Annals of Medicine and Surgery 62 (2021) 239–243

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

A case series of hilar cholangiocarcinoma: A single surgeon experience over 20-years

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ARTICLE INFO

Keywords:
Hilar cholangiocarcinoma
Curative resection
Hepatectomy
Lymphadenectomy

ABSTRACT

Objective: To report our experience in the surgical management of hilar cholangiocarcinoma in a nontransplant center.

Methods: We reviewed the medical charts of patients who underwent surgical resection of hilar cholangiocarcinoma from 1996 to 2016. The preoperative workup as well as the operative techniques were presented. The postoperative mortality and morbidity were detailed with particular emphasis on long survivals.

Results: Forty patients met our inclusion criteria,22 patients (55%) had surgical resection with curative intent. Thirty-day postoperative mortality occurred in three cases (13.6%), four patients had grade II, III Clavien-Dindo complications and only one required re-laparotomy (18%).

The median follow up duration was 43.4 months.

Conclusion: Hilar cholangiocarcinoma is a rare disease with complete surgical resection presenting the best chance of cure. In addition to the free resection margins, lymph node involvement and the histological type are the most significant factors of prognosis. Histologic type such as primary lymphoma and papillary carcinoma are associated with better survival outcomes. Portal vein embolization should be considered if extended right hepatectomy is contemplated.

1. Introduction

First described by Gerald Klatskin in 1965, Hilar or perihilar cholangiocarcinoma (HC) is the second most common malignancy involving the liver, while it is the most common site for biliary tumors [1–3]. Although it comprises 2% of malignancies in humans [4], HC has morbidity rates ranging from 40% to 70% and mortality rates of 5%–15% [5]. HC is most commonly seen in Asia, with incidence of 113 per 100,000 in men and 50 per 10,000 in women [6]. Several risk factors have been linked to the development of HC, including advanced age, male gender, primary sclerosing cholangitis (PSC), choledochal cysts, cholelithiasis, parasitic infections (biliary ascariasis, liver schistosomiasis, and liver flukes), inflammatory bowel disease, cirrhosis and chronic pancreatitis [6]. PSC is the most well-known risk factor for HC, with life time risk of 6%–36% [5].

Patients typically present in their 60s with painless jaundice, abdominal pain and weight loss. Other common findings are pruritic, clay-colored stool, and dark urine due to biliary stasis [7]. Serum tumor markers such as carcinoembryonic antigen (CEA) and CA19-9 are used for screening, diagnosis, and monitoring, with combined sensitivity and specificity of 89% and 86%, respectively. Imaging, (including ultrasound (US), computed topography (CT), magnetic resonance imaging (MRI)) remains the most important diagnostic step in assessing tumor resectability [8,9]. Overall, less than a half of HC cases are amenable to surgical resection [8]. A major advancement in the management of these tumors has been achieved in the last three decades especially in the operative and perioperative management. Nevertheless, the prognosis remains poor and the 5-year survival rate rarely exceeds 50% after surgical curative resection [10,11]. Management may entail chemoradiation, palliation by stenting, photodynamic therapy, but curative resection is the only hope for cure [10]. Reports from Middle East regarding clinical features and outcomes of this disease are scarce. Therefore, we present a 20-years single surgeon experience in diagnosing and treating cholangiocarcinoma, aiming to shed light into surgical intervention of this rare and technically demanding disease.

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https://doi.org/10.1016/j.amsu.2021.01.059
Received 25 December 2020; Received in revised form 17 January 2021; Accepted 17 January 2021
Available online 22 January 2021

2. Methods

2.1. Data collection

This is a single center, retrospective, medical record-based case series study. All surgically treated HC cases at Jordan University Hospital (JUH) between Feb.1996 and Feb. 2016 were included in this report. JUH is a tertiary referral, university hospital located in Amman, the capital of Jordan. It serves a large population from different backgrounds, offering almost all sub-specialties and treatment options. The eligibility criteria were: documented diagnosis of HC, documented surgical exploration, and having full medical records as well as satisfactory follow-up details. Files of all patients were reviewed, and the last follow up was checked, if not available the patient and their families were contacted. Data from patients who had incomplete documentation were not included in the study. Patient with advanced disease or distant metastasis such as those with involvement of celiac lymph nodes, grade 4 Bismuth lesions, involvement of the trunk of portal vein, proper hepatic artery, contralateral (to the site of the tumor) vascular extension, or patients who were unfit for surgery (ASA 4 or 5) were excluded from the study. Forty patients were found to be eligible to be included on this study.

