and other nonspecialists.

Keywords IgG4 · Sclerosing cholangitis · Primary sclerosing cholangitis · Autoimmune pancreatitis · Cholangiocarcinoma

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients show increased levels of serum IgG4 [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. IgG4-SC is frequently associated with autoimmune pancreatitis, and it shows a good response to steroid therapy [3–7]. Various cholangiographic features of IgG4-SC are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma [8, 9]. Therefore, it is not easy to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone [10, 11], and accurate diagnosis of IgG4-SC not associated with autoimmune pancreatitis is particularly difficult [12].

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Therefore, the Research Committee of IgG4-related Diseases (Chairman, Kazuichi Okazaki) and the Research Committee of Intractable Diseases of Liver and Biliary Tract (Chairman, Hirohito Tsubouchi) in association with the Ministry of Health, Labor, and Welfare of Japan, and the Japan Biliary Association (Chairman, Kazuo Inui) have set up a working group consisting of researchers specializing in IgG4-SC. After several meetings held on 15 October 2010, 1 February 2011, and 2 August 2011, and after the exchange of opinions via e-mail, this working group developed a tentative proposal for the clinical diagnostic criteria of IgG4-SC, including the clinical features of IgG4-SC, in order to avoid the misdiagnosis of PSC and malignant diseases. The open forum was held at the 47th Annual Meeting of the Japan Biliary Association on 17 September 2011, and the official announcement was made on the home page of the Japan Biliary Association, where extensive discussion of the tentative proposal can be found.

Disease concept of IgG4-SC

The working group analyzed the clinical features and conditions of IgG4-SC, resulting in the following disease concept of IgG4-SC.

IgG4-SC is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients show increased levels of serum IgG4 [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. Circular and symmetrical thickening of the bile duct wall is observed not only in the stenotic areas but also in the areas without stenosis that appear normal in the cholangiogram [13]. IgG4-SC is frequently associated with autoimmune pancreatitis [3–7]. IgG4-related dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis are also occasionally observed in IgG4-SC [14–17]. However, some cases of IgG4-SC do not show any other organ involvement [12].

IgG4-SC is more common in elderly men. Obstructive jaundice is frequently observed in IgG4-SC. The clinical and radiological features of IgG4-SC are resolved by steroid therapy, though long-term prognosis of this disease is not clear [4–7].

The differential diagnosis of IgG4-SC from PSC and neoplastic lesions such as pancreatic or biliary cancers is very important. It is also necessary to rule out secondary sclerosing cholangitis caused by diseases with obvious pathogenesis.

The new clinical diagnostic criteria of IgG4-SC 2012

The working group established their final proposal for the new clinical diagnostic criteria of IgG4-SC 2012 (Table 1).

Table 1 Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

Diagnostic items
(1) Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
(2) Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
(3) Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
(4) Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.
Diagnosis
Definite diagnosis
(1) + (3)
(1) + (2) + (4) a, b
(4) a, b, c
(4) a, b, d
Probable diagnosis
(1) + (2) + option
Possible diagnosis
(1) + (2)
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility

The diagnosis of IgG4-SC is based on the combination of the following 4 criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentrations, (3) coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. However, it is not easy to obtain sufficient biliary tract tissue to determine the characteristic histology of IgG4-SC by biopsy [[13], [18]]. Furthermore, the effectiveness of steroid therapy is an optional additional diagnostic criterion to confirm accurate diagnosis of IgG4-SC. The types of typical cholangiographic features are shown schematically [19]. The diseases to be discriminated from IgG4-SC and the necessary examinations for diagnosis are also described so that these diagnostic criteria can be used clinically [20].

Diagnostic imaging findings

Narrowing of the bile duct

Although magnetic resonance cholangiopancreatography provides useful information, the narrowing of the bile duct should be assessed by direct cholangiography such as endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography.

IgG4-SC associated with autoimmune pancreatitis frequently shows a stricture of the lower common bile duct. This stricture might be caused by both the thickening of the bile duct and the effect of inflammation and/or edema of the pancreas [21].

Dilation after the confluent stricture is a characteristic feature of IgG4-SC. The typical cholangiographic findings of PSC, such as a band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like outpouching are not observed in IgG4-SC (Fig. 1) [8].

The characteristic features of IgG4-SC can be classified into 4 types based on the regions of stricture as revealed by cholangiography and differential diagnosis (Fig. 2) [19]. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, and it should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. The modalities useful for differential diagnosis are intraductal ultrasonography (IDUS) [13], endoscopic ultrasound-guided fine needle aspiration [22], and cytology and/or biopsy of the bile duct [13, 14]. Type 2 IgG4-SC, in

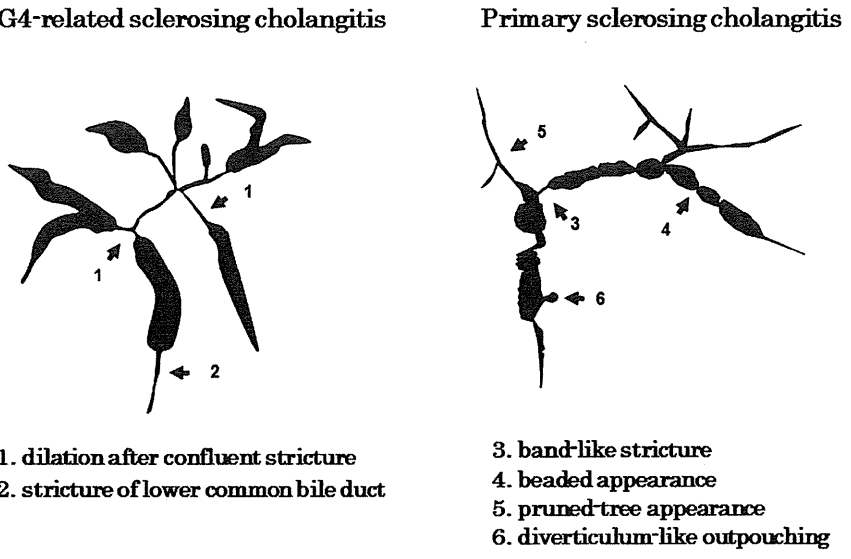

Fig. 1 The schematic comparison of cholangiographic findings between IgG4-related sclerosing cholangitis and primary sclerosing cholangitis. IgG4-related sclerosing cholangitis showing dilation after confluent stricture (>10 mm) and stricture of lower common bile duct. Primary sclerosing cholangitis showing band-like stricture (short stricture 1–2 mm), beaded appearance (short and annular stricture alternating with normal or minimally dilated segments), pruned-tree appearance (diminished arbolization of intrahepatic duct and pruning) and diverticulum-like outpouching (outpouchings resembling diverticula, often protruding between adjacent strictures)

