UNIVERSITÉ TOULOUSE III – PAUL SABATIER
FACULTÉS DE MÉDECINE

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THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

MÉDECINE SPÉCIALISÉE CLINIQUE

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par

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PRÉVENTION DE LA FISTULE BILIAIRE POST-OPÉRATOIRE APRÈS HÉPATECTOMIE PAR DRAINAGE BILIAIRE TRANSCYSTIQUE

UN ESSAI CLINIQUE PROSPECTIF RANDOMISÉ MULTICENTRIQUE

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DECEMBRE 2018

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RANDOMIZED CLINICAL TRIAL OF BILIARY FISTULA PREVENTION AFTER HEPATECTOMY BY TRANSCYSTIC BILIARY DRAINAGE

TABLE DES MATIÈRES

ABBREVIATIONS

ASA: American Society of Anesthesiologists score

BMI: Body Mass Index

ITT: Intent-to-treat

POD: Postoperative day

SD: Standard deviation

INTRODUCTION

Biliary fistula is one of the most common complications after hepatic resection and it remains a major cause of increased morbidity (1–3). The rate of biliary leakage after hepatectomy without biliary reconstruction has been reported to vary from 3.6% to 26% (3–14). In addition to increasing the morbidity and the duration of hospitalization, this complication can be fatal for the patient as a result of a vicious circle involving sepsis, liver failure, and death (2,6–8,11). No published study to date has provided a way to prevent such fistulas after hepatectomy.

The use of leak tests (15), abdominal drainage (16,17), or treatment of the hepatic slice by fibrin sealants (18) is not currently based on solid scientific recommendations but rather on routine procedures or the surgeons' intuitions (3,19). However, a case-control study published in 2003 by Hotta et al (5) of 66 patients reported a significant decrease in the biliary fistula rate after hepatectomy when a transcystic drain was placed at the end of the surgery: 3.6% versus 26.3% in the group without a transcystic catheter. It has been reported in literature that the biliary fistula risk increases with major hepatectomies, left hepatectomy, hepatectomies involving segment VIII, high blood loss, a prolonged operation time, pedicle dissection, a long duration for the Pringle maneuver, and a large parenchymal transection width (3,6,11,20,21).

Rational implementation of a transcystic catheter during hepatectomy to decrease the fistula levels is based on the fact that hyperpressure in bile ducts often occurs after hepatectomy (22,23) (especially due to pedicular clamping), which increases bile extravasation by recanalization of closed bile ducts. Setting up a transcystic catheter would allow for decompression of the intraductal pressure, thereby preventing bile leakage from the biliary branches (21).

This hypothesis is supported by two observations: 1/ The treatment of major and/or chronic biliary leakage after hepatectomy can be treated by biliary endoprosthesis or a biliary drain (nasobiliary or mixed drain) (6,12,24–26); 2/ surgical treatment of common bile duct

stones with external biliary drainage can reduce the risk of postoperative biliary fistula (27,28).

This study aimed to assess the effect of biliary drainage with a transcystic catheter on the occurrence of biliary fistula in the postoperative period.

METHODS

Trial Design and Population Study

This study is a prospective multicenter, open-label, randomized, superiority phase III clinical trial carried out from May 2009 to December 2016 at nine centers in France. Patients who underwent a hepatectomy that removed at least two segments on non-cirrhotic liver by laparotomy were randomized into two groups with a 1:1 ratio: a control group of patients without external biliary drainage and a transcystic group of patients with external biliary drainage by a transcystic catheter. The eligibility criteria are detailed in Table 1. Two inclusion criteria were definitively evaluated perioperatively: a hepatectomy of at least two segments and a non-cirrhotic liver.

All of the patients provided signed written informed consent before participating in the study. The inclusion and the randomization were performed by the surgeon during the procedure, after having carried out the hepatectomy and after having checked the eligibility criteria. Patients were randomly assigned to either transcystic group or control group by means of the closed envelope method. Each patient was monitored for three months after the surgery. The data were collected at each center and were sent to the investigator center for analysis. The trial was approved by the local ethics and committee, it complied with good clinical practices and the declaration of Helsinki, and it was funded by the French government (ClinicalTrials.gov Identifier # NCT01469442).

Surgery and Biliary Drainage Techniques

The hepatectomy was performed according to the usual practices of the operator and with their own equipment for parenchyma transection. Likewise, treatment of the liver slice, with or without hemostatic equipment, was at the operator's discretion. The biliary drain that was used was a transcystic drain. The caliber of the drain was as large as possible. After the hepatectomy and cholecystectomy, the remaining cystic duct was cut and the transcystic catheter was inserted into the common bile duct via the cystic duct and held in place by a

resorbable suture. Bile reflux into the drain was confirmed and cholangiography was performed to verify its proper positioning and the absence of leakage around the cystic duct. A bile leakage test (methylene blue or air test) was systematically performed to eliminate "obvious" biliary fistulas. An intra-abdominal drain was placed around the resected area at the end of the procedure. The type of drain was at the operator's discretion. The transcystic drain was externalized without traction. The transcystic drain was positioned in the most sloping position. The transcystic catheter was clamped at postoperative day 7 (POD7) and removed at least 5 weeks after the surgery. The operating technique was standard and was not specific to this study.