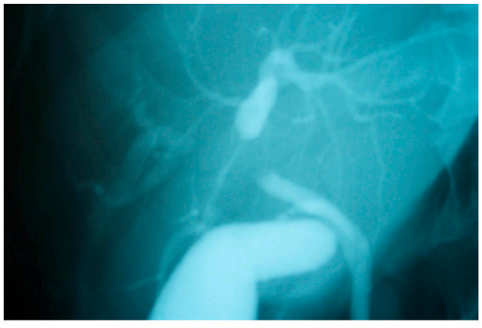
2.2. Diagnostic work up

Overall, 40 patients with a suspected diagnosis of hilar HC underwent surgical exploration and resection with curative intent after a preoperative evaluation by ultrasonography, multidetector computerized tomography (MDCT), magnetic resonance (MR)/cholangiopancreatography (MRCP) (Fig. 1A), or endoscopic retrograde cholangiopancreatography (ERCP) with or without stenting. In fact, patients evaluated by gastroenterologist routinely underwent ERCP and stenting before presenting to surgery. Just prior to surgical exploration all patients presented after 2003 underwent positron emission tomography (PET) scan to exclude distant metastasis. All patients underwent clinical examination as well as laboratory evaluation including complete blood count, kidney function test, liver function tests, INR, CA19-9, CEA.

2.3. Surgical details

All surgeries were performed by a single consultant hepatobiliary surgeon who had a dedicated fellowship training in hepatobiliary surgery in early 1990's. The surgeon followed a predefined internal protocol to perform such surgeries that was communicated with the team (residents and nurses) to ensure the smooth flow of preoperative evaluation, surgery and the consistency of the steps over time are dictated by the grade of the tumor. After thorough patients counselling and discussion, an informed consent was taken followed by proper multidisciplinary preoperative preparation. Surgeries were performed under general anesthesia and in supine position with all preoperative preparation such as prophylactic broad-spectrum antibiotics, pneumatic device, central venous line, arterial line and epidural catheter. Upon laparotomy, the whole peritoneal cavity was explored looking for metastases. The small bowel was inspected from duodenojejunal junction to ileocecal region, diaphragmatic surfaces inspected, and pelvis were inspected. The liver was assessed clinically by bimanual palpation and by intraoperative ultrasound. All suspicious lesions were biopsied and sent for frozen section examination, any proven positive spread outside the area of resection the surgery was converted to palliative rather than curative surgery.

Bismuth anatomic grading system was used, based on cholangiographic studies and surgery was planned on this grading. The curative



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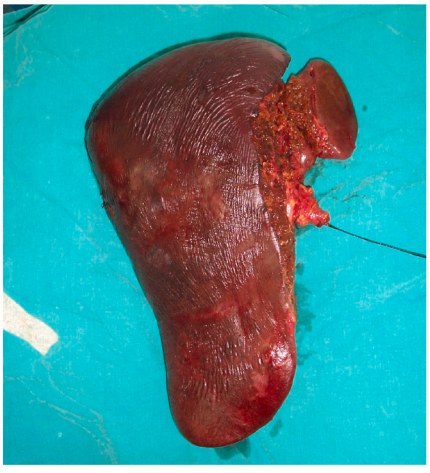

