

Staging laparoscopy for hilar cholangiocarcinoma in 100 patients

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Abstract

Purpose Accurate preoperative radiological staging of hilar cholangiocarcinoma remains difficult, and a number of patients are found to have irresectable advanced tumours or occult metastases at exploration. Staging laparoscopy can improve the detection of irresectable disease, avoiding unnecessary laparotomy. This study examines the role of staging laparoscopy in hilar cholangiocarcinoma, with a focus on yield over different time periods and identification of preoperative factors increasing the risk of irresectable disease.

Methods Retrospective case note review of all patients undergoing staging laparoscopy for radiologically resectable hilar cholangiocarcinoma, identified from the hepatobiliary multidisciplinary team database, was performed.

Results One hundred consecutive patients underwent staging laparoscopy between 1998 and 2011. Of these, 34 patients were found to be irresectable due to metastatic disease, and 11, due to extensive local disease. Fifty patients proceeded to exploratory laparotomy following staging laparoscopy, and 36 % (18/50) of whom were found to have irresectable disease: 12 patients due to advanced local disease and 6 patients due to metastases. The overall yield of laparoscopy was 45 %, and the accuracy was 71 %.

There was no significant difference in age, preoperative bilirubin, neutrophil/lymphocyte ratio, Ca19-9 levels or T stage between patients with resectable disease and with irresectable disease on laparoscopy. There was also no change

in the yield of laparoscopy over time, despite advances in radiological imaging.

Conclusion In this series, staging laparoscopy avoided unnecessary laparotomy in 45 % of patients with radiologically resectable hilar cholangiocarcinoma. No factor was able to predict positive yield, and therefore, all patients with potentially resectable hilar cholangiocarcinoma should undergo staging laparoscopy.

Keywords Laparoscopy · Neoplasm staging · Cholangiocarcinoma

Introduction

Resection is the only potential curative treatment for patients with hilar cholangiocarcinoma. Unfortunately, the majority of patients are not suitable for resection at presentation because of advanced local disease or distant metastases. Despite modern imaging techniques, the accuracy of preoperative radiological staging is poor, and a number of patients are found to have irresectable locally advanced tumours or occult metastases at surgical exploration.

Because of the significant morbidity and hospital stay associated with a negative laparotomy, a number of centres have utilised laparoscopy with or without intraoperative ultrasound to improve preoperative staging and to reduce the incidence of unnecessary laparotomy. This has shown to be particularly effective for those patients with T2/3 disease on radiological imaging [1].

Recently, there has been a suggestion that the yield of laparoscopy for hilar cholangiocarcinoma has decreased with the improved accuracy of imaging techniques, bringing into question its routine use in preoperative staging [2].

The aim of the present study was to examine the role of staging laparoscopy in hilar cholangiocarcinoma, with a

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particular focus on its usefulness over different time periods, and also to examine any factors which might increase the yield of laparoscopy by identifying patients at higher risk of irresectable disease.

Patients and methods

All patients referred to this unit with a provisional diagnosis of hepatopancreaticobiliary (HPB) malignancy are prospectively included on the HPB multidisciplinary team (MDT) database. From this database, we identified all patients referred since 1998 with a potential diagnosis of hilar cholangiocarcinoma. Those deemed potentially resectable following extensive radiological investigation and review of all imaging at a weekly HPB MDT conference were included in this study. All patients underwent ultrasound (US) and computed tomography (CT) evaluation, with a number also undergoing magnetic resonance cholangiopancreatography (MRCP). If there was concern about the quality of imaging performed at referring centres, the investigation was repeated in our unit. Preoperative biliary drainage, if required, was achieved by endoscopic or combined percutaneous endoscopic placement of plastic stents.

Staging laparoscopy was performed using a 10-mm umbilical port for the laparoscope with a further 12-mm port in the left or right upper quadrant as appropriate. A complete examination of the peritoneal cavity was performed including the liver, hepatoduodenal ligament, porta hepatis, pelvis and all peritoneal surfaces. Laparoscopic ultrasound was utilised in all patients unless clear peritoneal or liver metastases were identified and was used to assess for liver metastases, extent of hepatic disease and local vascular involvement by the tumour. Representative biopsies were taken from any suspicious lesions, and all peritoneal, liver or nodal metastases reported in this study were histologically proven. All staging laparoscopies were performed by or under the direct supervision of a consultant HPB surgeon. Initially, all intraoperative ultrasound studies were performed with a consultant radiologist; however, as the surgeons' expertise has increased, radiologists were only involved if there was doubt over the findings.

