Management Strategies in Resection for Hilar Cholangiocarcinoma

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Between 1960 and 1990, resection was performed in 23 of 122 patients who underwent surgical treatment for hilar cholangiocarcinoma. Local excision of the lesion alone was performed in 10 cases (43%). Hepatic resection for tumor extending to the secondary bile ducts or hepatic parenchyma was performed in 13 cases (57%): extended right hepatectomy (3), right hepatectomy (1), extended left hepatectomy (6), left hepatectomy (2), and left lobectectomy (1). In three other cases, resection by total hepatectomy and liver transplantation was performed, but these were not included in the analysis of results for resection. Significant operative complications occurred in only two cases (8.7%), and the operative mortality rate was zero. In four cases, complete excision of the tumor could not be achieved macroscopically (macroscopic curative resection rate 19/122; 15.6%). In nine cases, the margins of the resected specimens were free from tumor on histologic examination (microscopic curative resection rate, 9/122; 7.4%). In 10 cases, the resection margins were found to contain tumor on histologic examination. The overall survival rate was 87% at 1 year, 63% at 2 years, and 25% at 3 years (median survival, 24 months). The survival and freedom from recurrence rates for patients with free resection margins was superior to that for patients with involved resection margins or residual macroscopic disease. A potentially curative resection, with histologically negative margins and no recurrence to date, was achieved in seven patients using the following procedures: local excision for two type I lesions; left hepatectomy plus excision of segment 1 for two type IIIb lesions and one type IV lesion; right hepatectomy and right hepatectomy plus excision of segment 1 for two type IIIa lesions. These results indicate that improved survival in hilar cholangiocarcinoma can be achieved by resection, with minimal morbidity and zero mortality rates, if histologically free resection margins are obtained. To achieve this, we recommend the following procedures for each type of lesion, based on our experience and on anatomic considerations: local excision for type I; local excision plus resection of segment 1 for type II; local excision, resection of segment 1, and right or left hepatectomy for types IIIa and b; hepatectomy plus liver transplantation for type IV.

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IT IS NOW more than 25 years since the first reports of surgery for proximal cholangiocarcinoma involving the bile duct confluence, yet we still are confronted by many of the same questions and controversies regarding the management of this lesion.[1-10] Despite the fact that the lesion is usually slow growing, and does not have a high propensity for metastasis, the diagnosis is usually not made until the bile duct is occluded and the patient is jaundiced.[9,11] Even though the lesion may remain small, its location and close proximity to important structures in the hilum of the liver makes curative excision technically difficult and often impossible.[6,7,9,10] Thus, excision is associated with high reported operative morbidity and mortality rates, particularly when liver resection is also performed.[6,10] In addition, the results of excision, in terms of improvement of long-term survival, have been disappointing in most studies.[3,7,8,10] For these reasons, many recent reports recommend a palliative approach to management, using either surgical bypass or, more recently, percutaneous or endoscopic stent insertion, with or without radiotherapy, to achieve biliary decompression and alleviation of symptoms.[3,12-16]

There are reports, however, of long-term survival after excision, and several studies have suggested that, in a small but significant percentage of patients, improved survival after excision can be obtained.[4-10] In particular, the studies by Launois et al.,[4] Evander et al.,[5] Blumgart et al.,[6] and Reding et al.[17] have concluded that, in terms of length and quality of survival, excision offers the best form of treatment. Most of the controversy concerning excision to achieve a "cure" surrounds the ability of a local resection to completely remove all tumor tissue and thus significantly alter the natural history of the disease.[3] This is thought to be related principally to the tendency of the tumor to grow into the perineural tissue and thus spread for a considerable distance along the bile duct wall.[11,18] Histologic examination of resected specimens has demonstrated, in some studies, a positive correlation between

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Accepted for publication July 18, 1991.

absence of residual tumor in the resection margins and long-term survival.[7,10]

This has encouraged some authors to recommend a radical approach, including extensive liver resection and in some cases hepatectomy and transplantation.[8,10,19] Others have maintained that this indicates that the disease may be multifocal and that the addition of hepatic resection will not necessarily ensure that the resection margins are free from tumor.[3] Moreover, if hepatic resection is associated with significant operative morbidity and mortality rates, it may not produce any significant overall benefit.[3,10] Thus, in view of the diversity of opinion regarding resection to achieve a cure, this review was undertaken in an attempt to determine if resection has any beneficial effect in terms of alteration of the natural history of the disease, and also to allow us to develop guidelines for a more formalized approach for each type of lesion.

