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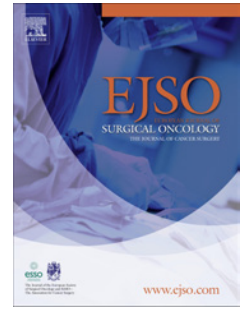
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Multidisciplinary management of hilar cholangiocarcinoma (Klatskin tumor): extended resection is associated with improved survival.

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Abstract

Background: Effective diagnosis and treatment of patients with hilar cholangiocarcinoma (HCCA) is based on the synergy of endoscopists, interventional radiologists, radiotherapists and surgeons. This report summarizes the multidisciplinary experience in management of HCCA over a period of two decades at the Academic Medical Center in Amsterdam, with emphasis on surgical outcome.

Methods: From 1988 until 2003, 117 consecutive patients underwent resection on the suspicion of HCCA. Preoperative work-up included staging laparoscopy, preoperative biliary drainage, assessment of volume/function of future remnant liver and radiation therapy to prevent seeding metastases. More aggressive surgical approach combining hilar resection with extended liver resection was applied as of 1998. Outcomes of resection including actuarial 5-year survival were assessed.

Results: 18 patients (15.3%) appeared to have a benign lesion on microscopical examination of the specimen, leaving 99 patients with histologically proven HCCA. These 99 patients were analyzed according to three 5-year time periods of resection, i.e. period 1 (1988-1993, n=45), 2 (1993-1998, n=25) and 3 (1998-2003, n=29). The rate of R0 resections increased and actuarial five-year survival significantly improved from $20\pm 5\%$ for the periods 1 and 2, to $33\pm 9\%$ in period 3 ($P<0.05$). Postoperative morbidity and mortality in the last period were 68% and 10%, respectively.

Conclusion: Extended surgical resection resulted in increased rate of R0 resections and significantly improved survival. Candidates for resection should be considered by a specialized, multidisciplinary team.

226 words

Introduction

The improved surgical treatment of hilar cholangiocarcinoma (HCCA) in the past two decades¹, not only owes to changed surgical strategy, but also to better patient selection and improved preoperative work-up of candidates for resection. The synergy of endoscopists, interventional radiologists, oncologists and surgeons, has equally contributed to these improved results.² Herein we summarize the multidisciplinary experience in diagnosis and management of HCCA over a period of two decades at the Academic Medical Center in Amsterdam, with emphasis on surgical outcome.

Patients and methods

Study population

From 1988 until 2003, 117 consecutive patients underwent resection on the suspicion of HCCA. These patients were considered according to three 5-year time periods, i.e. period 1 (1988-1993), 2 (1993-1998) and 3 (1998-2003). A full 5-year follow-up was obtained for the last group which has currently been analysed in patients with microscopically proven HCCA. Outcomes were evaluated by assessment of completeness of resection, postoperative morbidity and mortality.

Diagnosis and staging

Suspicion on HCCA was usually based on clinical presentation and imaging studies. Diagnosis could be confirmed by (brush) cytology but, microscopical evidence was not prerequisite for undergoing resection.

The Bismuth-Corlette classification was used to stage proximal tumor infiltration into the biliary tract.¹ Although direct cholangiography was the gold standard diagnostic procedure in the staging of HCCA, non-invasive diagnostic investigations as MRCP (magnetic resonance

cholangiopancreatography) were preferred in more recent years. Cross-sectional imaging studies such as CT and MRI were used to assess liver parenchymal invasion, vascular invasion in portal vein and/or hepatic arteries and hepatic or extrahepatic metastases. Ultrasound, in combination with Duplex evaluation of the portal venous and hepatic arterial systems also proved useful.³

Criteria for resectability

Resectability of HCCA was in the first place determined by proximal extent of tumor into the intrahepatic biliary tree. Whereas Bismuth type III tumors showing extension into the first segmental biliary ducts on one side of the liver are resectable using (extended) hemihepatectomy, Bismuth type IV tumors which involve the segmental ducts on both sides of the liver, are resectable in selected cases.