The Memorial Sloan Kettering Cancer Center criteria for irresectability were followed [3], namely, peritoneal metastases and discontinuous intrahepatic metastases; periduodenal, retropancreatic, common hepatic or coeliac nodal involvement; main portal vein involvement or bilateral involvement of secondary biliary radicles; or unilateral tumour extension to secondary biliary radicles with contralateral lobar atrophy or portal vein involvement. In those patients with irresectable disease, the majority were palliated with biliary stenting; however, a minority did undergo segment III hepaticojejunostomy if this had been unsuccessful.

Patient demographics, preoperative imaging, results of laparoscopic examination, findings at laparotomy and resections performed were analysed. Highest preoperative bilirubin, neutrophil/lymphocyte ratio (NLR) at presentation and preoperative Ca19-9 antigen levels were also analysed as potential factors that might identify those patients at higher risk of irresectable disease. NLR has been shown to be an adverse predictor of disease-free survival and has been associated with aggressive tumour biology in patients undergoing resection of intrahepatic cholangiocarcinoma [4].

Formal radiological staging of hilar cholangiocarcinoma has not routinely been used in our centre. Therefore, this was performed retrospectively using the T staging system proposed by the Memorial Sloan Kettering Cancer Center (MSKCC) [1]. Availability and quality of scans prior to the introduction of digital imaging was poor, and therefore, T staging was performed for those patients undergoing staging laparoscopy from 2005 onwards ($n=38$). This was carried out by a consultant radiologist with a specialist interest in HPB imaging who was blinded to the outcome of staging laparoscopy.

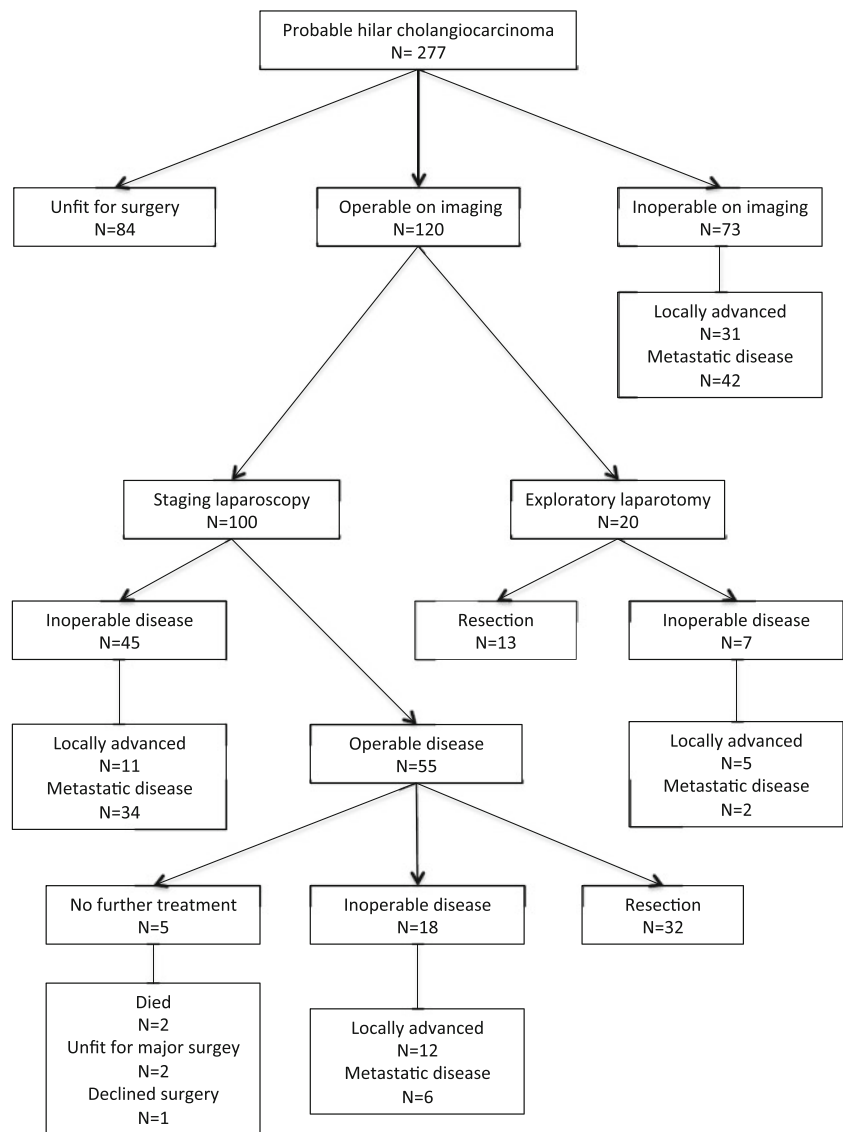
Statistical analysis was performed using the GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were compared using the Student's *t* test, and categorical variables were compared using Fisher's exact test. All tests were two-tailed, and $P \leq 0.05$ was taken as significant. The yield of laparoscopy was defined as the number of patients with irresectable disease at laparoscopy divided by the total number of patients undergoing laparoscopy. The accuracy of laparoscopy was defined as the number of patients with irresectable disease at laparoscopy divided by the total number of patients with unresectable disease at laparoscopy and laparotomy. The study was conducted in accordance with local research ethics committee standards.