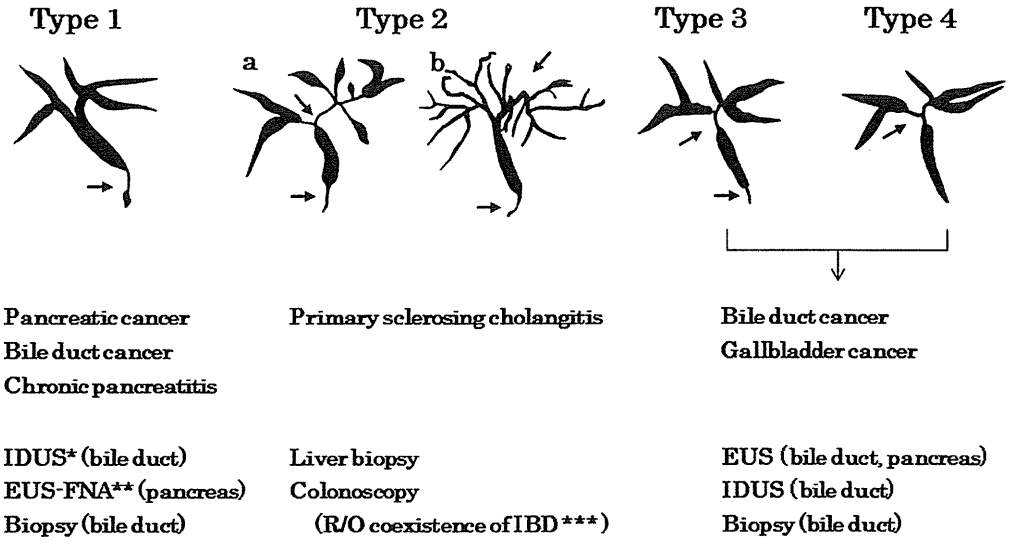

Fig. 2 The cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided into 2 types: extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in type 2a; narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed in type 2b. Stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in type 3; and strictures of the bile duct are detected only in the hilar hepatic lesions in type 4. **IDUS* intraductal ultrasonography, ***EUS-FNA* endoscopic ultrasound-guided fine needle aspiration, ****IBD* inflammatory bowel disease

which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Type 2 is subdivided into 2 further types: type 2a, with narrowing of the intrahepatic bile ducts with prestenotic dilation; and type 2b, with narrowing of the intrahepatic bile ducts without prestenotic dilation and

reduced bile duct branches, which is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of types 3 and 4 need to be discriminated from those of cholangiocarcinoma. The modalities useful for the differential diagnosis of types 3 and 4 are endoscopic ultrasonography (EUS), IDUS [13], and cytology and/or biopsy of the bile duct [13, 14]. Nevertheless, there are some IgG4-SC cases whose cholangiographic findings do not fit into any of the above 4 types.

Thickening of the bile duct

Abdominal ultrasonography (US) [23], abdominal computed tomography [24], abdominal magnetic resonance imaging, EUS, and IDUS show circular and symmetrical thickening of the bile duct wall, smooth outer and inner margins, and a homogenous internal echo [13]. These characteristic features are recognized not only in stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal on cholangiogram.

Hematological examination

Elevated level of serum IgG4 (135 mg/dl or higher, nephelometric method) is one of the diagnostic criteria for IgG4-SC [1]. Elevation of serum IgG4 levels is not necessarily specific to IgG4-SC because it is also observed in atopic dermatitis, pemphigus, asthma, etc.; in particular, elevated levels of serum IgG4 are also observed in some malignant cholangiopancreatic diseases (e.g., pancreatic cancer, cholangiocarcinoma) [25, 26].

Other organ involvement

IgG4-SC is frequently associated with autoimmune pancreatitis. It is particularly difficult to accurately diagnose IgG4-SC in cases not associated with autoimmune pancreatitis. Occasionally, IgG4-SC is associated with other systemic IgG4-related diseases, including IgG4-related symmetrical dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis [14–17]. These associations are helpful in the correct diagnosis of IgG4-SC. Although IgG4-related dacryoadenitis/sialadenitis is basically characterized by symmetrical bilateral swelling, unilateral swelling can be included only if pathological diagnosis is made. Inflammatory bowel disease (IBD) is not usually an associated feature, unlike the frequent association of IBD with PSC [27, 28].

Pathological findings of bile ducts

In IgG4-SC, fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact [29]. However, slight injury and/or neutrophil infiltration are occasionally observed in IgG4-SC with associated secondary cholangitis. PSC should be excluded if inflammation is observed, particularly in the epithelium of the bile duct wall.

Cytological examination is commonly used for the diagnosis of cholangiocarcinoma. Endoscopic transpapillary bile duct biopsy is performed to rule out cholangiocarcinoma; however, it is not easy to obtain sufficient biliary tract tissue to study the characteristic histology of IgG4-SC biopsy specimens (e.g., storiform fibrosis, obliterative phlebitis) [13]. Liver biopsy is sometimes useful to diagnose IgG4-SC cases with intrahepatic bile duct strictures [30–32].

Exclusion of secondary sclerosing cholangitis

It is necessary to rule out the following features of secondary sclerosing cholangitis with obvious pathogenesis, including common bile duct stones, cholangiocarcinoma, trauma, previous operation on the biliary tract, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, and biliary injury caused by intra-arterial chemotherapy.

Effectiveness of steroid therapy

This optional diagnostic criterion should be applied only to the IgG4-SC cases in which the effect of steroid therapy can be evaluated by imaging modalities. Accordingly, clinical conditions or hematological findings cannot be evaluated by this method. It is sometimes difficult to obtain sufficient biopsy specimens from patients suffering from diseases of not only the biliary tract but also of other organs, such as the pancreas, lachrymal gland, salivary gland, and retroperitoneum. However, efforts should be made to collect enough tissue samples for diagnosis and steroid trials should be strictly avoided.

The effectiveness of steroid therapy should be cautiously evaluated because some malignant lesions may occasionally improve after steroid administration [33]. If neoplastic lesions cannot be clinically ruled out after

steroid therapy, it is advisable to perform re-evaluation to rule out malignant cholangiopancreatic diseases.

Conclusion

These IgG4-SC 2012 clinical diagnostic criteria, established by a working group consisting of researchers specializing in IgG4-SC, are thought to be useful practically for general physicians and nonspecialists. In the future, detailed investigation of IgG4-SC cases, improvement in diagnostic modalities, and basic research should be undertaken to evaluate the clinical features and pathogenic mechanism of IgG4-SC.

Appendix: members of the working group for the clinical diagnostic criteria of IgG4-SC

The Research Committee of IgG4-related Diseases in association with the Ministry of Health, Labor, and Welfare of Japan (Chairman, Kazuichi Okazaki): K. Okazaki, K. Inui, S. Kawa, T. Kamisawa, S. Tazuma, K. Uchida, K. Hirano, H. Yoshida, T. Nishino, S.B.H. Ko, N. Mizuno, H. Hamano, A. Kanno, K. Notohara, O. Hasebe, T. Nakazawa, and H. Ohara.

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The Japan Biliary Association (Chairman, Kazuo Inui): K. Inui.

This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan.