Endpoints

The primary endpoint was the occurrence of a clinically relevant biliary fistula during the postoperative period (i.e., within 30 days of the surgery or during the initial hospitalization if the hospitalization lasted more than 30 days). A clinically relevant biliary fistula was defined as the occurrence of bile in the drainage fluid for more than 48 hours, intra-abdominal bile collection authenticated after percutaneous drainage or surgical revision, or biliary peritonitis discovered during surgical revision. No systematic postoperative examinations were conducted for this study. Imaging tests were performed based on the clinical findings.

The secondary endpoints were (1) overall morbidity defined by the occurrence of at least one complication during the postoperative period; (2) postoperative mortality defined as death within 30 days of the surgery or during the initial hospitalization; (3) a specific treatment for biliary fistula defined by any treatment undertaken to dry the biliary fistula (e.g., a stent, bile drain, etc.); (4) the duration of the hospital stay and admission to the intensive care unit.

Sample Size

This study compares the occurrence of biliary fistula between the two groups during the postoperative period. The following statistical parameters were used to calculate the number of subjects required: comparison of two percentages, with an alpha risk of 5% and a power of 80%. This trial was a superiority assay because the use of biliary drainage during hepatectomy is currently performed by surgeons without strong evidence of its benefit in the literature. Moreover, the use of transcystic drainage is only clinically relevant if this procedure is safe and results in a decrease in the postoperative biliary fistula rate. The conclusion of superiority trials can have major impacts by promoting changes to controversial clinical practices (29).

According to the literature (3–13), a biliary fistula rate of 15% could be expected in the control group. The sample size was estimated to reveal a difference of 10% between the two groups for the primary endpoint, since such a difference would be clinically relevant. The sample size calculated with a biliary fistula rate divided by 3 in the transcystic group, with an anticipated biliary fistula rate of 5%, was 304 patients (152 patients in each group). The cases lost to follow-up were not tacked into account in this study because the randomization was performed during the hepatectomy and the follow-up time was short, with a follow-up consultation at 3 months after the surgery that was systematic at all of the centers.

Statistical Analysis

All of the statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Univariable analyses were performed to explore the effect of potential risk factors on the primary endpoint using exact logistic regressions. Qualitative variables were described as numbers (percentages) and quantitative variables as means ± the standard deviation. The two groups were compared using the χ^2 or Fisher's exact tests when

appropriate. A *P*-value of less than 0.05 was considered statistically significant. Analyses were by intent-to-treat (ITT) and per-protocol.

RESULTS

Population study

In this trial, 310 patients were randomized by nine French centers, 307 were included in the intention-to-treat analysis, of which 158 patients were assigned to the transcystic group and 149 patients to the control group. The three excluded patients were withdrawn from the study on the day of the surgery. Seven patients were determined to not be eligible after randomization, mainly due to major deviations from the protocol (e.g., cirrhotic liver or a history of cholecystectomy), but they were included in the intention-to-treat main analysis. In the per-protocol analysis, 156 patients in the transcystic group and 144 patients in the control group were analyzed. A flowchart outlining the key aspects of this study is shown in Figure 1.

In terms of the demographic characteristics at inclusion, 60.8% of the patients were males and the age of the patients ranged from 28 to 87 years, with a mean age of 61.5 ± 11.1. Most of the patients had surgery for a malignant tumor (n = 291, 94.8%), including 195 patients (63.5%) for an adenocarcinoma. The surgery was usually performed using clamping (n = 230, 75.2%), with a mean duration of 34.2 min ± 30.9. The mean number of resected hepatic segments was 3.8 ± 0.94, the mean duration of the surgery was 4.7 hours ± 1.6, and the mean blood loss was 740 ml ± 637.9. The mean size of the transcystic catheter was 6 mm ± 5.1, and the mean the parenchymal transection length was 147.9 mm ± 56.2. The clinical and the surgical characteristics of the ITT population are detailed in Table 2.

Primary endpoint

Of the 307 patients considered in the ITT analysis, a clinically relevant postoperative biliary fistula occurred in 18 patients (5.9%): 9 patients (6%) in the control group and 9 patients (5.7%) in transcystic group, with no significant difference being noted between the two groups ($P = 1$). In the per-protocol analysis, there were again no significant differences between the two groups ($P = 1$) (Table 3). Nine patients had biliary peritonitis, three patients

had an external biliary fistula, and 11 patients had a bilioma. Details of the discovery of the primary endpoint are presented in Table 3.

Secondary endpoints

Among the ITT cohort, 147 patients (47.9%) reported at least one postoperative complication: 69 patients (46.9%) in the control group and 78 patients (49.4%) in the transcystic group, with no significant difference between the groups (P = 0.731). In the transcystic group, 5 patients (3.2%) had postoperative liver failure versus 2 patients (1.3%) in the control group, with no significant difference between the groups. Eleven patients died during the postoperative period, 7 patients (4.7%) in the control group and 4 patients (2.5%) in the transcystic group, with no significant difference between the groups (P = 0.367).