Results

Between January 1998 and September 2011, our HPB MDT assessed 277 patients with a probable diagnosis of hilar cholangiocarcinoma. Figure 1 shows the management pathway for all these patients. Of these, 120 patients were deemed resectable on radiological grounds. Twenty patients proceeded directly to exploratory laparotomy at the discretion of the surgeon, with two surgeons in this centre not routinely performing staging laparoscopy for hilar cholangiocarcinoma. Of these 20 patients, 13 went on to undergo resection, whilst the remainder had irresectable disease: five patients due to extensive local disease and two due to peritoneal metastases. One hundred patients underwent staging laparoscopy and constitute the study population.

The median age of patients undergoing staging laparoscopy was 64.5 years (interquartile range (IQR) 55.25–72),

Fig. 1 Outcome of all patients referred to the hepatobiliary MDT with a potential diagnosis of hilar cholangiocarcinoma



constituting 49 males and 51 females. In addition to US and CT, MRCP was performed in 63 patients. Of those patients who did not undergo MRCP, all but four underwent alternative biliary imaging by either endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. One patient also underwent PET-CT. The median number of imaging studies per patient was 3. The T staging following radiological evaluation was T1 in 63 % (24/38), T2 in 26 % (10/38) and T3 in 11 % (4/38).

Staging laparoscopy was completed successfully in 99 patients; in the remaining patient, it was not possible to gain adequate views due to dense intra-abdominal adhesions following previous surgery. The findings of staging laparoscopy are shown in Table 1. All decisions where patients were deemed inoperable due to extensive hepatic disease were made following intraoperative ultrasound (IOUS) during staging laparoscopy. The overall yield of laparoscopy was 45 %, and the accuracy was 71 %.

Median length of stay following staging laparoscopy was 3 days (IQR 1–14.5 days), excluding those patients who proceeded to exploratory laparotomy during the same admission. There were no complications related directly to staging laparoscopy, other than one minor wound infection and one port site haematoma. Complications of ongoing biliary obstruction were seen in 11 % (11/100) of patients following staging laparoscopy and included cholangitis ($n=7$), hepato-renal failure ($n=2$), pancreatitis ($n=1$) and bile leak from a dislodged external biliary drain ($n=1$). The 30-day mortality following staging laparoscopy was 3 % (3/100) caused by hepato-renal failure ($n=1$), multi-organ failure due to cholangitis ($n=1$) and cardiac arrest of unknown cause ($n=1$).

Of the 55 patients deemed resectable following staging laparoscopy, 50 went on to exploratory laparotomy. The remaining five patients did not proceed to further surgery; two died whilst awaiting laparotomy (one patient from perforation at ERCP and one from multi-organ failure due to

Table 1 Findings at staging laparoscopy

Findings at laparoscopy (<i>n</i> =100)	no.
Resectable	55
Irresectable	45
Locally advanced disease	11
Peritoneal metastases	23
Liver metastases	7
Liver and peritoneal metastases	1
Nodal metastases	3

cholangitis), two were deemed unfit for major surgery on reassessment following laparoscopy (one patient developed widespread cholangitic liver abscesses, and one developed a left hepatic artery pseudoaneurysm), and one patient declined any further treatment. Of the 50 patients proceeding to exploratory laparotomy, 18 were found to have irresectable disease. In seven patients, the tumour was irresectable due to extensive hepatic involvement with bilateral extension to secondary biliary radicles. In five patients, vascular involvement precluded resection (left portal vein/right hepatic artery in one, main portal vein in three, main portal vein/common hepatic artery in one). Six patients were found to have metastatic disease: two patients with liver metastases (one with a very small lesion on the surface of the left lobe and one with bilobar small metastases not seen at laparoscopy), two patients with peritoneal disease and two patients with lymph node involvement outside the field of resection (one duodenal and one para-aortic). The median length of stay for patients after exploratory laparotomy and inoperable disease was significantly longer than that following staging laparoscopy and inoperable disease (16 days (9.75–22.75) vs. 2 days (1–17.5); $P=0.0067$).