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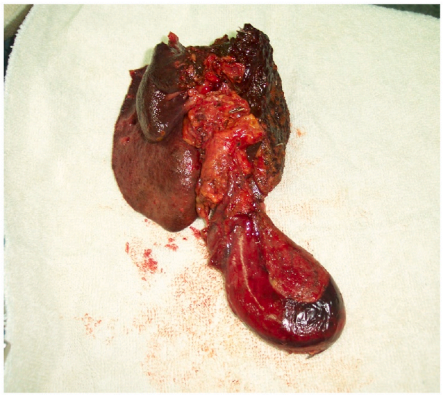

C

Fig. 1. MRCP and surgical specimens.
Fig. 1A: MRCP showing grade IIIB, B: righthemiliver, caudate lobe with en-bloc resection of lymph nodes of portahepatis,C: left hemiliver, gallbladder with en-bloc resection of portahepatis lymph nodes.

intent resection started by dissecting the distal bile duct at the level of the pancreas, the margin is checked routinely by frozen section examination, en-bloc lymphadenectomy upwards, all tissues in the portahepatis were dissected except the portal vein (PV), and the hepatic artery (HA) until the hepatic biliary confluence.

Bismuth grade I lesions were managed by local resection, lymphadenectomy of the portahepatis and Roux-en-Y hepaticojejunostomy, while grade II lesions were managed by adding caudate lobectomy. Grade IIIA that was involvement of the confluence with extension to the right hepatic duct reaching the sectoral ducts was managed by adding right hepatectomy (resection of segments V,VI,VII,VIII) and caudate lobectomy that means extended right hepatectomy to caudate lobectomy, lymphadenectomy of the portahepatis and Roux-en-Y hepaticojejunostomy. Grade IIIB lesions with extension to left hepatic duct reaching the sectoral ducts was managed by extended left hepatectomy to caudate lobectomy, portahepatis lymphadenectomy and Roux-en-Y hepaticojejunostomy. For grade IV surgery was not performed. Frozen section was taken from the proximal bile duct(s), before performing the hepaticojejunostomy. Portal embolization was used after 2016, for patients presumed to undergo extended right hepatectomy.

During surgery, if curative resection was abandoned due to the presence of metastases, patients underwent palliative intrahepatic cholangioenteric bypass based on segment III, or segment V ducts or both, that is why an initial diagnostic laparoscopy was not performed. No liver transplantation was attempted as this is not available at our institution. The hepaticojejunostomy was performed by end to side using 5-0 PDS sutures in an interrupted fashion with the knot to the outside, we rarely used stents. Any mortality within 30 days from the time of surgery was considered operation related mortality. At end of surgery the peritoneal cavity was drained by two drains. The whole specimens were sent for histopathology for examination after orientation by one members of the surgical team.

After surgery and extubation, all patients were sent to the intensive care unit for at least 48 h for observation where they received standardized care by intensivist and ICU personnel and this included closing monitoring, fluid management, and thromboprophylaxis. Patient were transferred to the ward for four to five days after resuming diet and removing the drains. Follow up was variable but patients were generally assessed one week after discharge. The second visit was scheduled after four weeks that was followed by at least three-monthly visit for the first year where patient had clinical examination and laboratory evaluation including tumor markers and liver function test. CT scan was usually performed six month after surgery to assess the early oncologic outcome of surgery, and repeated every six month in the first five years. Tumor markers were repeated every six months for the first five years as well. Patients were followed up by multidisciplinary team including a medical oncologist (among other disciplines as indicated) to evaluate patients and the need for adjuvant therapy in those who experience recurrence or metastasis.

2.4. Data analysis

Statistical analysis is performed by SPSS (Statistical package for social sciences) version 22. Descriptive statistics were only used, as the aim of this case series was to present our experience in HC in our institution and because of limited sample size for robust statistical analyses such as multivariable regression.

Our report is in concordance with Consensus Preferred Reporting Of CasESeries in Surgery (PROCESS) Guidelines (Supplementary Table 1) [12]. The Unique Identifying Number (UIN) of this case series is research registry is 6460 [13].