After clamping, the transcystic catheter has to be unclamped in 9 patients. Among these 9 patients, 4 patients had septic complications after clamping: 3 patients developed hyperthermia and one patient had hyperleukocytosis.

The median duration of the biliary fistula was 12 days (5-22) for the control group and 25 days (17.5-32) for the transcystic group. The median delay between discovery of the biliary fistula and specific treatment was 10 days (8-11) for the control group and 15 days (9.5-17.5) for the transcystic group. These differences were not statistically significant. Among the patients with biliary fistula during the postoperative period (9 patients in each group), 6 patients (75.0%) in the control group received a specific treatment (1 endoprosthesis, 3 percutaneous bilioma drainages, 2 revision surgeries, and 1 another type of specific treatment). Five patients (62.5%) in the transcystic group received a specific treatment (1 endoprosthesis, 2 percutaneous bilioma drainages, 1 revision surgeries, and 1 another type of specific treatment). There was not a significant difference between the groups (P = 1).

In the control group, 43 patients (29.1%) were transferred to the intensive care unit versus 44 patients (28.0%) in the transcystic group. The proportions were not significantly different between the groups ($P = 0.899$).

The reoperation rate was 7.2%. This rate was not significantly different between the control group (10.1%) and the transcystic group (4.4%) ($P = 1$).

There was a significant difference in the duration of the hospitalization between the groups, with a median duration of 10 days for the control group and 11 days for the transcystic group ($P = 0.042$).

Estimation of risk factors of postoperative biliary fistula

Univariable analysis of risk factors of the occurrence of biliary fistula after hepatectomy is reported in Table 4 (Tables 4a and 4b). Only the parenchymal transection length was significantly associated to the risk of biliary fistula during the postoperative period (an odds ratio = 1.01; 95% confidence interval 1.000-1.020; $P = 0.049$), with a higher risk when the length increases. A trend was also observed for the of the parenchymal transection width (odds ratio = 1.01; 95% confidence interval 1.000-1.018; $P = 0.052$) (Table 4b).

DISCUSSION

This prospective randomized trial evaluates the effect of biliary drainage with a transcystic catheter during hepatectomy on the occurrence of postoperative biliary fistula. The primary endpoint was the occurrence of a biliary fistula during the postoperative period (i.e., within 30 days of the surgery or during the initial hospitalization if the hospitalization lasted more than 30 days), including external biliary fistula, bilioma, and biliary peritonitis. This study shows that the presence of a transcystic catheter during hepatectomy does not reduce the risk of postoperative biliary fistula even in presence of any of the risk factors identified for postoperative bile leak (hepatectomies involving segment VIII, large parenchymal transection width…).

Hotta et al. (5) reported a significant decrease in the rate of biliary fistula after hepatectomy when a transcystic drain was placed at the end of the surgery (3.6% versus 26.3% in the control group). However, the results were subject to numerous potential biases, in particular because the study was retrospective, non-randomized, monocentric, and it had a very limited number of included patients (66 patients). A beneficial impact on postoperative biliary fistula has also been reported with T-tube insertions in the choledochal duct in a subgroup of patients with extended hemihepatectomies (30). By contrast, other authors have not found any evidence of a difference in the frequency of bile leakage in patients with or without transcystic tube insertion (10,21,31). Some studies, including experimental animals studies, even indicate that external biliary drainage is not only useless but that it is in fact associated with significantly worse liver regeneration after hepatectomy due to loss of bile acid from the intestine during the external drainage (31–33). In this study, there was not a significant difference in terms of postoperative liver failure between the groups.

The results of this randomized trial are a reason to bring an end to the controversy regarding the use of biliary drainage during hepatectomy which is variable between surgical teams and only based on retrospective studies (5,10,21,31).

The proportion of biliary leakage in the control group (6%) was considerably below the expected rate of 15% assumed for the sample size computation in the study protocol. The rates of biliary fistula that have been reported in the literature vary from 3.6% all the way to 26% (3–14), with a trend of increasing rates in the past decade due to the higher complexity of liver resections in recent times (1–3,34), whereas the trend for morbidity and mortality is a decrease due to improvements in terms of surgical skills and techniques. First, the primary hypothesis of a biliary fistula rate after hepatectomy of 15% was mainly based on retrospective observational studies, which are clearly subject to significant biases (3–14). Secondly, in this study, the definition of bile leakage was not based on the ISGLS definition (1) because the ISGLS definition was released in 2011 whereas the study protocol was devised in 2008. Therefore, no systematic postoperative examinations were carried out for this study, which implies that the bilirubin concentration in the drainage fluids was not systematically determined after the surgery. This may have led to an underestimation of the rate of biliary fistula (particularly grade A of the ISGLS), although it did not impact the primary endpoint of this study because the two groups were comparable as a result of the randomization. Moreover, the lack of bilirubin measurements did not affect the results of this study because only the ISGLS grade A biliary fistulas were not described, while ISGLS grade B/C biliary fistulas were assayed, which is clinically more relevant (Grade B bile leakage requires active therapeutic intervention but is manageable without relaparotomy, whereas in Grade C, bile leakage relaparotomy is required) (1). Thirdly, the inclusion of patients took place in high-volume centers with considerable expertise in hepatic surgery. Therefore, the biliary fistula rate would presumably have been higher if this study had included centers with less expertise.