Extra-hepatic metastases were usually a contraindication for resection. In the first two periods, the intraoperative finding of lymphnode metastases was a reason to abandon resection. In the last period, resection was carried out when lymphnode metastases were confined to the hepatic pedicle or the hepatoduodenal ligament. Tumor positive lymphnodes along the common hepatic artery or celiac axis were always considered a contraindication for resection. The portal vein bifurcation was resected along with the tumor when invasion was present. Massive involvement of the main trunk of the portal vein and/or hepatic artery precluded resection. Volume (>40%) and function of future remnant liver and the possibility of portal vein embolization were also considered.

Preoperative work-up

Staging laparoscopy was performed in the assessment of resectability, as we had shown that a laparotomy can be avoided in 25-40% of our patients with HCCA, mostly because of the

detection of small peritoneal or liver metastases.⁴ Similar results of staging laparoscopy in HCCA have been reported by other centers.⁵

Preoperative biliary drainage of at least the future liver remnant was performed to ensure optimal postoperative function and regeneration of the liver remnant.

CT volumetry was used to assess the volume of the remnant liver relative to total liver volume, mainly in the last period. When the volume of the future remnant liver was less than 40%, preoperative portal vein embolization (PVE) was considered.

To prevent postoperative implantation metastases, low-dose irradiation (3.5Gy on 3 consecutive days until operation) was applied in patients with potentially resectable hilar tumors as of 1990.

The algorithm shown in **figure 1** summarizes diagnosis and treatment of patients with HCCA in our center.

Type of resection

Local resection was the technique mainly used in the first two periods (1988-1998). The bile ducts at the liver hilum were dissected and transected proximally at the level of the segmental biliary ducts, and distally in the CBD.

A more extensive surgical approach as proposed by Japanese surgeons, has been applied in our center as of 1998, in which hilar resection was combined with large liver resections for the majority of HCCA.⁶ According to this strategy, radical resection of HCCA encompassed excision of the liver hilum *en bloc* with (extended) hemihepatectomy including the caudate lobe, excision of the portal vein bifurcation when involved and complete lymphadenectomy of the hepatoduodenal ligament.⁷

For biliary reconstruction, end-to-side anastomoses of the segmental ducts and a Roux-en-Y jejeunal loop were constructed.

Survival and statistical analysis

Actuarial 5-year survival data were analysed by constructing survival curves using the Kaplan-Meier method. The log-rank significance test was used for comparison of survival between groups. Factors influencing survival were analysed using univariate analysis. SPSS 16.0 for Windows (SPSS Inc, Chicago, Ill) was used as statistical software and a p value < 0.05 was considered significant.

Results

Outcomes of resection

Of all 117 patients who had undergone resection, 18 patients (15.3%) appeared to have a benign lesion on microscopical evaluation of the specimen, leaving 99 patients with histologically proven HCCA. The latter patients were divided according to the period of resection: period 1 (1988-1993) n=45; period 2 (1993-1998) n=25 and period 3 (1998-2003) n=29.

More hilar resections were combined with partial hepatectomies, especially during the third time period. (**Table 1**) Complete resection of segment I was performed in 15 patients⁷, all in the third period, and portal vein reconstruction was performed in 7 patients, of which 6 patients in the last period⁸. With this more extensive surgical approach, the proportion of margin negative resections increased from 13% in period 1 to 59% in period 3 (p<0.05).

Table 2 shows the stages of tumors resected in each period, according to the American Joint Committee (AJCC) on Cancer and Union Internationale Contre le Cancer (UICC).

Survival

Actuarial five-year survival increased significantly from 20±5% for the periods 1 and 2, to 33±9% in period 3 ($P<0.05$). (**Fig. 2**) Postoperative morbidity and mortality were considerable but did not increase with more extensive surgical strategy (68% and 10%, respectively, in period 3). The period of resection was associated with survival in univariate analysis. Hence, mainly in the last 5-year period when a more aggressive surgical approach was carried out, more hilar resections were combined with partial liver resections including segments 1 and 4, leading to a higher rate of R0 resections and improved survival.