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手術手技

術中胆道損傷に対する胆嚢管切開による3管合流部アプローチを用いたCチューブドレナージ術

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はじめに

胆道狭窄は，胆管切開に伴う晩期合併症としていまだに問題となる胆道外科の大きな課題である。このため，とくに良性胆道疾患の治療において胆管切開は可及的に避けるべきである。われわれは胆嚢管切開による3管合流部アプローチを用い胆管切開を回避し，胆管狭窄予防に努めてきた。本法は，術中胆道造影の際の胆嚢管カニュレーション困難例にも応用可能であり，胆管非拡張例においてとくに有用であると考えている。

術中胆道損傷は回避しなければならない術中合併症であるが，高度胆嚢炎症例やMirrizi症候群・confluence stone症例では，3管合流部付近の解剖が不明瞭となっていることも多く，術中胆道損傷のリスクは高い。今回，術中胆道損傷を来した症例に対し，当科で行っている胆嚢管切開による3管合流部アプローチを応用し，RTBDチューブではなく，経胆嚢管的にCチューブを挿入し，胆道損傷を修復，ドレナージする手技を考案し，良好な結果を得たので報告する。

Ⅰ．手術適応

本アプローチ法は，胆管切開を必要とする総胆管結石症，胆嚢管カニュレーション困難例のみならず，術中胆管損傷症例に対して応用が可能な手技である。

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key words
胆道損傷，隔壁様部位，Cチューブドレナージ

Ⅱ．手術手技

1．術前診断，胆道損傷判明

症例は胆石症による急性胆嚢炎で，前日にPTGBD（経皮経肝胆嚢ドレナージ術）が施行されていた。術前のPTGBD造影では，前区域枝の分岐部の肝門部に胆嚢頸部が近接して存在していた（図1a）。同部の剝離の際に前区域枝の側面を損傷し，胆汁漏出を認め，同部を縫合したが，術中胆道造影で胆道損傷が明らかとなった（図1b）。損傷胆管の太さから，直接縫合のみでは狭窄を来すことが危惧された。

2．胆嚢管の縦切開

胆嚢・胆嚢管を周囲から剝離したのちに，胆嚢管の胆嚢側を結紮し，胆管側で胆嚢管を短軸方向に切開して内腔を確認した。同部より胆嚢管の右側壁を縦軸方向に沿って切開をした（図2a）。このとき切開は胆嚢管の頭側～腹側の方向で行う。胆嚢管を総胆管の合流部まで十分に剝離を進める（図2b）。

3．胆嚢管・総胆管の隔壁構造の同定と切開

胆嚢管切開を胆嚢管の右腹側で胆管合流部まで行うと，開放された胆嚢管の奥に，胆嚢管と胆管

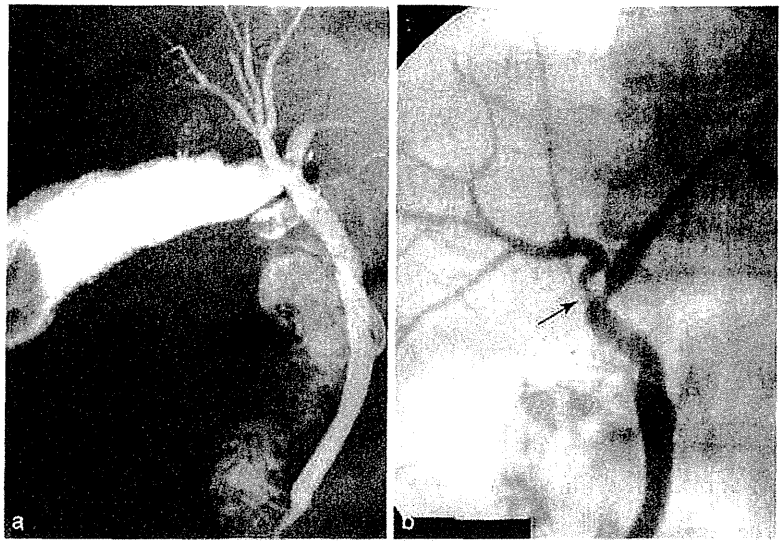

図1　胆道造影

a）術前のPTGBD造影。
b）術中胆道造影（矢印：胆管損傷部位）。

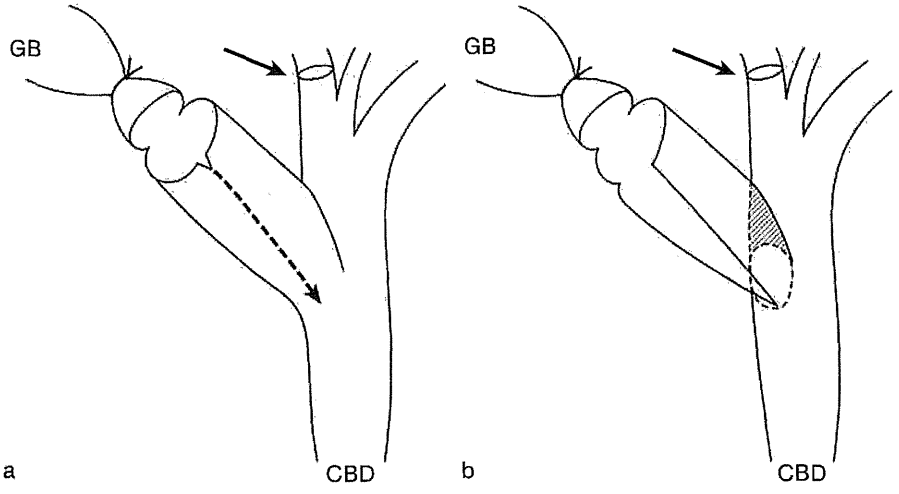

図2　胆嚢管の切開

a）胆嚢管の結紮，横切開，縦切開（矢印：胆管損傷部位）。
b）胆嚢管の縦切開（斜線部：隔壁，矢印：胆管損傷部位）。

の合流部が見える。この部位は先の胆嚢管の露出では直視できない部分であり，胆嚢管と胆管は鋭角をなして合流している。この部位が胆嚢管胆管の隔壁構造となっている。この隔壁構造に対して，縦に切開を入れることによって，胆嚢管と総胆管の角度が鈍角となり，胆嚢管から肝側胆管へのアプローチを行うことが可能となる（図3）。隔壁構造の長さは個人差が大きいため，この際に穿孔を避けるため隔壁構造を切りすぎないように注意が必要である。

4．Cチューブの挿入

この切開部位から膵管チューブ5Fr.を肝側に向かって挿入したが，隔壁構造が切開されているため，肝側へのチューブの挿入は容易である（図4a）。今回の症例では，前区域枝の損傷であったため，損傷部位をチューブが通るように挿入し，術中胆道造影を行い，損傷部位の位置を確認し

た。

5. 胆管損傷部位の修復

チューブをステントとして，内腔を確認し，損傷部位の胆管を5-0バイオシンで数針，端端で粗に結節縫合した。(図4b)。途中でCチューブより生理食塩液でリークテストを行い，大きなリークのないことを確認した。

6. 胆嚢管の縫合・閉鎖

縦に切開した胆嚢管は胆管側から5-0バイオシンで結節縫合し，閉鎖した。この再建した胆嚢管とCチューブを結紮し，固定した（図4b)。これにより，RTBDチューブが挿入できないような細い胆管の損傷時にも修復，対応が可能である。