Patients and Methods

Patients

This study is based on 136 consecutive patients with hilar cholangiocarcinoma, treated at Hôpital Paul Brousse, Paris, between January 1960 and December 1990. Patients were assessed for surgical treatment using preoperative ultrasound, computed tomographic (CT) scan, celiac and mesenteric angiography, and assessment of general medical condition. One hundred twenty-two patients were considered suitable for surgical treatment.

In most cases, resection was only performed if it was considered as potentially curative, although in two cases, one with necrosis of the left hepatic lobe and one with a large tumor, excision was performed to obtain the most effective palliation. The potential for curative resection was assessed by intraoperative ultrasonography, intraoperative transhepatic cholangiography, and frozen section histologic examination. The disease was considered incurable if there was lymph node involvement outside the hepatic pedicle, intraperitoneal tumor spread, or distant metastases. Involvement of the main trunk of the portal vein or hepatic artery, bilateral tumor extension to the secondary hepatic ducts, or parenchymal spread within the two lobes of the liver also were considered to indicate incurable disease. Since the introduction of liver transplantation, however, contraindications to curative surgical treatment only exist with extrahepatic disease.

Using these criteria, 23 patients were considered suitable for resection and are the focus of the study (resectability rate, 19%). Details for each patient are given in Table 1. There were 12 men and 11 women, with a mean age of 50 years (range, 22 to 82 years; median, 48 years). All but five patients had been previously investigated or treated at another institution. Ten patients (43%) had undergone surgical exploration and drainage by a bilioenteric anastomosis or transtumoral intubation. Percutaneous external biliary drainage had been performed in one case, and in 2 cases, biliary drainage had been performed by endoscopic intubation. Patients considered unsuitable for resection after investigation were treated by surgical bypass or transtumoral intubation, if this had not already been performed.

Recently, three patients with type IV lesions have been treated by hepatectomy and liver transplantation. One of these patients had extension of the tumor to the middle third of the bile duct and also underwent a Whipple pancreaticoduodenectomy, 1 month after transplantation. These three patients were not included when analyzing results, however, because the main aim of the study was to concentrate on factors influencing survival after resection, without transplantation.

Anatomic Types

Tumors were divided into four anatomic types using a modification of the original Bismuth–Corlette classification (Fig. 1).[20] This classification was based on ultrasonic, cholangiographic, and macroscopic pathologic appearances at operation. There were three type I and three type II cases. Sixteen cases were type III; in nine of these, tumor extension involved the right hepatic duct (IIIa) and in seven it involved the left hepatic duct (IIIb). There were four type IV lesions.

Surgical Procedures

The surgical procedure undertaken depended on the intraoperative evaluation of the anatomic type of the lesion (Table 1). Local excision of the tumor and suprapancreatic bile duct was performed in 10 cases. Hepatic resection, for tumor extending to the secondary bile ducts or hepatic parenchyma, was required in 13 cases. The liver resections comprised one left lobectomy (segments 2 and 3), eight left hepatectomies, extended to include the caudate lobe (segment 1) in six cases, one right hepatectomy, and three extended right hepatectomies—to include segment 4 (one case), segment 1 (one case), or both segments 1 and 4 (one case).

In all cases, all lymphatic and areolar tissue in the hepatic pedicle was excised. Seven patients had local lymphatic spread at the time of surgery. In three, this was confined to the juxtatumoral nodes, and in four, the nodes in the hepatic pedicle were involved. Bilioenteric continuity was re-established using a Roux-en-Y loop of jejunum.