In total, 32 patients underwent resection following staging laparoscopy. All patients had excision of their extrahepatic biliary tree (the supraduodenal bile duct and gallbladder), and 94 % (30/32) of patients underwent concomitant liver resection as follows: 24, right trisectionectomy (with one concomitant portal vein resection); 5, left lobectomy; and 1, right trisectionectomy with Whipple's pancreaticoduodenectomy. Laparotomy was performed immediately following laparoscopy

in 19 patients; the median time span between laparoscopy and laparotomy was 6.5 days (IQR 0–16.5 days).

Further analysis was performed in an effort to identify factors determining unresectable disease at laparoscopy, which might allow more selective use of staging laparoscopy in hilar cholangiocarcinoma. There was no significant difference in age, highest preoperative bilirubin, neutrophil/lymphocyte ratio at presentation, preoperative Ca19-9 antigen levels or T staging between those patients with resectable disease and those patients with irresectable disease (Table 2).

Further analysis was performed to investigate whether the yield of staging laparoscopy had changed over time, with improvements particularly in radiological imaging. Up to and including 2004, the yield of staging laparoscopy was 44 % (18/41), and from 2005 onwards, the yield was 46 % (27/59) ($P=1.00$). The pattern of irresectable disease also did not change significantly over time with 72 % (13/18) of patients irresectable due to metastatic disease (liver, peritoneal or nodal) in the earlier period and with 77 % (21/27) in the latter period ($P=0.732$).

Discussion

Despite advances in preoperative imaging, many patients with hilar cholangiocarcinoma will be found to have unresectable disease at exploratory laparotomy. Patients with unresectable disease have a median survival of around 8 months [1], and it is, therefore, important to avoid the hospital stay and prolonged recovery associated with a negative laparotomy and any delay before the start of palliative chemotherapy.

Although there are a number of reports in the literature of the use of staging laparoscopy for hepatobiliary malignancies, only a few report specific outcomes for hilar cholangiocarcinoma (see Table 3). It is of interest the wide variation in yields reported across these studies. The yield of staging laparoscopy is dependent on two main factors: the quality of the preoperative imaging and the quality of the laparoscopic technique. One way of potentially improving the quality of the laparoscopic technique is to include IOUS assessment. This allows more objective evaluation of the extent of local tumour in-

Table 2 Characteristics of patients with resectable vs. irresectable disease at staging laparoscopy

	Resectable (<i>n</i> =55)	Irresectable (<i>n</i> =45)	<i>P</i> value
Age (median (IQR))	64 (53–71)	67 (57.5–73.5)	0.279
Bilirubin ($\mu\text{mol/L}$)	230 (± 21.5)	253 (± 28.1)	0.516
Neutrophil/lymphocyte ratio	5.4 (± 0.83)	5.4 (± 0.49)	0.993
Ca19-9 antigen (Ku/L)	1,632 (± 512)	5,636 (± 3133)	0.216
Radiological T staging	(<i>n</i> =19)	(<i>n</i> =19)	
T1	13	11	0.753
T2	4	6	
T3	2	2	

All data are presented as mean \pm SEM unless otherwise stated

Table 3 Studies of staging laparoscopy in hilar cholangiocarcinoma

Author	Year	No.	Yield (%)	Accuracy (%)	Use of IOUS
Ruys [2]	2011	175	14	32	4/175
Tilleman [5]	2002	110 ^a	41	59	74/110
Present study	2013	100	45	71	All
Connor [6]	2005	84	42	53	All
Weber [1]	2002	56	25	42	23/56
Goere [7]	2006	20	25	45	None