The 7-year duration of this study reflects the difficulty with patient inclusion by the centers, which is likely due to patients being reluctant to have to put up with a drain for several weeks after the surgery. This long study duration should, however, not be considered

to be a liability because there has been no tangible progress in the past ten years in terms of prevention or treatment of postoperative biliary fistula, so this study was not influenced by time in regard to the primary endpoint.

In this study, only an increase in the parenchymal transection length was significantly associated with the risk of biliary fistula during the postoperative period. A similar trend was also observed for the parenchymal transection width. Other known predictive factors of biliary fistula such as major hepatectomies, left hepatectomy, hepatectomies involving segment VIII, high blood loss, a prolonged operation time, pedicle dissection, and a long duration of the Pringle maneuver (3,6,11,20,21) were not independent predictors of biliary fistula in this study. This was presumably due to an insufficient number of patients because the number of subjects calculated for this study was based on the primary endpoint. The fact that an increase in the length and the parenchymal transection width are relevant risk factors in this study suggests that these factors have a major effect on the occurrence of postoperative biliary fistula and must hence be considered very carefully by surgeons during liver resections.

This prospective randomized trial does not demonstrate superiority of transcystic biliary drainage during hepatectomy to prevent biliary fistula. The use of transcystic drainage during hepatectomy to prevent postoperative biliary fistula should not be recommended.

Vu permis d'imprimer
Le Doyen de la Faculté
De Médecine Rangueil

8/04/19

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REFERENCES

1. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011 May;149(5):680–8.

2. Zimmitti G, Roses RE, Andreou A, Shindoh J, Curley SA, Aloia TA, et al. Greater complexity of liver surgery is not associated with an increased incidence of liver-related complications except for bile leak: an experience with 2,628 consecutive resections. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2013 Jan;17(1):57–64; discussion p.64-65.

3. Mohkam K, Farges O, Vibert E, Soubrane O, Adam R, Pruvot F-R, et al. Risk score to predict biliary leakage after elective liver resection. Br J Surg. 2018 Jan;105(1):128–39.

4. Guillaud A, Pery C, Campillo B, Lourdais A, Sulpice L, Laurent S, et al. Incidence and predictive factors of clinically relevant bile leakage in the modern era of liver resections. HPB. 2013 Mar;15(3):224–9.

5. Hotta T, Kobayashi Y, Taniguchi K, Johata K, Sahara M, Naka T, et al. Postoperative evaluation of C-tube drainage after hepatectomy. Hepatogastroenterology. 2003 Apr;50(50):485–90.

6. Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M, et al. Bile leakage after hepatic resection. Ann Surg. 2001 Jan;233(1):45–50.

7. Capussotti L, Ferrero A, Viganò L, Sgotto E, Muratore A, Polastri R. Bile leakage and liver resection: Where is the risk? Arch Surg Chic Ill 1960. 2006 Jul;141(7):690–4; discussion 695.

8. Yoshioka R, Saiura A, Koga R, Seki M, Kishi Y, Yamamoto J. Predictive factors for bile leakage after hepatectomy: analysis of 505 consecutive patients. World J Surg. 2011 Aug;35(8):1898–903.

9. Squires MH, Lad NL, Fisher SB, Kooby DA, Weber SM, Brinkman A, et al. Value of primary operative drain placement after major hepatectomy: a multi-institutional analysis of 1,041 patients. J Am Coll Surg. 2015 Apr;220(4):396–402.

10. Nanashima A, Abo T, Shibuya A, Tominaga T, Matsumoto A, Tou K, et al. Does the placement of a cystic duct tube after a hepatic resection help reduce the incidence of post-operative bile leak? HPB. 2013 Jul 1;15(7):517–22.

11. Tanaka S, Hirohashi K, Tanaka H, Shuto T, Lee SH, Kubo S, et al. Incidence and management of bile leakage after hepatic resection for malignant hepatic tumors. J Am Coll Surg. 2002 Oct;195(4):484–9.

12. Nagano Y, Togo S, Tanaka K, Masui H, Endo I, Sekido H, et al. Risk factors and management of bile leakage after hepatic resection. World J Surg. 2003 Jun;27(6):695–8.

13. Reed DN, Vitale GC, Wrightson WR, Edwards M, McMasters K. Decreasing mortality of bile leaks after elective hepatic surgery. Am J Surg. 2003 Apr;185(4):316–8.