3. Results

Out of 40 patients who had surgical exploration, only 22 (55%) underwent a surgery with curative intent. The other18 patients had either peritoneal or liver metastases or very small future remnant liver (FRL). Table 1 and Table 2 show patient's characteristics and the type of performed surgery. Out of the 22 patients who underwent curative surgery, 14 (64%) were males and 8 (36%) were females with mean age of 59.1 years. Five patients [23] had Diabetes, and a similar number had hypertension. 9 patients have smoked cigarettes or Hookah, while only 2 patients were drinking alcohol regularly. The Bismuth grade were as follows: 7 IIIA, 6 IIIB, 5II, and 4 I. Table 3 summarizes the mortalities and Table 4 summarizes the morbidities.

There were three operative mortalities (13.6%), two due to liver failure secondary to insufficient remnant liver and one secondary to pulmonary embolism at post-operative day 8 despite prophylactic low molecular weight heparin administration and other prophylactic measures. Four (18%) patients developed major complications, three biliary fistulae that ceased after few weeks with conservative management (grade II Clavien-Dindo), and one intraabdominal collection that required reoperation(grade III Clavien-Dindo). As far as survival, four patients exceeded 9 years, two are still alive one of them operated in 1998, the other living patient was found to have primary lymphoma at biliary confluence that required adjuvant chemotherapy. The average survival is 43.3 months (range:3–286 months) Table 5.

4. Discussion

Cholangiocarcinoma is a rare disease it accounts to less than 2% of all malignancies [4] It is divided into intrahepatic and extrahepatic (perihilar or hilar from the cystic duct to left and right hepatic ducts) and distal cholangiocarcinoma. Hilar cholangiocarcinoma represents 60–70% of cases(1,5). The management of this challenging disease is multidisciplinary and surgery represents the only hope for cure [7,14]. Progression has been made in the management of this disease especially in operative and perioperative care and the mortality and morbidity has declined with significant improvement in survival[15–17].

Bismuth classification system was used for preoperative assessment of resectability [18]. This classification uses cholangiographic studies to assess the anatomical description and the local extension of the tumor. Type I below left and right hepatic ducts confluence), type II (involves the confluence), types IIIA and IIIB (involving the common hepatic duct and the either the right or left hepatic ducts, respectively), and type IV (reaching the confluence with both hepatic ducts) [18,19]. This classification system; however, has a limited prognostic value as it does not take the vascular involvement into account(19). Although it has been the standard way for preoperative assessment in HC, many other classification systems have been proposed to resolve the abovementioned limitations [5]. Future studies should focus on formulating a unified guidelines for classifying HC, to make it easier to discuss therapeutic plans and research results.

Four of our patients who underwent resection with curative intent survived more than 9 years. Histopathology of the tumor seems to play an important role in survival, as one of our cases is a primary lymphoma

Table 1
The general demographic characteristics of 22 patients who were included in the study.

Variable	Categories	N (%)
	Total	22 (100)
Age *		59.1 ± 1.9
BMI *, **		27.5 ± 2.7
Gender	**Males**	14 (64)
	Females	8 (36)
Comorbidities	**Hypertension**	5 (23)
	Diabetes	5 (23)
	Smoking history	9 (41)
	Alcohol consumption	2 (9)

*Presented as Mean ± standard deviation
** Body Mass Index

Table 2
The surgical details for each patient.