Discussion

Difficulty in diagnosis

HCCA is a difficult tumor in terms of diagnosis and management. The diagnosis may be confirmed using brush or needle cytology. Sensitivity is however, limited due to failure to obtain a representative microscopical specimen. For these reasons, microscopical evidence of the tumor is often not available. Many of our patients are, therefore, operated without confirmed diagnosis and currently, up to 15% of resected tumors are ultimately diagnosed as benign, usually inflammatory lesions.⁹ Similar experiences have been published, reporting incidences of benign lesions in up to 18% of cases resected on the suspicion of HCCA.¹⁰ Despite more advanced imaging techniques, the incidence of benign biliary strictures mimicking malignant strictures at the liver hilum has not decreased in the past ten years in our center. We recently detected lymphoplasmacellular infiltrates in lesions of 47% of the patients who were misdiagnosed as HCCA, which is compatible with an autoimmune type of cholangitis. This inflammatory condition has an analogy with IgG4-related, lymphoplasmacytic sclerosing pancreatitis as has been described in pancreatic ductal strictures.⁹

Since tests that can reliably distinguish between benign and malignant hilar strictures are lacking, and complete resection is the only curative treatment for HCCA, every suspicious lesion at the hepatic hilum should be considered malignant unless proven otherwise. We accept with this policy, that 10-15% of patients with benign strictures are exposed to major surgery. On the other hand, long-term relief of bile duct obstruction is offered in this category of patients who usually are difficult to manage endoscopically or by percutaneous biliary drainage. Several techniques have emerged to better discriminate benign from malignant hilar lesions. Peroral or percutaneous cholangioscopic biopsy, endoscopic ultrasound and intraductal ultrasound in combination with biliary brushing have shown promising results, however require specific expertise.¹¹

Resectability of tumor determined by biliary anatomy at the liver hilum

The anatomy of the biliary ducts at the hepatic duct confluence ultimately determines whether tumor free ductal margins can be obtained with preservation of sufficient remnant liver in Bismuth type IV tumors.⁶ The liver hilum features great variation in the anatomy of the biliary ducts. The hepatic duct confluence consists in 16% of cases of the right anterior (B5/8) and right posterior (B6/7) sectorial ducts draining together with the left hepatic duct into the common hepatic duct, forming a trifurcation. Invasion of the left segmental ducts in combination with the right sectorial ducts at the liver hilum, although by definition a Bismuth type IV tumor, does not preclude a potentially curative resection. It is therefore crucial that each patient is assessed on an individual basis by an experienced multidisciplinary team.

Preoperative biliary drainage

Preoperative biliary drainage in HCCA is controversial. Obstructive jaundice affects liver functional reserve and reduces the regenerative capacity of the liver after resection. Jaundice

for these reasons, is considered a significant risk factor in patients with HCCA requiring major liver resection. Although we recently showed in a randomized, multicentric trial, that preoperative biliary drainage had no beneficial effects in patients with distal bile duct carcinoma undergoing subtotal pancreatoduodenectomy, the discussion is different in patients with HCCA requiring extensive liver resection.¹² The advantages of preoperative biliary drainage in the setting of HCCA are the treatment of segmental cholangitis, definition of proximal extent of the tumor and improved function and regenerative capacity of the remnant liver.¹³ Drawbacks are the risk of thrombosis, hemobilia, infectious complications and tumor cell seeding.¹⁴ Because the advantages of preoperative biliary drainage outweigh the disadvantages, we pursue preoperative biliary drainage of at least the future liver remnant in patients with potentially resectable HCCA. In our experience, percutaneous transhepatic biliary drainage outperformed endoscopic biliary drainage, showing fewer infectious complications and less drainage procedures.¹⁵