Histologic Findings

A histologic diagnosis was established in every case. The most frequent finding was an infiltrating cholangio-

TABLE 1. *Clinical, Pathologic, and Follow-up Details for Resection of Hilar Cholangiocarcinoma in 23 Patients*

Patient No.	Sex	Age (yr)	Intraoperative Classification	Surgical Procedure	Pathologic Group	Follow-up (mo)	Recurrence		Alive or Dead	Remarks
							Local	Distant		
1	F	33	IIIA	Excision	A	15	Yes	Yes	Dead	—
2	M	43	II	Excision	A	32	Yes	Yes	Dead	Portal vein invasion
3	M	22	II	Excision	A	6	Yes	Yes	Dead	Portal vein invasion
4	F	37	IIIb	Excision, left lobectomy	A	32	Yes	Yes	Dead	Left lobe necrosis
5	F	71	I	Excision	B	132	No	No	Dead	Papillary tumor
6	M	63	IIIa	Excision	B	38	Yes	Yes	Dead	—
7	M	58	IIIb	Excision, left hepatectomy + segment I	B	8	Yes	Yes	Dead	—
8	M	60	IIIb	Excision, left hepatectomy + segment 1	B	24	Yes	Yes	Dead	—
9	F	63	IIIa	Excision, right hepatectomy + segments I + IV	B	16	Yes	Yes	Dead	—
10	M	36	IIIa	Excision	B	33	Yes	Yes	Dead	—
11	F	38	IIIb	Excision, left hepatectomy	B	32	No	Yes	Alive	Left liver atrophy
12	F	59	II	Excision	B	15	Yes	Yes	Dead	—
13	M	46	IIIa	Excision, left hepatectomy + segment I	B	17	Yes	No	Alive	—
14	F	55	IIIb	Excision, left hepatectomy	B	6	Yes	No	Alive	—
15	M	82	I	Excision	C	48	No	No	Alive	—
16	F	48	IIIa	Excision	C	14	Yes	Yes	Dead	—
17	M	43	IIIa	Excision, right hepatectomy + segment IV	C	22	Yes	Yes	Dead	—
18	M	56	I	Excision	C	39	No	No	Alive	—
19	F	63	IV	Excision, left hepatectomy + segment I	C	29	No	No	Alive	Left liver atrophy
20	F	41	IIIb	Excision, left hepatectomy + segment I	C	31	No	No	Alive	—
21	M	44	IIIb	Excision, left hepatectomy + segment I	C	30	No	No	Alive	Left liver atrophy
22	M	54	IIIa	Excision, right hepatectomy + segment I	C	15	No	No	Alive	—
23	F	61	IIIa	Excision, right hepatectomy + segment I	C	12	No	No	Alive	—

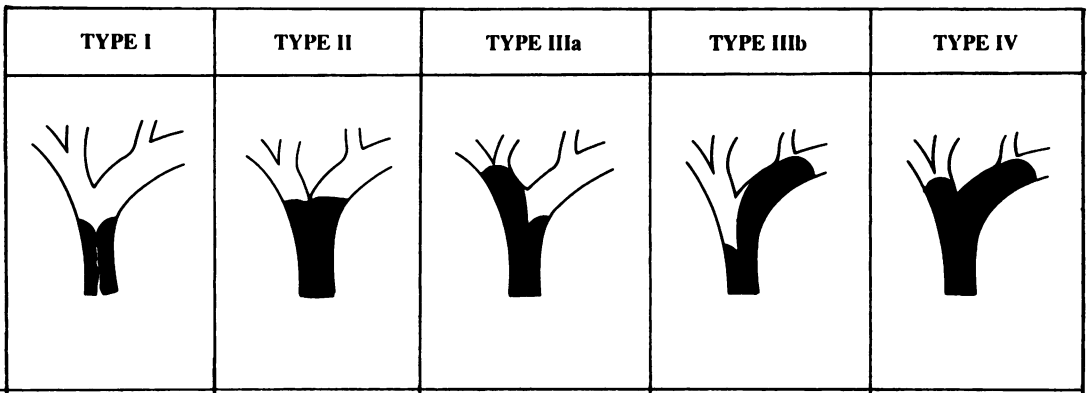
carcinoma (91%). In two patients, with recurrent lesions, malignancy was only confirmed at 3 and 5 years after the first biopsy was performed. In the first patient, the tumor was slow growing, without perineural infiltration, thus making histologic confirmation difficult. The second patient presented with a papillary tumor with polypoidal growth into the bile duct confluence. She survived for 11 years, free from recurrence, after several tumorectomies followed by excision of the bile duct confluence.