術後3カ月目に造影し，胆汁瘻，胆管狭窄がないことを確認し，チューブを抜去した。その後の経過は良好である。

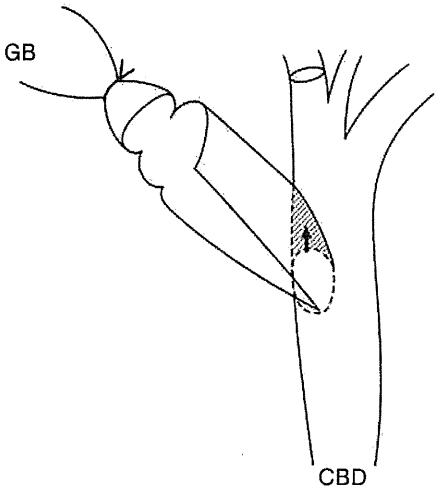

図3　胆嚢管胆管の隔壁構造の切開

胆嚢管胆管の隔壁構造の切開（斜線部：隔壁，矢印：切開部位)。

Ⅲ. 考　察

術中胆道損傷症例では，損傷部位の修復と胆道ドレナージが必要である。総胆管，総肝管レベルでは，術後の狭窄の可能性が少ないため，損傷部位の修復とTチューブドレナージ挿入，Cチューブドレナージ挿入，あるいはRTBDチューブによるドレナージ。ENBDチューブが留置されている症例では，単純閉鎖が行われている。しかし，2次分枝より末梢の胆管損傷では，単純閉鎖では胆管の狭窄を来す可能性があり，RTBDチューブによるドレナージと胆管内腔の確保が行われることが多いが，胆管が細いときにはしばしば困難である。このため，われわれの考

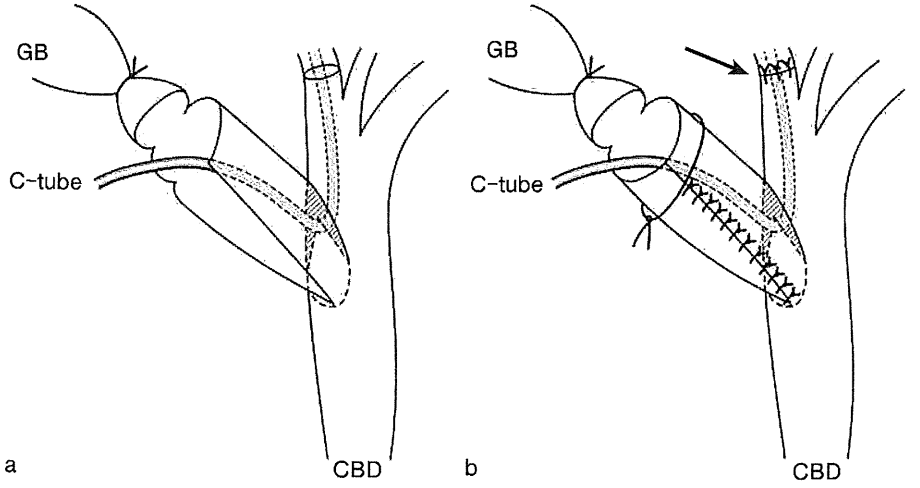

図4　Cチューブドレナージチューブの挿入

a) Cチューブドレナージチューブの挿入（斜線部：隔壁)。
b) 胆管損傷部の修復（矢印)，胆嚢管切開部の縫合閉鎖，Cチューブの結紮固定（斜線部：隔壁)。

案した胆嚢管切開による3管合流部アプローチを応用した隔壁構造の切開によるCチューブドレナージ術は新たなドレナージ法として有用と考える。

本法を考案するに至った背景として，Mirrizi症候群，胆嚢管胆管瘻の形成，低位胆嚢管合流型のバリエーションの存在に注目した。Mirrizi症候群では胆嚢・総胆管瘻を形成することがあり，胆嚢頸部あるいは胆嚢管への結石嵌頓や炎症により胆嚢，総胆管の壁が菲薄化し，さらに圧迫壊死を生じ，内瘻を形成したと考えられている[1]。胆嚢胆管瘻のあるMirrizi症候群では，術前に入れたENBDチューブが有用であり，術後にも利用できたとその有用性が報告されている[2]。

上田らは，胆嚢管のらせん構造が消失した胆嚢管低位合流型において総胆管と胆嚢管の伴走部分の隔壁様構造に注目している。隔壁様部位の長さは，平均36.5 mmで全胆嚢管長の平均56.6％であったと報告している。手術では可能な限り胆嚢管を剝離して胆管との移行部直前と考えられる部位で切離したが，術後の胆道造影で，隔壁様部分は全例で遺残していたことが確認されている[3]。この報告より，総胆管と胆嚢管の間の隔壁部分はほぼ一層の構造であるため両者を剝離することは困難であると考えられる。彼らは，長い年月における走行異常のため伴走胆嚢管に慢性炎症が加わった結果，胆嚢管と胆管の漿膜が2次的に膠原線維成分に置き換わって隔壁様になったものと推察している。この隔壁構造は，剝離を試みると胆道損傷を引き起こし，隔壁様部位の構造を念頭において胆嚢管の切開部位を決定する必要があると結論づけている[3][4]。

胆嚢管胆管の隔壁構造に注目した本法によるドレナージ法は有用であるが，今後の症例の蓄積と長期観察による術後の胆管狭窄などの合併症の検討が必要である。

おわりに

術後胆管狭窄を予防する工夫として総胆管に切り込まない胆嚢管切開による3管合流部へのアプローチは，分枝胆管の胆道損傷の修復に有用である。

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J Gastrointest Surg (2012) 16:1171–1180
DOI 10.1007/s11605-012-1840-7

ORIGINAL ARTICLE

Resection Margin with Anatomic or Nonanatomic Hepatectomy for Liver Metastasis from Colorectal Cancer

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Received: 14 December 2011 / Accepted: 7 February 2012 / Published online: 28 February 2012

Abstract
Background When hepatectomy is used as a primary treatment for liver metastasis from colorectal cancer (CRCLM), the balance between surgical curability and functional preservation of the remnant liver is of great importance.
Methods A total of 108 patients who underwent initial hepatectomy for CRCLM were retrospectively analyzed with respect to tumor extent, operative method, and prognosis, including recurrence.
Results The 1-, 2-, 3-, and 5-year overall survival rates (OS) for all patients were 90.5%, 77.8%, 63.2%, and 51.6%, respectively. Multivariate analysis indicated serum carbohydrate antigen 19-9 (CA 19-9) level after hepatectomy (<36 or ≥36 mAU/mL) and presence of recurrence as independent prognostic factors of OS (P=0.0458 and 0.0249, respectively), and tumor depth of colorectal cancer (<se (a2) vs. ≥se (a2)) and serum CA 19-9 level after hepatectomy as the significant factors affecting disease-free survival (DFS) (P=0.0025 and 0.00138, respectively). Neither resection margin nor type of hepatectomy (anatomic or nonanatomic) for CRCLM was a significant prognostic factor for OS or DFS or CRCLM recurrence, including intrahepatic recurrence.
Conclusions In CRCLM, we believe that nonanatomic hepatectomy with narrow margin is indicated, and optimal treatment would include functional preservation of as much of the remnant liver as possible.