^a Included six patients with gallbladder carcinoma

volvement. Although no comparative study has been conducted of staging laparoscopy for hilar cholangiocarcinoma with or without IOUS, it is interesting to note that the three studies with the highest yield, the current study and those by Tilleman et al. [5] and Connor et al. [6], all made use of IOUS. Those against the use of IOUS argue that inflammation from biliary stents makes interpretation difficult, and those patients with extensive vascular involvement should be detected on preoperative imaging. Another concern about deeming patients irresectable on the basis of advanced local disease on IOUS is that it is not possible to assess the actual false positive rate, i.e. patients deemed irresectable on IOUS who are indeed resectable, without subjecting these patients to a trial dissection. As such, the true accuracy of IOUS or indeed staging laparoscopy has not been determined, and the commonly used definition of accuracy is actually only the true negative rate. It is a valid criticism of this study that the assumption was made in the 11 patients deemed inoperable on staging laparoscopy due to extensive hepatic disease that the appearances were due to tumour rather than an inflammatory response. Of note, in three of these patients, there was macroscopic invasion of tumour into extrahepatic tissues clearly precluding resection. Furthermore, over the later years of the study, the practice of the unit evolved, with a smaller proportion of patients deemed inoperable on staging laparoscopy due to extensive local disease.

A further factor influencing the yield of staging laparoscopy is the surgical strategy adopted by the unit. The less aggressive the strategy, the more patients may be excluded due to unfavourable findings at laparoscopy. It is worthy of mention that the surgical approach taken by this unit is not highly aggressive. Only one patient underwent portal vein resection and patch repair, and no arterial resections were carried out. There remains little evidence for hepatic artery resection in hilar cholangiocarcinoma, and long-term survival in reported studies is dismal [8]. However, three patients in this study had tumours deemed inoperable due to portal vein involvement, which may have been resected in other more aggressive units. Clearly, this would have an influence on the yield of staging laparoscopy seen in this study.

The other reason for high yields for staging laparoscopy, such as those in this study, is poor quality preoperative

imaging. It is not possible to refute this argument completely without an independent expert review of all the imaging. However, it is possible to indirectly assess the quality of imaging by other means. The imaging modalities used are clearly important, and in this study, all patients deemed potentially fit for surgery were assessed with at least two imaging techniques, and 63 % of patients underwent MRCP. A further indicator is the number of patients deemed irresectable at presentation. In the current study, 26 % (73/277) of all patients presenting to this centre with a provisional diagnosis of hilar cholangiocarcinoma were deemed irresectable on radiological grounds (see Fig. 1). This is in keeping with other centres [1, 3] and suggests that operability was not dramatically over-assessed on radiological imaging. Furthermore, the T staging gives an overall indicator of extent of disease and, again, the T staging of patients undergoing staging laparoscopy in this study compares favourably to those in other studies. Nevertheless, there were at least six patients in this study for whom the extent of hepatic disease was clearly underestimated on imaging and were subsequently found to be irresectable due to extensive hepatic disease at staging laparoscopy. It is recognised that the assessment of tumour involvement by CT is not definitive, with estimates of sensitivity from meta-analysis reported at 86 % [9].

It is also important to interpret the yields of staging laparoscopy in light of the actual findings precluding resectability. Peritoneal disease and small liver metastases are unlikely to be identified on even the highest quality radiological imaging. In the current study, the yield of staging laparoscopy for occult metastatic disease was 34 %. Therefore, even if it is argued that radiological imaging might have underestimated the extent of local disease in this study, 34 % of patients were still saved from unnecessary laparotomy on sole basis of small volume metastatic disease undetectable on preoperative imaging, but detected at laparoscopy. Interestingly, the yield for metastatic disease in the current study was higher than that reported by Weber et al. (25 %) [1], Connor et al. (25 %) [6] and Ruys et al. (13 %) [2]. Why this should be the case is not clear, but it does not appear to be related to more advanced local disease in our population, as the T staging of the study populations appears similar or indeed favourable in the current study.

Ideally, staging laparoscopy would be targeted to those patients at higher risk of locally advanced or occult metastatic disease. Useful predictors would include preoperative blood tests and radiological staging. Unfortunately, this study has not identified any significant differences in preoperative bilirubin, NLR or Ca19-9 antigen levels between patients with irresectable or resectable disease at laparoscopy precluding their use in this setting. The study from MSKCC previously suggested the yield of staging laparoscopy to be significantly lower in T1 vs. T2/3 hilar cholangiocarcinoma [1]. The current study does not support this finding, with 46 % (11/24) of patients with T1 tumours having irresectable disease on laparoscopy. This

was due to occult metastases in 80 % (9/11) of these patients rather than locally advanced disease and, therefore, cannot be explained by inaccurate radiological staging.