Based on macroscopic and microscopic appearances, patients were classified into three groups (Table 2). In four patients, complete excision of the tumor was not achieved macroscopically (Group A). In two of these, an extension of the tumor into the portal vein bifurcation was discovered during dissection. In one case, with partial necrosis of the left lobe of the liver, a left lobectomy and excision of the tumor was performed. In one other case, excision of the tumor was performed to allow an adequate bypass. Thus, of the 23 resections performed, a macroscopic curative resection was achieved in 19 (macroscopic curative resection rate 19/122; 15.6%).

The definitive histology report showed, in 10 cases, a microscopic extension of the tumor involving the surgical resection margins or lymph nodes outside the hepatic pedicle. These resections were retrospectively classified as being palliative (Group B). Thus, after histologic analysis, a potentially curative resection was performed in nine patients (Group C) (microscopic curative resection rate, 9/122; 7.4%). The reclassification of lesions, based on postoperative histologic findings, is detailed in Figure 1.

Outcome and Follow-up

Operative mortality was defined as death during or within 2 months after surgery. Follow-up ranged from 6 months to 11 years (mean, 26 months) and included clinical assessment, measurement of liver function tests, and ultrasound examination. A special emphasis was placed on the extension of the tumor at the time of resection (macroscopic or microscopic), the type of recurrence (local or distant), and the time interval between resection and recurrence. In addition, the time interval between local recurrence and death due to secondary spread was analyzed to focus, retrospectively, on patients who could pos-



	TYPE I	TYPE II	TYPE IIIa	TYPE IIIb	TYPE IV
Operative classification	3	3	9	7	4
Postoperative histological classification	2	2	6	6	9

FIG. 1. Modified Bismuth–Corlette classification of hilar cholangiocarcinoma in 26 patients, based on operative findings and postoperative histologic examination (3 patients who underwent liver transplantation included).

sibly have benefitted from an alternative surgical approach.

Results

Operative Morbidity and Mortality Rates

In all cases, excision of the tumor and restoration of bilioenteric continuity produced immediate relief of jaundice and disappearance of symptoms. Two patients developed a postoperative bile leak. The first, who had an extensive liver resection (6 segments), developed biliary peritonitis and required reoperation. The second developed an external biliary fistula, which closed spontaneously after 25 days. One patient developed a wound infection, and two developed a postoperative respiratory infection. No patient developed evidence of liver dysfunction secondary to a biliary stricture. There was no operative mortality.

Survival and Recurrence

The survival and recurrence rates for patients in groups A, B, and C are displayed in Table 1 and Figure 2. When analyzing survival figures, one patient was excluded. This was a 70-year-old patient who had a papillary type lesion and a prolonged survival (11 years), not typical of the remainder of the group. Death was due to cardiovascular disease.

TABLE 2. *Classification Based on Gross and Histologic Appearances*

Group	Pathologic Appearance	N
A	Gross residual tumor	4
B	Microscopic residual tumor at resection margins	10
C	Resection margins free from tumor microscopically	9

The overall survival rate was 87% at 1 year, 63% at 2 years, and 25% at 3 years. Mean survival was 25.5 months (median, 24 months). Currently, 10 patients are alive, 6 to 48 months after surgery, seven of them free from recurrence. All four group A patients died of recurrent disease within 32 months. In group B patients, the survival rate was 82% at 1 year, 43% at 2 years, and 12% at 3 years. The free-from-recurrence rate was 44% at 1 year, 22% at 2 years, and 0 at 3 years.

The survival rate in group C patients was 100% at 1 year, 71% at 2 years, and 50% at 3 years. Seven patients are currently alive, free from recurrence, including two patients with juxtatumoral lymph node involvement (29 and 39 months after surgery). One 82-year-old patient with juxtatumoral lymph node involvement survived for more than 4 years, free from disease, but was subsequently lost to follow-up. Two patients in group C died of recurrence of their tumor at 14 and 22 months postoperatively. One of these, operated on early in the series, had a resection of a type IIIa tumor with resection of the hilar plate, but no liver resection. She presented at 10 months postoperatively with evidence of recurrence at the anastomosis and in the hepatic pedicle. The other patient, with a type IIIa lesion with pedicle lymphatic involvement, was treated by resection and extended right hepatectomy. He died of disseminated spread of the tumor. In group C, there was a trend toward improved long-term survival

because survival and free-from-recurrence rates were similar at 2 and 3 years (Fig. 2).