Volume assessment of future liver remnant

Although in patients with normal liver parenchyma, 25-30% of remnant liver suffices to ensure sufficient postoperative liver function, livers in jaundiced patients such as in HCCA, are seriously compromised, even after recent biliary drainage. Therefore, in patients with HCCA, we regard 40% volume as the safe lower limit in a decompressed liver. Calculation of volume based on CT however, only provides indirect information on the functional capacity of the liver remnant. We therefore recently use ^{99m}Tc-mebrofenin scintigraphy in conjunction with CT volumetry to determine function of the future remnant liver. This quantitative liver function test was shown to correlate with clinical outcome after resection, however, needs additional validation in other centers.¹⁶ When future remnant liver volume or function is deemed insufficient, preoperative portal vein embolization (PVE) is considered.¹⁷ In our

experience however, there are certain drawbacks of the use of PVE in patients with HCCA. PVE predetermines the side of the liver to be resected, and this cannot be changed when during exploration the type of resection is reconsidered on the basis of intraoperative findings. In addition, when the patient is found to be unresectable, the persisting embolized liver segments may give rise to septic complications since the affected bile ducts are often infected and incompletely drained.¹⁸

Preoperative radiation therapy to prevent seeding metastases

The bile of patients with HCCA is contaminated with tumor cells continuously exfoliating from the epithelial tumor. These tumor cells may give rise to seeding metastases as is a known complication of percutaneous biliary drainage in which seeding metastases occur along the track of the tube, as reported in up to 6% of cases.¹⁴ The risk of free tumor cells in the bile is enhanced after perturbation while during resection, bile spill potentially leads to seeding metastases in the operative field. Endoscopic stenting for drainage in patients with HCCA in our center, was associated with a significantly higher risk of implantation metastases presenting in the drain track scar or laparotomy scar following resection.¹⁹ Therefore, to destruct tumor cells contained in the bile, we preoperatively apply low-dose irradiation (3x3.5Gy) in patients with potentially resectable hilar tumors. Since this protocol was used, implantation metastases were not anymore encountered in 82 consecutive patients followed-up after resection after previous (endoscopic) biliary drainage.¹⁹

Of note is that more recent surgical refinements have controlled bile spill during resection and may as well have contributed to the decreased risk of postoperative seeding metastases. After transection of the common bile duct, the stump is meticulously closed to avoid bile spill whereas the proximal, segmental bile ducts are cut in the liver remnant after the parenchymal transection has been completed.

The extent of resection

Most HCCA (type II, III, and IV) require hilar resection in combination with substantial resection of liver parenchyma. The single most important prognostic factor for long-term survival is complete (R0) resection of the tumor.²⁰ Margin negative resections are however difficult to achieve due to the central location of the tumor at the liver hilum and proximal infiltration into the segmental bile ducts. The right and left portal vein and the hepatic artery branches run in direct proximity of the tumor. Surgery with curative intent therefore requires hilar resection in combination with extended liver resection, often in combination with excision of the unilateral portal vein and bifurcation. Several series have shown that these extensive resections lead to an increased rate of R0 resections and hence, improved survival.^{1;2;21-23}

The concept of hilar resection in conjunction with liver resection is based on a three-dimensional perception of the tumor located centrally in the liver. Tumor extension occurs from the bile duct confluence to the right and left along the main hepatic and segmental bile ducts. In addition, the tumor potentially invades anteriorly into the duct(s) of segment 4 and posteriorly, into the bile ducts draining segment 1. It is therefore crucial that the central sector of the liver along the antero-posterior axis including segments 1 and 4 is considered with resection. A right-sided resection therefore, usually entails an extended right hemihepatectomy including the segments 4 and 1, leaving only segments 2 and 3 as liver remnant. There is an advantage of a left-sided approach of resection since segment 4 is an anatomical part of the left liver, hence preserving most of the right liver.