14. Donadon M, Costa G, Cimino M, Procopio F, Del Fabbro D, Palmisano A, et al. Diagnosis and Management of Bile Leaks After Hepatectomy: Results of a Prospective Analysis of 475 Hepatectomies. World J Surg. 2016 Jan;40(1):172–81.

15. Zimmitti G, Vauthey J-N, Shindoh J, Tzeng C-WD, Roses RE, Ribero D, et al. Systematic use of an intraoperative air leak test at the time of major liver resection reduces the rate of postoperative biliary complications. J Am Coll Surg. 2013 Dec;217(6):1028–37.

16. Belghiti J, Kabbej M, Sauvanet A, Vilgrain V, Panis Y, Fekete F. Drainage after elective hepatic resection. A randomized trial. Ann Surg. 1993 Dec;218(6):748–53.

17. Brooke-Smith M, Figueras J, Ullah S, Rees M, Vauthey J-N, Hugh TJ, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. HPB. 2015 Jan;17(1):46–51.

18. de Boer MT, Klaase JM, Verhoef C, van Dam RM, van Gulik TM, Molenaar IQ, et al. Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial. Ann Surg. 2012 Aug;256(2):229–34.

19. Farges O, Vibert E, Cosse C, Pruvot FR, Le Treut YP, Scatton O, et al. “Surgeons’’ intuition" versus ‘prognostic models’: predicting the risk of liver resections.” Ann Surg. 2014 Nov;260(5):923–8; discussion 928-930.

20. Benzoni E, Cojutti A, Lorenzin D, Adani GL, Baccarani U, Favero A, et al. Liver resective surgery: a multivariate analysis of postoperative outcome and complication. Langenbecks Arch Surg. 2007 Jan;392(1):45–54.

21. Sakamoto K, Tamesa T, Yukio T, Tokuhisa Y, Maeda Y, Oka M. Risk Factors and Managements of Bile Leakage After Hepatectomy. World J Surg. 2016 Jan;40(1):182–9.

22. Ijichi M, Takayama T, Toyoda H, Sano K, Kubota K, Makuuchi M. Randomized trial of the usefulness of a bile leakage test during hepatic resection. Arch Surg Chic Ill 1960. 2000 Dec;135(12):1395–400.

23. Aktekin A, Gurleyik G, Odabasi M, Muftuoglu T, Saglam A. Trans-cystic biliary catheterization and decompression in liver and biliary surgery. Hepatogastroenterology. 2013 Aug;60(125):985–8.

24. Nakai T, Kawabe T, Shiraishi O, Shiozaki H. Prevention of bile leak after major hepatectomy. Hepatogastroenterology. 2004 Oct;51(59):1286–8.

25. Sherman S, Shaked A, Cryer HM, Goldstein LI, Busuttil RW. Endoscopic management of biliary fistulas complicating liver transplantation and other hepatobiliary operations. Ann Surg. 1993 Aug;218(2):167–75.

26. Farhat S, Bourrier A, Gaudric M, Dousset B, Scatton O, Chaussade S, et al. Endoscopic treatment of biliary fistulas after complex liver resection. Ann Surg. 2011 Jan;253(1):88–93.

27. Gurusamy KS, Koti R, Davidson BR. T-tube drainage versus primary closure after laparoscopic common bile duct exploration. Cochrane Database Syst Rev. 2013 Jun 21;(6):CD005641.

28. Yin Z, Xu K, Sun J, Zhang J, Xiao Z, Wang J, et al. Is the end of the T-tube drainage era in laparoscopic choledochotomy for common bile duct stones is coming? A systematic review and meta-analysis. Ann Surg. 2013 Jan;257(1):54–66.

29. Denost Q, Rouanet P, Faucheron J-L, Panis Y, Meunier B, Cotte E, et al. To Drain or Not to Drain Infraperitoneal Anastomosis After Rectal Excision for Cancer: The GRECCAR 5 Randomized Trial. Ann Surg. 2017;265(3):474–80.

30. Eurich D, Henze S, Boas-Knoop S, Pratschke J, Seehofer D. T-drain reduces the incidence of biliary leakage after liver resection. Updat Surg. 2016 Dec;68(4):369–76.

31. Otao R, Beppu T, Isiko T, Mima K, Okabe H, Hayashi H, et al. External biliary drainage and liver regeneration after major hepatectomy. Br J Surg. 2012 Nov;99(11):1569–74.

32. Ueda J, Chijiiwa K, Nakano K, Zhao G, Tanaka M. Lack of intestinal bile results in delayed liver regeneration of normal rat liver after hepatectomy accompanied by impaired cyclin E-associated kinase activity. Surgery. 2002 May;131(5):564–73.

33. Saiki S, Chijiiwa K, Komura M, Yamaguchi K, Kuroki S, Tanaka M. Preoperative internal biliary drainage is superior to external biliary drainage in liver regeneration and function after hepatectomy in obstructive jaundiced rats. Ann Surg. 1999 Nov;230(5):655–62.

34. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012 Mar;255(3):405–14.

FIGURE AND TABLES

Figure 1. Flowchart. ITT, intent-to-treat; POD, postoperative day.