Correlation Between Histologic Findings and Tumor Progression

There was a good correlation between histologic findings and progression of the disease. Microscopic extension of the tumor to the resection margin was associated with local recurrence in all cases except one. In addition, local recurrence was not observed in any cases when the resection margin was free from tumor on histologic examination.

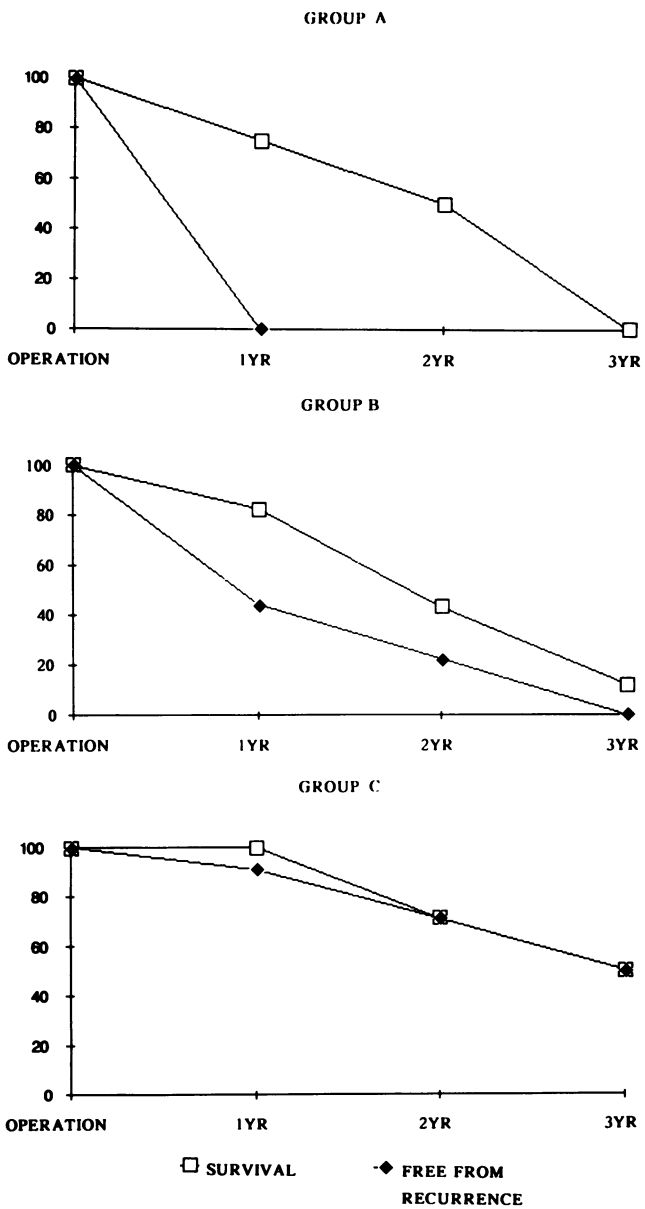


FIG. 2. Survival and recurrence-free rates (percentage) for patients in groups A, B, and C.

Effect of Local Lymphatic Involvement at the Time of Surgery

Local lymphatic involvement, either juxtatumoral or in the hepatic pedicle, was present in seven patients. Three patients with free resection margins but juxtatumoral nodal involvement were free from recurrence at 29, 39, and 48 months. Four patients (three with tumor invasion of the resection margin) with nodal involvement in the hepatic pedicle all presented with multifocal recurrence. Thus, local lymph node involvement, as a single factor, did not appear to influence outcome and was less important than microscopic involvement of the resection margins.

Temporal Relationship Between Surgery, Recurrence, and Death

The time interval between surgery and evidence of recurrence (either symptomatic or detected by investigation) was variable, ranging from 1 to 26 months. In group A patients, the free-from-recurrence period ranged from 1 to 11 months (mean, 4.5 months). In group B patients, this period ranged from 1 to 26 months (mean, 14 months). The mean time interval between recurrence and death was 8 months. In group C, recurrence (two patients) was at 10 and 20 months.