	Age (year)	sex	Bismuth grade	Type of resection	LN+	margin
1	63	M	IIIB	Extended right	2/11 positive	Free
2	75	F	IIIA	extended left	1/5 positive	Free
3	52	M	I	Local resection	0	Free
4	60	F	I	Local resection + whipple	3 positive	involved
5	42	M	IIIB	extended right	3/13 Positive	Free
6	65	M	II	Caudate lobectomy	0/5	Free
7	65	F	II	Caudate lobectomy	0	Free
8	70	F	I	Local resection	0	involved
9	67	M	II	Caudate lobectomy	0	involved
10	54	M	IIIA	Extended right	3/9 positive	involved
11	45	M	IIIA	Extended right	6/6 positive	Free
12	70	M	IIIB	Extended left	4/6 positive	Free
13	54	F	IIIA	Extended right	3/6 positive	Free
14	67	F	I	Local resection	4 positive	involved
15	72	M	IIIA	Extended right	4 positive	free
16	58	F	IIIB	Extended left	5 positive	free
17	64	M	IIIA	Extended right	3 positive	free
18	63	M	IIIB	Extended left	2 positive	free
19	51	M	IIIA	Extended right	0	free
20	57	F	IIIB	Extended left	2 positive	free
21	64	M	II	Caudate lobectomy	0	free
22	23	M	II	Caudate lobectomy	0	free

Table 3
The characteristics of the 3 post-operative mortalities in this series.

	age	Cause	grade
1	45	Pulmonary embolism	IIIA
2	70	liver failure	IIIB
3	72	liver failure	IIIB

Table 4
The characteristics of the 4 post-operative morbidities in this series.

	age	Type	Grade	evolution
1	63	Biliary fistula	IIIB	Healed after 4 weeks
2	62	Intraabdominal collection	II	reoperated and drained
3	70	biliary fistula	IIIB	died
4	64	Biliary fistula	IIIB	Healed after 3 weeks

Table 5
The characteristics of the long survivors of this series.

	Survival (weeks)	margin	Lymph node status	Type of histology
1	488	free	2/11	Moderately diff. adenocarcinoma
2	1144(still alive)	free	3/13	Papillary adenocarcinoma
3	486(still alive)	free	0	lymphoma
4	520	free	0	Moderately diff. adenocarcinoma

of the hepatic biliary confluence, and he had curative resection with adjuvant chemotherapy highlighting the role of multidisciplinary approach. Lymphoma should be considered in the differential diagnosis of a proximal bile duct stricture and it carries a more favorable prognosis than adenocarcinoma [20].

Free resection margin and negative lymph node involvement by malignancy has been found by most studies as the most significant factors of better survival(5). The resectability has improved for locally advanced cases and in patients with associated biliary disease like primary sclerosing cholangitis, orthotopic liver transplantation seems to offer good option with improved survival where resection is not feasible provided that patients go through a protocol of external beam radiotherapy, chemotherapy and brachytherapy using Iridium-192 beads delivered intraluminally [16]. Portal vein embolization (PVE) before major liver resection, has become an approach to minimize morbidity and mortality related to postoperative liver failure. In fact, we utilized this approach in our small case series after 2016 [17,21]. Photodynamic therapy followed by biliary stenting has proved to be superior to biliary stenting alone for palliation of unresectable perihilar choangiocarcinoma[22,23].

5. Conclusions

HC remains associated with poor prognosis, despite the improvement in perioperative care and in operative techniques. Free resection margins with lymph node involvement are the most significant factors of prognosis. Histologic type such as primary lymphoma and papillary carcinoma are also accompanied with long survival. Portal vein embolization should be considered if extended right hepatectomy is contemplated to minimize the risk of postoperative liver failure. Our results also shed light into the importance of multidisciplinary team work for proper risk-stratification and patient counselling. The inconsistency of patients' referral is one of the major challenges that hepatobiliary surgeons are facing. Given the rarity of this condition and the retrospective nature of the current literature, prospective or multicenter studies are needed to identify the factors associated with survival outcomes and compare different surgical techniques. Future research should focus on identifying preventable risk factors of morbidity and mortality.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Was approved by the IRB at the faculty of Medicine and Jordan University Hospital – June 2020

Sources of funding

None

Author contribution

Single author

Registration of research studies

1.Name of the registry:
2.Unique Identifying number or registration ID: ResearchRegistry6460
3.Hyperlink to your specific registration (must be publicly accessible and will be checked):
Indicated in manuscript

Guarantor

I accept full responsibility for this work.
Salam Daradkeh MD 17/01/2021

Declaration of competing interest

No competing conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.01.059.

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