Keywords Liver metastasis from colorectal cancer · Resection margin width · Type of hepatectomy · Intrahepatic recurrence

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Abbreviations

CRC	Colorectal cancer
CRCLM	Liver metastasis from colorectal cancer
CEA	Carcinoembryonic antigen
CA 19-9	Carbohydrate antigen 19-9
HCC	Hepatocellular carcinoma
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ICG-R15	Indocyanine green retention rate at 15 min
HBV	Hepatitis B virus
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
CT	Computed tomography
MRI	Magnetic resonance imaging

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal malignancy worldwide. Many advanced cases with hepatic or peritoneal metastases are encountered despite recent improvement in the diagnosis and management of CRC, which has enabled early detection followed by early treatment. For further improvement of the prognosis of CRC, it is particularly important to prolong survival in advanced cases with distant metastasis.

The liver is usually the first site of spread in CRC, and approximately 25% of patients present with liver metastases at the time of initial diagnosis of CRC. A further 40–50% of patients develop liver metastasis from colorectal cancer (CRCLM) within 3 years of resection of the primary tumor. Hepatectomy for CRCLM is recommended as the most effective therapy.[1–10] However, to date, 57% to 78% of patients develop a recurrence of the disease after curative resection of CRCLM, and intrahepatic recurrence occurs in approximately 50%.[4,5,8,11] The curative rate by initial hepatectomy is only 20% to 30% of cases.[4,5,10] Moreover, the overall 5-year survival rates are in the range of 20% to 58%, and the median survival times are 24–46 months.[5–7,9,10,12–14] The prognosis is not sufficiently favorable and needs to be improved. Several clinicopathologic factors have been associated with recurrence and prognostic determinants after initial hepatectomy. Among these factors, the type of liver resection and resection margin both depend upon surgical technique.

Anatomic hepatectomy refers to the en bloc removal of a hepatic segment supplied by a major branch of the portal vein and hepatic artery around the main tumor because intrahepatic metastasis via vascular invasion of CRC is reported as a key factor influencing prognosis.[15] In contrast, nonanatomic hepatectomy allows for the preservation of maximal hepatic parenchyma.[16,17] Indeed, in patients with hepatocellular carcinoma (HCC), anatomic resection was reported to offer a survival benefit over nonanatomic resection.[18–20] However, the data are limited and less consistent for CRCLM.

In addition, some authors have shown that a resection margin of more than 1 cm was an adverse prognostic factor for long-term survival, but others found no correlation between the width of the resection margin and long-term prognosis.[21–26] From these conflicting studies, prognostic significance of the optimal type of resection and margin width remain unclear and controversial despite extensive studies.

Given the lack of resolution on this issue, we investigated our experience with hepatectomy for CRCLM. The purpose of this study was to determine current trends of hepatectomy as a primary treatment for CRCLM and to retrospectively investigate whether the method of hepatectomy influenced patient survival and the pattern of tumor recurrence at a single institution.

Materials and Methods

Patient Population and Selection

From August 18, 1995 to December 16, 2009, a total of 108 patients underwent initial hepatectomy for CRCLM at Osaka Medical College Hospital in Takatsuki City, Japan. Curative resection was defined as complete removal of the tumor with a clear microscopic margin. One patient died after surgery; as such, in-hospital mortality rate was 0.9%. No patient was lost to follow-up during the study period. Two patients underwent noncurative operations, and the remaining 106 patients with hepatectomy with curative intent were retrospectively reviewed.

Hepatectomy

In our patients, hepatectomy for CRCLM is performed when the following three conditions are met: (1) the primary CRC was curatively resected, (2) metastasis is located only in the liver, and (3) there is no limitation regarding the number or size of CRCLM as far as hepatic functional reserve is warranted after liver resection. All procedures were performed by four experienced hepatobiliary surgeons (YI, FH, MH, and KU) during the study period. All patients received potentially curative hepatectomy with removal of gross tumor with negative macroscopic margin. With respect to hepatic hilar lymph nodes, we do not routinely perform lymph node dissection, since node-positive cases in this region were strongly associated with extremely poor survival in our previous experience (data not shown).

Synchronous (as opposed to metachronous) CRCLM was defined as simultaneous presentation of liver metastasis at the time of CRC operation, and was detected in 20 patients (18.9%). Patients received either synchronous or metachronous hepatectomy, mainly based on each patient's condition and whether or not emergency surgery was needed.

Operative procedures were classified according to conventional terminology derived from eight segments of the liver as suggested by Couinaud.[27] Anatomic resection was defined as resection of the neoplasm together with the portal vein related to the neoplasm and the corresponding hepatic territory. This includes bisegmentectomy, (extended) right hepatectomy, (extended) left hepatectomy, or a combination of these. Nonanatomic resection was defined as resection of a lesion without regard to segmental, sectional, or lobar anatomy. Extended monosegmentectomy or sectionectomy, defined as additional partial resection contiguous to a

segment or a section resected anatomically, were classified as anatomic resections.

Patients were also classified by the width of the resection margin into three groups: group I, ≤1 mm; group II, 2–9 mm; and group III, ≥10 mm. Width of resection margin was assessed by the pathologists and defined as the shortest microscopic distance from the edge of tumor to the line of transection. In case of multiple liver metastases, the closest margin was recorded as the final margin. These three groups, along with type of resection (anatomic or nonanatomic), were compared for postoperative recurrence rates and the site of recurrence, including intrahepatic recurrence.

We principally performed partial or nonanatomic hepatectomy, whereas systemic or anatomic hepatectomy was used preferentially in cases in which this procedure had advantages in terms of operative time, blood loss, safety, and/or invasiveness. Hepatectomy was performed following the standard technique as previously reported.[28] An ultrasonic dissector (SonoSurg system; Olympus Inc., Tokyo, Japan) was used for parenchymal transection, and small vessels were ligated or coagulated using a soft-coagulation system or bipolar electrocautery. During the resection procedure, the surgical margin was carefully confirmed using intraoperative ultrasonography in order to obtain a surgical margin of 5–10 mm when possible.

Preoperative Factors

Data examined included preoperative factors, surgical factors, and pathological factors. Preoperative factors investigated were age, gender, viral infection status, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, platelet count, albumin, total bilirubin, prothrombin time, Child–Pugh classification,[29] degree of liver damage,[30] indocyanine green retention rate at 15 min (ICG-R15), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9). CEA and CA19-9 were defined as positive when values were >5.0 ng/mL and 36 mAU/mL, respectively, according to the cut-off levels at our institution. Patients testing positive for hepatitis B virus surface antigen (HBsAg) were considered positive for hepatitis B virus (HBV) infection, and those testing positive for hepatitis C virus (HCV) antibody were considered positive for HCV infection. Preoperative tumor numbers were determined by preoperative imaging including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography, with images analyzed by two specialist radiologists.

Surgical and Pathological Factors

Surgical factors comprised surgical duration, intraoperative blood loss, blood transfusion requirement, and operative method. Pathological factors evaluated included size of the largest tumor, number of tumors, tumor cell differentiation (well differentiated vs. others), serosal invasion, vascular invasion (macroscopic and microscopic portal and/or hepatic vein invasion), surgical margin status, and background liver histology. Two specialists in pathology reviewed specimens for confirmation of the pathological diagnosis. In this study, surgical margin status was assessed by the pathologists and defined as the distance of the lesion(s) closest to the cut surface of the liver and microscopically classified into three groups: a surgical margin of ≤1, 2–9, and ≥10 mm.