Local recurrence was present long (>15 months) before metastases occurred in four patients; three group B patients with microscopic residual tumor in the bile duct and one group A patient. These patients (one type II, three type III) all underwent local excision. In retrospect, it is possible that more extensive resections may have achieved a cure or prolonged survival.

Assessment of Curability of Resection

The extent of the surgical procedure and the effect on the development of local recurrence was assessed for each type of lesion. The four patients with macroscopic residual tumor were not included in this analysis. Three patients, who were found on postoperative histologic examination to have lymphatic involvement other than the local nodes, were also excluded as, in these cases, there was already distant spread and recurrence was always associated with distant metastasis. Total excision of tumors with local spread only was achieved in 16 patients (Table 3).

Local excision, without liver resection, was performed in eight cases. Three of these were type I lesions. In two of these, the resection margins were histologically negative, and neither developed local recurrence. In the third, prolonged survival (11 years), without recurrence, was achieved after several tumorectomies and subsequent bile duct excision. The other five cases (two type II, three type IIIa) all had macroscopic or microscopic involvement of

TABLE 3. *Assessment of Curability of Resection for Tumors With Local Spread Including Juxtatumoral Lymphatic Involvement*

Surgical Procedure	N	Free From Recurrence	Local Recurrence	Distant Metastasis
Local excision				
Type I	3	3		
Type II	2	1	1	
Type IIIa	3		1	2
Liver resection				
Left hepatectomy + segment 1				
Type IIIb	4	2	1	1
Type IIIa	1		1	
Type IV	1	1		
Right hepatectomy				
Type IIIa	1	1		
Right hepatectomy + segment 1				
Type IIIa	1	1		

the resection margins and all developed local recurrence. Thus, local excision of the lesion, without liver resection, achieved free resection margins and prevented local recurrence in type I lesions only.

Local excision plus liver resection was performed in eight cases. Six patients (four type IIIb, one type IIIa, one type IV) underwent a left hepatectomy plus excision of segment 1. Three of these patients (two type IIIb, one type IV) had histologically negative resection margins and are free from recurrence. Two patients (both type IIIa) underwent right hepatectomy (one patient also had excision of segment 1). In each of these, the resection margins were histologically negative and neither developed local recurrence. Thus, in eight patients with type III or IV lesions, in whom local excision of the lesion was accompanied by liver resection, only three developed local recurrence.

Therefore, a potentially curative resection, with histologically negative resection margins and no evidence of recurrence to date, was achieved in eight cases using the following procedures: local excision for three type I lesions; left hepatectomy plus excision of segment 1 for two type IIIb lesions and one type IV lesion; right hepatectomy and right hepatectomy plus excision of segment 1 for two type IIIa lesions.

Discussion

When analyzing our survival figures, it was important to assess patients according to the potentially curative nature of the resection. As expected, in patients in whom a macroscopic clearance of the tumor was not achieved (group A), there was no improvement in survival and all patients died, within 32 months, of progression of their disease. In cases where the tumor was completely excised macroscopically but where, on microscopic examination, the resection margins were still found to be involved (group B), the survival and free-from-recurrence figures were superior to those for patients in group A. Moreover, when patients in whom the resection margins were clear (group C) were analyzed, the survival and free-from-recurrence figures were superior to those of the other two groups. Thus, these results suggest that by completely excising the lesion it is possible to alter the natural history in terms of progression of the disease and long-term survival. The difference between groups B and C, however, illustrates that to achieve a curative resection, removal of all tumor tissue, with free resection margins, must be obtained. This emphasizes the importance of extensive preoperative and perioperative assessment so that resection is only performed when potentially curative and inappropriate extensive resection is avoided (*i.e.*, to achieve a microscopic curative resection rate equal to the overall resection rate).

The second aim of this study was to determine the exact type of surgical procedure needed in each particular case, to ensure a radical resection and thus a potential cure. This clearly relates to the controversy as to whether liver resection, and if so what type, should be added to local excision.[3,8,10]

Local excision of the lesion was performed in eight cases with local spread of the tumor only. Five of these patients developed local or distant recurrent disease. The only patients who had negative resection margins and were free from recurrence after local excision were those with type I lesions, in other words, confined to the bile duct confluence but not involving the superior aspect. Thus, it seems that local excision without hepatic resection is sufficient for type I lesions only.