The Berlin surgical group advocates a no-touch technique following oncological rules to resect right-sided HCCA in conjunction with extended liver resection. The surgical strategy consists of performing hilar resection en bloc with extended right hemihepatectomy and

unconditional resection of the portal vein bifurcation followed by end-to-end reconstruction. Dissection of the portal vein in the direct vicinity of the tumor is hence avoided. In a selection of patients operated according to these oncological principles, the 5-year survival rate was 57%.²⁴

Postoperative morbidity and mortality

Hilar resection in combination with extensive liver resections are undertaken at the cost of considerable morbidity and mortality (68% and 10%, respectively, in period 3 of this series). Most series report a hospital mortality of 5-10%. The challenge for the near future is to decrease mortality of the extended liver resections that are necessary to radically remove the tumor. The most important cause of postoperative mortality is liver failure.²⁴ Hence, quantitative assessment of volume and function of the future remnant liver is crucial in the evaluation of patients undergoing large liver resections for HCCA.

Survival

Overall, 5-year survival rates of 20% up to 35% have been reported after resection of HCCA.^{1;2;21;22;25} The nearly 34% 5-year survival rate of our patients in the last group compares favorably with these results. The most important independent prognostic factor for long-term survival was the period of resection. The Mayo clinic has reported good results of the combination of chemoradiation and orthotopic liver transplantation (OLT) in patients with HCCA presenting with unresectable disease.²⁶ In a series of highly selected patients, 5-year actuarial survival for all patients that began neoadjuvant therapy was 55%, and 5-year survival after OLT was 71%. This experience needs to be confirmed in additional liver transplant centers but readdresses the potential of total hepatectomy and liver transplantation in the treatment of HCCA.²⁶

Adjuvant treatment

The role of additional therapy after resection in patients with hilar cholangiocarcinoma is controversial. The success of neoadjuvant chemoradiation in patients with advanced HCCA according to the Mayo clinic experience has renewed interest in the use of chemoradiation in patients with resectable HCCA. So far, however, no adjuvant regimens have shown a survival benefit. Postoperative radiotherapy was part of our treatment protocol as of 1983. We previously analysed 91 patients who had undergone resection between 1983 and 1998, of which 20 patients had no additional radiotherapy, 30 patients had only external radiotherapy (46 ± 11 Gy) and 41 patients had a combination of external (42 ± 5 Gy) and intraluminal brachytherapy (10 ± 2 Gy).²⁷ Median survival after treatment with adjuvant radiotherapy was significantly longer than after resection without additional radiation (24 months vs. 8 months, respectively). To investigate whether the retrospectively observed survival benefit was real, a randomized trial was attempted but this failed due to insufficient accrual. Because of the lack of evidence and the additional toxicity of postoperative irradiation, the trial was abandoned in 2004. Recent experimental studies have shown encouraging results of new chemotherapy regimens including targeted therapy with anti-EGFR and antiangiogenic drugs.²⁸

Photodynamic therapy (PDT) holds promise as a novel treatment in patients with advanced disease. A randomized study in patients with unresectable type III and type IV tumors showed that PDT improved survival, decreased cholestasis and improved quality of life scores as compared to stenting alone. In the neoadjuvant setting, patients with advanced HCCA underwent preoperative PDT followed by a potentially curative (R0) resection.²⁹ The benefits of PDT await further confirmation in randomized studies.

Conclusion

The multidisciplinary efforts of all specialities involved in the treatment of HCCA, has culminated in an institutional expertise that has greatly improved the surgical results of patients with HCCA. A more aggressive surgical approach applied in our center as of 1998, has contributed to an increased rate of R0 resections and significantly improved survival. The outcomes support the plea that patients with this rare and complex tumor are managed in highly specialized centers.

2995 words

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Legends

Figure 1

Algorithm for multidisciplinary management of patients with hilar cholangiocarcinoma (HCCA)

Figure 2

Kaplan-Meier survival curves of 99 patients who had undergone resection for hilar cholangiocarcinoma (HCCA) from 1988 to 1998 (n=70) and from 1993 to 2003 (n=29).

Actuarial five-year survival increased significantly from $20\pm 5\%$ to $33\pm 9\%$, for the first and last period, respectively (log-rank test, $p < 0.05$).