Patient Follow-Up

Patients were closely followed until October 31, 2011. Patients were examined for CRCLM recurrence by ultrasonography and contrast-enhanced CT every 3–6 months, and blood tests including CEA and CA 19-9 were followed up at 1–2 months after discharge and every 2–3 months thereafter. When recurrence was suspected, contrast-enhanced CT and/or MRI were performed to assess the occurrence of new lesions in the remnant liver, while systemic recurrence was examined by fluorodeoxyglucose-positron emission tomography (FDG-PET) or gallium scintigraphy. Chest and pelvic CT was also performed generally every 6 months for identification of local and pulmonary metastasis or recurrence. Recurrence was defined as intra- and/or extrahepatic recurrence of CRC and was diagnosed when at least two imaging studies confirm the new lesions showing typical features of CRC/CRCLM, compared with previous images. As the principles underlying selection criteria, disease-free survival (DFS) was defined as the time interval between hepatectomy and the first occurrence of recurrent lesion(s).

Classification of Intrahepatic Recurrences

Intrahepatic recurrences were classified according to the correlation between the location of the primary tumor and sites of recurrence at the time of initial recurrence. Five classifications were used: (1) marginal recurrence, intrahepatic recurrence only in the vicinity of the cut surface; (2) same segment, single recurrence only in the same segment as the primary tumor; (3) adjacent segment, single recurrence only in the adjacent segment in the ipsilateral lobe; (4) distal segment, single recurrence only in the contralateral lobe; and (5) multiple segments, recurrences were multiple and located in either both liver lobes or the contralateral lobe.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. Continuous variables were compared using

Student's *t* test. Categorical variables were compared by the likelihood ratio test or Fisher exact test, as appropriate. Factors that were found to be significant by univariate analysis were also subjected to multivariate logistic regression analysis to determine adjusted odds ratios. Actuarial overall survival (OS) rates and DFS rates were calculated by the Kaplan–Meier method to analyze differences. Univariate analyses were performed using the log-rank test. Multivariate analyses were performed by Cox proportional hazards regression. Values of $P<0.05$ were considered statistically significant.

Results

Characteristics of Colorectal Cancer

The primary tumor was in the colon in 74 cases (70.0%) and in the rectum in 32 cases (30.0%). Among the patients with colonic tumors, tumors were located in the ascending colon in 16 (21.6%), transverse colon in 11 (14.9%), and descending colon in 47 (63.5%). Sixty percent of the primary tumors had involved regional lymph nodes, and 36.9% and 60.2% had well or moderately differentiated histology, respectively. The histological depth of invasion in the colorectal wall is denoted as follows: se, serosa; ss, subserosa; a1, subadventitia; and a2, adventitia. In 73 patients (68.9%), the depth of the primary tumors was within the subserosal layer (<se (a2)) of the colorectal wall.

Characteristics of Liver Metastasis from Colorectal Cancer

Liver metastases were diagnosed synchronously in 20 patients (18.9%). Sixty patients (56.6%) had a solitary liver metastasis, whereas 46 patients (43.4%) had multiple liver metastases (mean number, 3.5±2.3; range, 2–13). In 60 patients with solitary liver metastasis, the tumor location was unilobar (right in 29, left in 31), and 22 patients (20.3%) had bilobar disease resected. The mean and median diameter of the largest liver metastases was 3.4±1.9 cm (range, 0.3–10 cm) and 3.0 cm, respectively. Portal vein invasion was observed in eight patients (7.5%), and hepatic vein invasion was in four patients (3.8%).

Analyzed Prognostic Factors

The 1-, 2-, 3-, and 5-year OS rates for all patients were 90.5%, 77.8%, 63.2%, and 51.6%, respectively (Fig. 1a). Univariate analysis showed that significant prognostic factors were tumor depth of CRC (<se (a2) vs. >se (a2); $P<0.0001$), the presence of lymph node metastasis ($P=0.0341$), CEA after liver resection (<5 or >5 ng/mL; $P=0.0336$), CA 19-9 after hepatectomy (<36 or >36 mAU/mL; $P=0.0458$), the presence of recurrence ($P<0.0001$), intrahepatic recurrence ($P=0.0026$), and chemotherapy before hepatectomy ($P=0.0291$; Table 1). Multivariate analysis, which was performed for prognostic factors found to be significant by univariate analysis, identified CA 19-9 after hepatectomy (<36 or ≥36 mAU/mL; $P=0.0458$) and presence of recurrence ($P=0.0249$) as significant prognostic factors (Table 1).

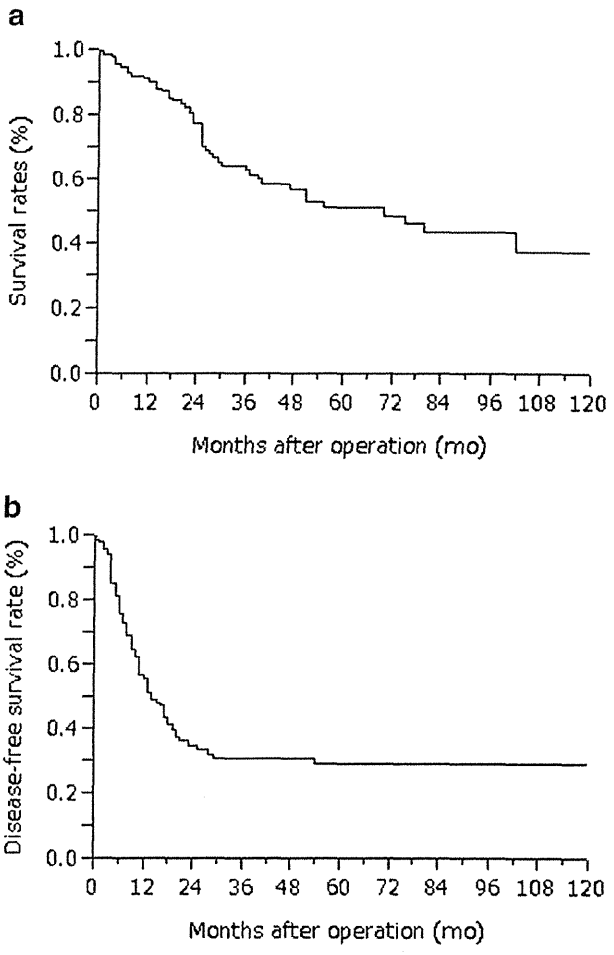

Fig. 1 **a** Overall survival (OS) curves: 1 year, 90.5%; 3 years, 63.2%; 5 years, 51.6%. **b** Disease-free survival (DFS) curves: 1 year, 56.2%; 3 years, 31.3%; 5 years, 29.4%

Analyzed Disease-Free Survival Factors

The 1-, 2-, 3-, and 5-year DFS rates for all patients were 56.2%, 34.8%, 31.3%, and 29.4%, respectively (Fig. 1b), and are shown in Table 2. According to univariate analysis of the factors listed in Table 2, tumor depth of CRC (<se (a2) vs. ≥se (a2); $P=0.0012$), CEA before hepatectomy (<5 or ≥5 ng/mL; $P=0.0246$), CEA after hepatectomy (<5 or ≥5 ng/mL; $P=0.0166$), CA 19-9 after hepatectomy (<36 or ≥36 mAU/mL; $P=0.0462$), and the location of CRCLM (unilobar vs. bilobar; $P=0.0397$) were found to