In two type II cases, in which local excision was performed, both had involvement of the resection margins (one microscopic; one macroscopic) and both developed early recurrent disease. In type II cases, there is no communication between the right and left duct systems on the cholangiogram, and the superior aspect of the biliary confluence is involved. In this situation, the biliary ducts draining the caudate lobe (segment 1) are almost inevitably involved by tumor,[21] and for these lesions local excision of the tumor probably always will need to be accompanied by resection of the caudate lobe. For some large type II lesions, tumor extension may involve the parenchyma of segment 4, and resection of segment 4 also may be necessary.

When the lesion involves the superior aspect of the biliary confluence and extends into one of the main hepatic ducts (type IIIa or IIIb), a radical tumor clearance can not be achieved by local excision because there inevitably will be ductal involvement of the caudate lobe and the secondary bile ducts on the involved side.[21] Three

of our patients with type III lesions who were treated by local excision had residual disease, and all developed recurrence. In contrast, in four of the seven patients with type III lesions, who underwent local excision plus hepatectomy, free resection margins and no evidence of recurrence were achieved. Thus, it seems that for type III lesions, treatment should consist of local excision and resection of the caudate lobe plus resection of the hepatic segments drained by the involved duct; in other words, a right hepatectomy for type IIIa lesions and a left hepatectomy for type IIIb lesions. For some large type IIIa lesions, with tumor extension involving the parenchyma of segment 4, resection of segment 4 also may be necessary (one case in our series).

In these patients, the feasibility of extensive liver resection depends on the remaining volume of functioning hepatic parenchyma and, in particular, an extended right hepatectomy for a type IIIa lesion may not leave sufficient functioning parenchyma. In some cases, however, tumor extension with involvement of the major branch of the hepatic artery or portal vein may result in unilateral liver atrophy, with corresponding hypertrophy of the other hemiliver, thus making a major liver resection possible. In some cases, with deteriorating preoperative liver function or sepsis, preoperative percutaneous transhepatic biliary drainage may be indicated to improve hepatocellular function and reduce the risk of liver failure in the immediate postoperative period. Although prospective studies of this technique in patients with obstructive jaundice from various causes have failed to demonstrate any significant overall benefit,[22,23] Nimura et al.[21] advocate its use routinely before liver resection in patients with hilar cholangiocarcinoma, and we have found it useful in certain selected cases. There may be some type III cases without hypertrophy of the uninvolved hemiliver, however, in which, despite optimal preoperative drainage and preparation, resection would be associated with a very high risk of postoperative liver failure. In these cases, liver transplantation may be indicated.

When the tumor has extended to involve the secondary bile ducts or hepatic parenchyma bilaterally, or the main trunk of the hepatic artery or portal vein (type IV), resection techniques almost always fail to achieve a radical excision of all tumor tissue, although in one of our patients with a type IV lesion, which involved principally the left side, histologically free resection margins were obtained. She has survived more than 3 years, free from recurrence, after excision of the tumor plus a left hepatectomy and excision of the caudate lobe. For type IV lesions, hepatectomy and liver transplantation may be indicated. This offers the only chance of complete tumor removal and potential cure in these cases, although results have generally been poor, with a high incidence of tumor recurrence.[24,25] One of our three patients treated by transplantation developed recurrence in the hepatic pedicle, 8 months after transplantation. Results from Pichlmayr et al.[19] are more encouraging, particularly for patients treated in recent years.

We believe from our results that it is justifiable to conclude that long-term survival can be achieved in selected cases of hilar cholangiocarcinoma by adopting a policy of tumor excision, with liver resection if required, to obtain tumor-free resection margins. Consequently, based on our findings and anatomic considerations of the hepatic hilus, we now perform local excision for type I; local excision plus resection of segment 1 for type II; local excision, resection of segment 1, and right or left hepatectomy for types IIIa and IIIb and hepatectomy plus liver transplantation for type IV lesions. We believe that this formalized type of approach provides the best chance of achieving a curative resection and providing improved long-term results. The very low morbidity and mortality rates that may be achieved with these procedures also justify the "attempt at cure" and counters any arguments in favor of a minimal palliative approach.

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