Table 1. Types of resection and R0 resection rate in 99 patients with hilar cholangiocarcinoma according to resection period. More hilar resections were combined with partial hepatectomies, segment 1 resections and portal vein reconstructions in the last time period, leading to a higher rate of R0 resections..

	1988-1993 n=45	1993-1998 n=25	1998-2003 n=29	Total n=99
Local resection	41 (91%)	12 (48%)	8*# (28%)	61 (62%)
Hilar resection with hemihepatectomy (HH)	4 (9%)	13 (52%)	21*# (72%)	38 (38%)
- right HH	1 (25%)	7 (54%)	11 (52%)	19 (50%)
- left HH	3 (75%)	6 (46%)	10 (48%)	19 (50%)
- Segment 1 resection	0 (0%)	0 (0%)	15*# (71%)	15 (39%)
- portal vein resection	0 (0%)	1 (8%)	6* (29%)	7 (18%)
R0 resection rate	6 (13%)	8 (32%)	17*# (59%)	31 (31%)

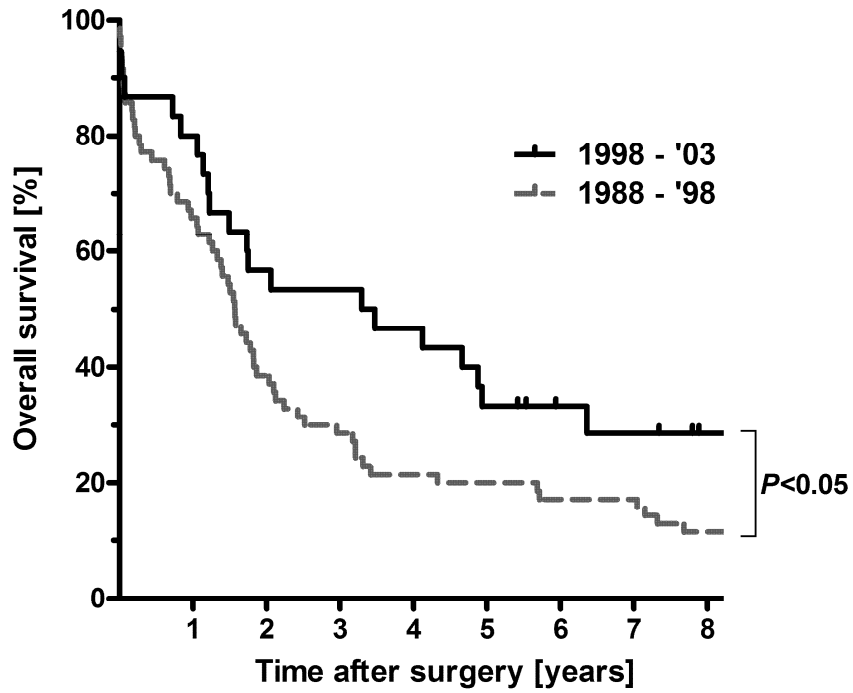
*, # Significantly different compared to period 1 and 2, respectively (p<0.05)

Table 2. Staging according to AJCC/UICC, of 99 patients with hilar cholangiocarcinoma divided into resection period.

AJCC/UICC	1988-1993 n=45	1993-1998 n=25	1998-2003 n=29	Total n=99
Stage 0	1 (2%)	1 (4%)	2 (7%)	4 (4%)
Stage IA	6 (13%)	2 (8%)	3 (10%)	11 (11%)
Stage IB	12 (27%)	13 (52%)	7 (24%)	32 (33%)
Stage IIA	8 (18%)	5 (20%)	11 (38%)	24 (24%)
Stage IIB	18 (40%)	4 (16%)	6 (21%)	28 (28%)



ACCEPTED MANUSCRIPT



No. at risk

	0	1	2	3	4	5	6	7	8
Period 1988 - '98	70	55	40	30	21	15	10	7	9
Period 1998 - '03	29	25	17	13	11	8	6	4	4

ACCEPTED