Table 1 Univariate and multivariate analysis of clinicopathological factors for prognosis in 106 patients undergoing curative resection

Variables	Categorization	*P* value	
		Univariate	Multivariate
Depth of CRC	<se (a1), ≥se (a2)	<0.0001*	0.2005
Lymph node metastasis	Present, absent	0.0341*	0.9118
CEA after hepatectomy (ng/mL)	<5, ≥5	0.0336*	0.5552
CA 19-9 after hepatectomy (mAU/mL)	<36, ≥36	0.0458*	0.0458*
Type of hepatectomy	Anatomic, non-anatomic	0.0514	–
Surgical margin of CRCLM (mm)	≤1, >1	0.0738	–
Surgical margin of CRCLM (mm)	≤1, 2–9, ≥10	0.2010	
Tumor exposure	Present, absent	0.2406	–
Recurrence	Present, absent	<0.0001*	0.0249*
Intrahepatic recurrence	Present, absent	0.0026*	0.1301
Chemotherapy before hepatectomy	Present, absent	0.0291*	0.0684

CRC colorectal cancer, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CRCLM* liver metastasis from colorectal cancer

* Statistically significant

be significant factors for DFS rates. Multivariate analysis indicated tumor depth of CRC (<se (a2) vs. ≥se (a2); $P=0.0020$) and CA 19-9 after hepatectomy (<36 or ≥36 mAU/mL; $P=0.0138$) as the significant prognostic factors (Table 2).

Risk Factors for Intrahepatic Recurrences after Hepatectomy

Risk factors for intrahepatic recurrence were analyzed. Univariate analysis showed that CEA before hepatectomy was the only significant risk factor ($P=0.0074$), and neither type of hepatectomy nor resection margin width was significant for intrahepatic recurrence in the current series ($P=0.6676$ and 0.5524, respectively). Moreover, there was no significant correlation between portal or hepatic vein invasion and intrahepatic recurrence rate ($P=0.2837$ and 1.0000, respectively).

We performed a subgroup analysis of 32 patients with anatomic resection with respect to intrahepatic recurrence. Univariate and multivariate analyses in anatomic resection indicated CEA after hepatectomy ($P=0.0083$). Seventy-four patients with nonanatomic resection were also analyzed, and univariate and multivariate analyses identified CEA before hepatectomy as the only significant risk factor ($P=0.0291$).

Recurrence Rate and Pattern of Tumor Recurrence

Up to October 2011, recurrences occurred in 72 of 105 patients (68.6%), and intrahepatic recurrence was found in 45 of 72 patients (62.5%). Forty-two of 45 patients (93.3%) experienced intrahepatic recurrence within 24 months after resection. The frequencies of intrahepatic recurrence were as follows: marginal, 8.9%; same segment, 8.9%; adjacent segment, 13.3%; distal segment, 13.3%; and multiple segments, 55.6%. The frequency of intrahepatic recurrence in multiple segments was high, and most of these recurrences were distant from the resection margin. In addition, most of the multiple segmental recurrences occurred in both lobes of the remnant liver.

Table 2 Univariate and multivariate analysis of clinicopathological factors for disease-free survival (DFS) rates in 106 patients undergoing curative resection

Variables	Categorization	*P* value	
		Univariate	Multivariate
Depth of CRC	<se (a1), ≥se (a2)	0.0012*	0.0025*
CEA before hepatectomy (ng/mL)	<5, ≥5	0.0264*	0.1727
CEA after hepatectomy (ng/mL)	<5, ≥5	0.0166*	0.4971
CA 19-9 after hepatectomy (mAU/mL)	<36, ≥36	0.00462*	0.0138*
Location of CRCLM	Unilobar, bilobar	0.0397*	0.1090
Type of hepatectomy	Anatomic, non-anatomic	0.2372	–
Surgical margin of CRCLM (mm)	≤1, >1	0.1683	–
Surgical margin of CRCLM (mm)	≤1, 2–9, ≥10	0.1192	
Tumor exposure	Present, absent	0.4096	–

CRC colorectal cancer, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CRCLM* liver metastasis from colorectal cancer

* Statistically significant

Effects of the Type of Hepatectomy

With regard to the type of hepatectomy, 32 patients (30.2%) underwent an anatomic hepatectomy, and 74 patients (69.8%) underwent a nonanatomic hepatectomy. Baseline characteristics were compared by resection type. Twelve patients (37.5%) had multiple metastases, which were microscopically diagnosed from resected specimens, in 32 patients with the anatomical resection, and 34 patients (46.0%) had in 74 with the nonanatomic resection. There were no significant differences between the two groups in terms of resection type (P=0.5230). The mean number of liver metastases was 1.8±1.4 (range, 1–7) in the anatomic resection group and 2.2±2.2 (range, 1–13) in the nonanatomic resection group (P=0.2687). The distribution of liver metastases was also similar in the two groups (P=0.5100). However, in the anatomic resection group, there were significantly more larger tumors (4.1 vs. 3.1 cm, P=0.0074). The number of larger tumors was the only significant difference between the two groups.

With regard to clinical outcome, no differences in OS and DFS rates between these groups were noted (P=0.0514 and P=0.2372, respectively; Fig. 2). Moreover, there were no significant differences between the two groups in terms of type of recurrence and site of intrahepatic recurrence (Table 3).

Effects of Resection Margin Width on Postoperative Intrahepatic Recurrence

Among 104 patients with macroscopically complete resection of CRCLM, mean resection margin width was 9.4± 7.4 mm (range, 0–36 mm). All patients were classified by the width of the resection margin into three groups. Thirteen patients (12.5%) were in group I (≤1 mm margin), and 43 patients (41.3%) were in group II (2–9 mm margin), and 48 patients (46.2%) were in group III (≥10 mm margin). There were no significant differences in any of the host, tumor, or surgical factors among these groups (data not shown). The 1-, 3-, and 5-year OS rates were 84.6%, 36.9%, and 36.9%, respectively, in group I; 90.7%, 65.2%, and 57.7%, respectively, in group II; and 89.4%, 67.8%, and 48.2%, respectively, in group III (P=0.2010). The 1-, 3-, and 5-year DFS rates were 46.2%, 15.4%, and 15.4%, respectively, in group I; 65.1%, 41.3%, and 41.3%, respectively, in group II; and 51.1%, 25.5%, and 20.4%, respectively, in group III (P= 0.1192, Fig. 3). No differences in OS and DFS rates in terms of resection margin width, and no significant differences between the three groups in terms of type of recurrence and site of intrahepatic recurrence were similar to the type of hepatectomy (Table 4). Moreover, there were no significant differences in OS and DFS rates between the resection margin ≤1 and >1 mm (P=0.0738 and 0.1683, Tables 1 and 2), and if tumors were exposed on the cut surface of the liver during hepatic parenchymal resection, the OS and DFS rates of those patients were not significantly different from the other

Table 3 Pattern of intrahepatic recurrence according to the extent of hepatectomy