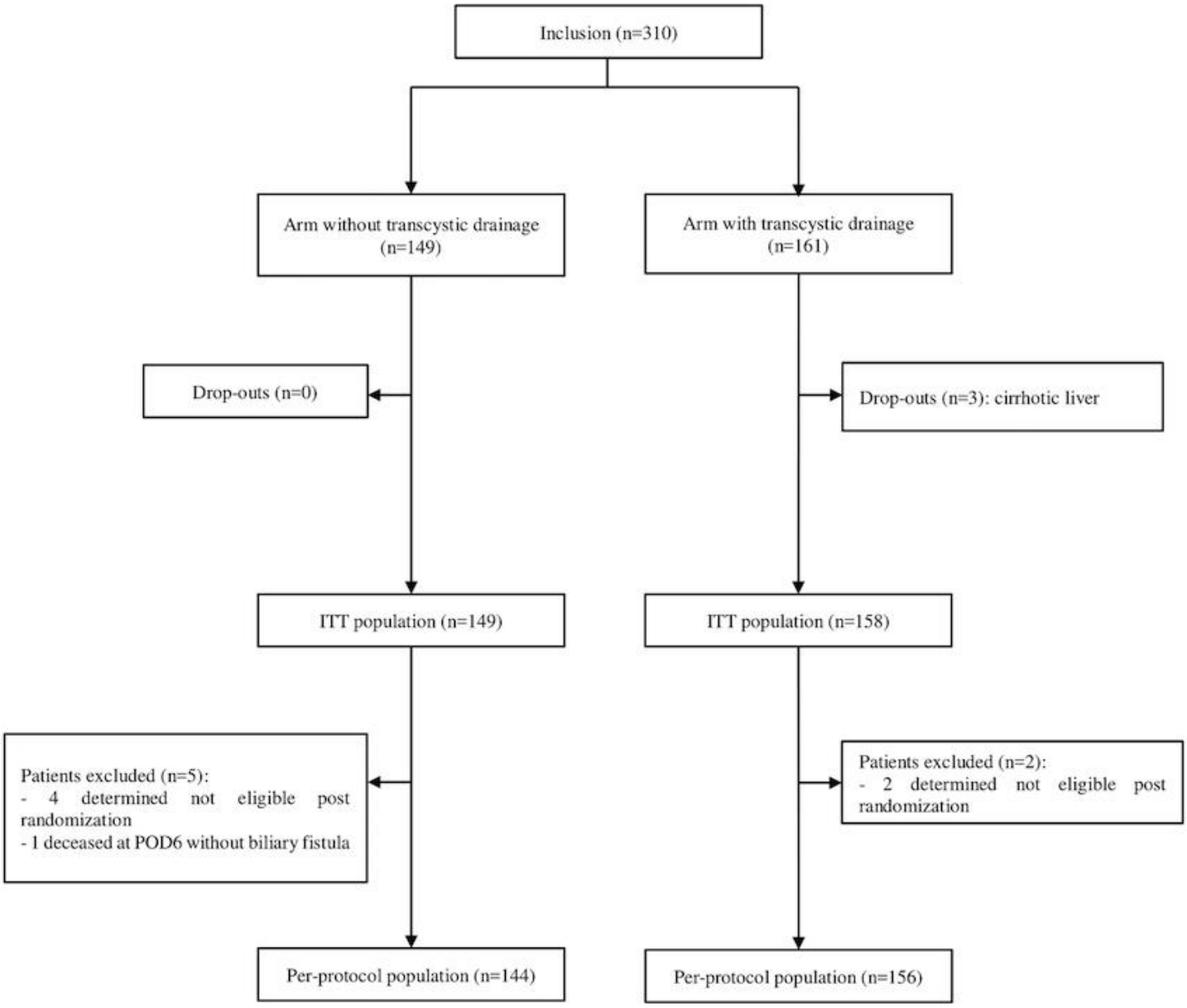

Table 1. Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years Resection of at least 2 segments of the liver parenchyma (including repeat resection) Benign or malignant disease Laparotomy approach Information of the patient and signed informed consent Eligible for health insurance Non-cirrhotic liver	Age <18 years Emergency procedure Laparoscopic approach Biliary-intestinal anastomosis History of cholecystectomy Cirrhotic liver Resection of less than 2 segments of the liver parenchyma Preoperative jaundice (total bilirubin > 30 µmol/l) Preoperative biliary drainage Transcystic drainage required during the procedure Preoperative or intraoperative evidence (or suspicion) of obstructed biliary flow Individuals under a partial or total guardianship Individuals who are wards of the state

Table 2. Clinical and surgical characteristics (ITT population). ASA, American Society of Anesthesiologists score; BMI, body mass index; SD, standard deviation. *Comorbidities: high blood pressure, diabetes, chronic obstructive pulmonary disease, coronary heart disease, anticoagulation therapy, or antiplatelet treatment.