The study by Ruys et al. found a significant fall in the yield of staging laparoscopy for hilar cholangiocarcinoma over time, from 41 % between 1993 and 2000 to 14 % between 2000 and 2010 [2]. As such, they have suggested that the role of staging laparoscopy in hilar cholangiocarcinoma be reconsidered. It is important to note, however, that the accuracy of staging laparoscopy also fell over the time periods above, from 72 to 32 %, which accounts for a significant proportion of the fall in yield. This fall in accuracy included 33 patients with metastatic disease missed at laparoscopy. Certainly, the findings of the current study refute the suggestion that the yield of laparoscopy has decreased in recent years, with no change in yield between 1998–2004 and 2005–2011. Indeed, whilst radiological imaging remains unable to accurately detect peritoneal and small volume liver metastases, the yield of staging laparoscopy will remain significant. PET-CT provides a potential enhancement to the radiological staging of hilar cholangiocarcinoma and may be seen as an alternative to staging laparoscopy. PET-CT has been shown to accurately detect metastatic disease and lymph node involvement [10], although the reported sensitivities are 42–67 and 33–55 % for lymph node metastases and for distant metastases, respectively [11, 12].

At present, there is no accurate method of predicting those patients at risk of positive findings at laparoscopy. In particular, the T stage of the tumour does not influence the likelihood of occult metastatic disease.

This study has demonstrated a high yield of staging laparoscopy in patients with hilar cholangiocarcinoma deemed resectable after extensive radiological imaging. Overall, 45 % of patients were potentially saved an unnecessary laparotomy by undergoing staging laparoscopy. It is the authors' view that given our centre's patient population and surgical approach, all patients with potentially resectable hilar cholangiocarcinoma should undergo staging laparoscopy. However, whether this approach is valid for all centres, particularly those with a more aggressive surgical approach, requires further study.

Conclusion

All patients with potentially resectable hilar cholangiocarcinoma on radiological grounds should undergo staging

laparoscopy, as this procedure potentially prevents a futile laparotomy in approximately 45 % of patients.

Conflicts of interest None.

References

- Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR (2002) Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. *Ann Surg* 235:392–399
- Ruys AT, Busch OR, Gouma DJ, van Gulik TM (2011) Staging laparoscopy for hilar cholangiocarcinoma: is it still worthwhile? *Ann Surg Oncol* 18:2647–2653
- Burke EC, Jarnagin WR, Hochwald SN, Pisters PWT, Fong Y, Blumgart LH (1998) Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 228:385–394
- Gomez D, Morris-Stiff G, Toogood GJ, Lodge JP, Prasad KR (2008) Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. *J Surg Oncol* 97:513–518
- Tilleman EH, de Castro SM, Busch OR, Bemelman WA, van Gulik TM, Obertop H et al (2002) Diagnostic laparoscopy and laparoscopic ultrasound for staging of patients with malignant proximal bile duct obstruction. *J Gastrointest Surg* 6:426–30, discussion 430–1
- Connor S, Barron E, Wigmore SJ, Madhavan KK, Parks RW, Garden OJ (2005) The utility of laparoscopic assessment in the preoperative staging of suspected hilar cholangiocarcinoma. *J Gastrointest Surg* 9: 476–480
- Goere D, Waghholikar GD, Pessaux P, Carrere N, Sibert A, Vilgrain V et al (2006) Utility of staging laparoscopy in subsets of biliary cancers: laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 20:721–725
- Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M et al (2007) Combined vascular resection for hilar cholangiocarcinoma: does it work or not? *Surgery* 141:581–8
- Ruys AT, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, van Gulik TM (2012) Radiological staging in patients with hilar cholangiocarcinoma: a systematic review and meta-analysis. *Br J Radiol* 85: 1255–62
- Fritshcer-Ravens A, Bohuslavizki KH, Broering DC, Jenicke L, Schafer H, Buchert R et al (2001) FDG PET in the diagnosis of hilar cholangiocarcinoma. *Nucl Med Commun* 22:1277–85
- Li J, Kuelh H, Grabellus F, Muller SP, Radunz S, Antoch G et al (2008) Preoperative assessment of hilar cholangiocarcinoma by dual modality PET/CT. *J Surg Oncol* 98:438–43
- Ruys AT, Bennink RJ, van Westreenen HL, Engelbrecht MR, Busch OR, Gouma DJ et al (2011) FDG-positron emission tomography/computed tomography and standardized uptake value in the primary diagnosis and staging of hilar cholangiocarcinoma. *HPB (Oxford)* 13:256–62