Site of intrahepatic recurrence	Anatomic group (n=32)	Non-anatomic group (n=74)	Total (n=106)	P value
Marginal	3 (9.4%)	1 (1.4%)	4 (3.8%)	0.1310
Same segment	0 (0%)	4 (5.4%)	4 (3.8%)	
Adjacent segment	2 (6.3%)	4 (5.4%)	6 (5.7%)	
Distal segment	1 (3.1%)	5 (6.8%)	6 (5.7%)	
Multi-segmental	6 (18.8%)	19 (25.7%)	25 (23.6%)	
Total	12 (37.5%)	33 (44.6%)	45 (42.5%)	

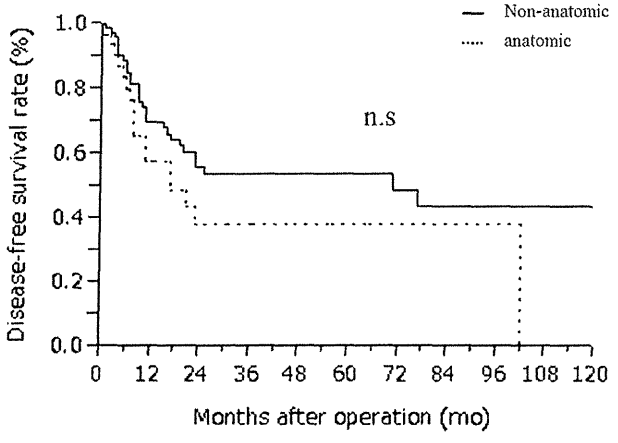

Fig. 2 DFS stratified by the type of hepatectomy. Median DFS rate was 11.0 months in the anatomic resection group and 16.5 months in the nonanatomic resection group. The 5-year DFS rate was 25.4% and 31.3%, respectively (P=0.2372)

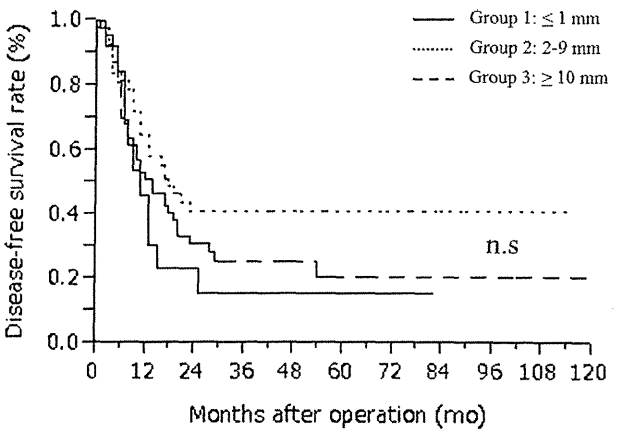

Fig. 3 Kaplan–Meier DFS estimates based on hepatectomy margin status. Median DFS rates were 11.0, 18, and 14 months in patients with resection margins of ≤1, 2–9, and ≥10 mm, respectively (P=0.1192)

Table 4 Pattern of intrahepatic recurrence according to the resection margin of hepatectomy

Site of intrahepatic recurrence	Resection margin, ≤1 mm (n=13)	Resection margin, 2–9 mm (n=43)	Resection margin, ≥10 mm (n=48)	Total (n=104)	P value
Marginal	2 (15.4%)	1 (2.3%)	0	3 (2.9%)	0.1378
Same segment	0	2 (4.7%)	2 (4.2%)	4 (3.8%)	
Adjacent segment	0	2 (4.7%)	4 (8.3%)	6 (5.8%)	
Distal segment	0	2 (4.7%)	4 (8.3%)	6 (5.8%)	
Multiple segments	5 (38.5%)	11 (25.6%)	10 (20.8%)	26 (25.0%)	
Total	7 (53.8%)	18 (41.9%)	20 (41.7%)	45 (43.3%)	

patients without tumor exposure (P=0.2406 and 0.1683, respectively).

Repeat Therapies for Intrahepatic Recurrence

In 72 patients with recurrence, intrahepatic recurrence was evident in 45 of 72 patients (62.5%), and 20 patients (27.8%) had recurrences in the lung. Among the 45 patients with intrahepatic recurrence, 26 patients (57.8%) underwent a second hepatectomy, as well as combinational chemotherapy. Treatment for intrahepatic recurrence in the other patients was systemic chemotherapy in 13 (28.9%). The other six patients (13.3%) were treated with best supportive care. The differences in survival rates between patients underwent various therapies for CRCLM recurrences, and those without the therapy were significant (P<0.0001). For the various therapies for CRCLM recurrences, there were significant differences between repeat hepatectomy or systemic chemotherapy and best supportive care (P<0.0001; Table 5).

Discussion

Hepatic resection has been recognized as a gold standard treatment for CRCLM, and the surgical techniques for hepatic resection have recently improved. However, the optimal resection method for cure has yet to be established, and long-term prognosis after curative resection is still unsatisfactory because of the high incidence of recurrence. Several studies[1,5,8,11] have reported that the cumulative 5-year recurrence rate was 57% to 78%, and the most common site of recurrence was the remnant liver.

Table 5 Univariate analysis of treatment type for prognosis in 45 patients with intrahepatic recurrence

Treatment	Number	3-year survival rate (%)	Median survival (months)	P value
Repeat hepatectomy	26	66.6	38	<0.0001*
Systemic chemotherapy	13	13.0	25	
No therapy	6	0.0	6	

* Statistically significant

Makuuchi et al.[31] introduced the concept of anatomic resection by systematic removal of a hepatic segment confined by the tumor-bearing portal unit around the main tumor because intrahepatic metastasis via vascular invasion of HCC is a key factor influencing prognosis. On the other hand, nonanatomic resection has been recommended to maximally preserve nontumorous liver parenchyma. Among the advantages of preserving as much liver parenchyma as possible is reduction of the risk of postoperative hepatic failure.[32–34] With respect to the resection margin, using a wide resection margin to ensure histological clearance is a general principle of surgical oncology, and hepatectomy with a wide resection margin theoretically gives a higher potential for cure. However, preserving nontumorous liver parenchyma in CRCLM patients is also an important consideration, since regeneration of the liver after hepatectomy is generally limited, especially in a liver with pathological changes, such as steatosis and sinusoidal congestion induced by preoperative chemotherapy.[35,36] Therefore, the balance between surgical curability and preservation of liver function has been discussed for many years, although the optimal liver resection margin and type of hepatectomy (anatomic or nonanatomic) remain controversial.

In our study, multivariate analysis following univariate analysis indicated that the independent and significant prognostic factors were CA 19-9 after hepatectomy (<36 or >36 mAU/mL) and the presence of recurrence. The significant factors for DFS were tumor depth of CRC and CA 19-9 after hepatectomy (<36 or >36 mAU/mL). With respect to surgical techniques, neither type of hepatectomy (anatomic or nonanatomic) nor resection margin width represented significant prognostic or risk factors.

One potential question is whether it is necessary to perform anatomic hepatectomy for CRCLM patients. In patients with HCC, numerous studies[18–20] have revealed that anatomic resection was a significantly favorable factor for OS and DFS. This is partly because intrahepatic metastases via Glissonian pedicle were more common in these patients. In the patients with CRCLM, anatomic resection