	Control group (n=149)		**Transcystic group (n=158)**		**Total (n=307)**	
	n	**%**	**n**	**%**	**n**	**%**
Age at inclusion, years, mean (± SD)	61.5	11.7	61.5	10.7	61.5	11.1
Sex ratio (M/F)	90/59	60.4/39.6	97/61	61.4/38.6	187/120	60.9/39.1
BMI, kg/m^2, mean (± SD)	25.7	4.79	25.4	4.12	25.5	4.46
ASA						
1-2	116	77.9	111	70.3	227	73.9
3-4	33	22.1	47	29.7	80	26.1
Presence of at least one comorbidity*	86	57.7	83	52.5	169	55.0
Diabetes	28	18.8	24	15.2	52	16.9
High blood pressure	63	42.3	62	39.2	125	40.7
Treatment at inclusion						
Corticosteroids	2	1.3	4	2.5	6	2.0
Chemotherapy	82	55.0	91	57.6	173	56.4
Anti-angiogenic drugs	23	15.4	37	23.4	60	19.5
Number of resected hepatic segments, mean (± SD)	3.8	0.92	3.8	0.96	3.8	0.94
Number of resected hepatic segments						
2-3 resected segments	37	24.8	43	27.2	80	26.1
≥ 4 resected segments	112	75.2	115	72.8	227	73.9
Surgery duration, hours, mean (± SD)	4.5	1.5	4.8	1.7	4.7	1.6
Blood loss, ml, mean (± SD)	707.8	529	773	773.8	740	637.9
Hepatectomy						
Left side	32	21.5	29	18.4	61	19.9
Other	117	78.5	129	81.6	246	80.1
Blood transfusion	46	30.9	45	28.5	91	29.6
Weight of resected liver, g, mean (± SD)	822.7	828.8	797.5	624	809.6	728.1
Technique of liver transection						
Kellyclasia	9	6.0	26	16.5	35	11.4
Ultrasonic energy	93	62.4	94	59.5	187	60.9
Pressurized water jet	48	32.2	51	32.3	99	32.2
Other	5	3.4	7	4.4	12	3.9
Pedicle clamping	113	75.8	117	74.1	230	74.9
Clamping time, min, mean (± SD)	30.8	15	37.4	40.1	34.2	30.9
Length of hepatic slice, mm, mean (± SD)	146.5	53.6	149.1	58.5	147.9	56.2
Width of hepatic slice, mm, mean (± SD)	109.8	53	104.3	52.7	106.8	52.8
Positive bile leak test	37	24.8	33	20.9	70	22.8
Treatment of the slice of the liver	100	67.1	100	63.3	200	65.1
Intra-abdominal drainage	104	69.8	131	82.9	235	76.5
Type of intra-abdominal drainage						
Suction drain	67	45.0	85	53.8	152	49.5
Non-suction drain	37	24.8	46	29.1	83	27.0
Transcystic catheter, mm, mean (± SD)	-	-	6	5.1	-	-
Bile leak around the cystic duct at cholangiography	-	-	12	7.6	-	-
Associated actions to surgery						
Colorectal surgery	5	3.4	7	4.4	12	3.9
Thermoablation	16	10.7	26	16.5	42	13.7
Other associated actions	19	12.8	28	17.7	47	15.3
Malignant disease	139	93.3	152	96.2	291	94.8
Microvesicular steatosis, %, mean (± SD)	4.4	12.7	3.5	10.7	3.9	11.7
Macrovesicular steatosis, %, mean (± SD)	9.3	15.9	10.1	17	9.7	16.4

Table 3. Details of the postoperative biliary fistula. ITT: Intent-to-treat**. ***Patients could have more than one event.

	Control group (n=149)		**Transcystic group (n=158)**		***P***
	n	**%**	**n**	**%**	
Primary endpoint (postoperative biliary fistula), ITT analysis	9	6	9	5.7	1
Primary endpoint (postoperative biliary fistula), per-protocol analysis	9	6.3	9	5.8	1
During initial hospital admission* External biliary fistula Biliary peritonitis Bilioma	 7 3 3	 4.7 2 2	 2 0 7	 1.3 0 4.4	
Rehospitalization for biliary fistula within 30 days of the surgery*	0	0	1	0.6	

Table 4. Predictive factors of postoperative biliary fistula: Nominal (4a) and continuous (4b) variables (univariable analysis).

Table 4a.

		Postoperative biliary fistula				
	n	**n**	**%**	**OR**	**95% CI**	***P***
Randomization group Transcystic group	158	9	5.6	0.94	0.320-2.757	1.000
Body Mass Index > 27	97	7	7.2	1.66	0.510-5.206	0.464
Diabetes Yes	52	4	7.7	1.43	0.328-4.809	0.731
Chemotherapy Yes	173	11	6.4	1.41	0.464-4.786	0.685
Anti-angiogenic drugs Yes	60	3	5	0.86	0.154-3.235	1.000
Hepatectomy Left side	61	3	4.9	0.80	0.143-2.954	1.000
Blood loss > 300 ml	197	14	7.1	3.58	0.519-155.22	0.336
Blood transfusion Yes	91	9	9.9	2.43	0.823-7.187	0.115
Clamping > 30 min	98	5	5.1	1.13	0.251-5.069	1.000
Steatotic liver Yes	70	4	5.7	0.93	0.216-3.100	1.000
Positive bile leak test Yes	70	6	8.6	1.78	0.510-5.651	0.418
At least one treatment of the slices of the liver (fibrin sealants)	200	12	6	1.01	0.338-3.388	1.000
Intra-abdominal drainage Yes	232	15	6.5	1.66	0.450-9.180	0.637
Suction drain Yes	152	10	6.6	1.29	0.445-3.887	0.775
Sinusoidal obstruction syndrome Yes	63	5	7.9	1.88	0.465-6.823	0.433
Malignant disease Yes	291	18	6.1	1.46	0.295-3.229	0.742
Cholangiocarcinoma Yes	36	3	8.3	1.543	0.272-5.881	0.714

Table 4b.

	OR	**95% CI**	***P***
Surgery duration (hours) Increase by 1-hour	1.17	0.874-1.540	0.266
Length of the hepatic slice Increase of 1 mm	1.01	1.000-1.020	0.049
Width of the hepatic slice Increase of 1 mm	1.01	1.000-1.018	0.052
Microvesicular steatosis 1% increase	0.93	0.711-1.033	0.460
Macrovesicular steatosis 1% increase	0.98	0.925-1.025	0.553

RANDOMIZED CLINICAL TRIAL OF BILIARY FISTULA PREVENTION AFTER HEPATECTOMY BY TRANSCYSTIC BILIARY DRAINAGE

ABSTRACT:

Background: Biliary fistula is one of the most common complications after hepatectomy. This study evaluates the effect of transcystic biliary drainage during hepatectomy on the occurrence of postoperative biliary fistula.

Methods: This prospective multicenter randomized trial (Clinical Trial NCT01469442) with two groups (transcystic group versus control group) was carried out from 2009 to 2016. The patients underwent a hepatectomy (≥ 2 segments) on non-cirrhotic liver. The primary endpoint was the occurrence of biliary fistula after surgery. The secondary endpoints were morbidity, postoperative mortality, hospital stay duration, reoperation, rehospitalization, and complications caused by the catheter. Intent-to-treat and per-protocol analyses were performed.

Results: A total of 310 patients was randomized at nine centers. In intent-to-treat, 158 patients were randomized in the transcystic group and 149 in the control group. Seven patients were removed from the per-protocol analysis due to protocol deviations. The biliary fistula rate was 5.9% in intent-to-treat, 6% per-protocol. This rate was similar for the transcystic group and the control group: 5.7% vs 6% (P=1). There were no differences in terms of morbidity (49.4% vs. 46.9%, P=0.73), mortality (2.5% vs. 4.7%, P=0.36), and reoperations (4.4% vs. 10.1%, P=1). The median hospital stay duration was significantly higher for the transcystic group (11 days vs. 10 days, P=0.042). The biliary fistula risk was correlated with the width and the length of the hepatic slice.

Conclusion: This randomized trial does not demonstrate superiority of transcystic drainage during hepatectomy to prevent biliary fistula. The use of transcystic drainage during hepatectomy to prevent postoperative biliary fistula should not be recommended.

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PRÉVENTION DE LA FISTULE BILIAIRE POST-OPÉRATOIRE APRÈS HÉPATECTOMIE PAR DRAINAGE BILIAIRE TRANSCYSTIQUE

UN ESSAI CLINIQUE PROSPECTIF RANDOMISÉ MULTICENTRIQUE

RÉSUMÉ EN FRANÇAIS :

Contexte et objectif de l'étude : La fistule biliaire est une des complications majeures après hépatectomie. Cette étude évalue l'intérêt d'un drainage biliaire transcystique lors des hépatectomies en prévention de l'apparition d'une fistule biliaire post-opératoire.

Méthodes : Cet essai clinique prospectif randomisé multicentrique (Clinical Trial NCT01469442) réalisé de 2009 à 2016 comparait deux groupes : le groupe transcystique versus le groupe contrôle. Les patients inclus étaient opérés d'une hépatectomie (≥ 2 segments) sur foie non cirrhotique. Le critère de jugement principal était l'apparition d'une fistule biliaire après la chirurgie.

Résultats : Un total de 310 patients a été randomisé dans 9 centres. En intention de traiter, 158 patients ont été randomisés dans le groupe transcystique et 149 patients dans le groupe contrôle. Le taux de fistule biliaire était de 5.9% en intention de traiter et de 6% en per-protocole. Ce taux était similaire pour les deux groupes : 5.7% pour le groupe transcystique et 6% pour le groupe contrôle (P=1). Il n'y avait pas de différence entre le groupe transcystique et le groupe contrôle en termes de morbidité (49.4% vs. 46.9%, P=0.73), de mortalité (2.5% vs. 4.7%, P=0.36) et de taux de réopération (4.4% vs. 10.1%, P=1). La durée médiane d'hospitalisation était significativement plus longue pour le groupe transcystique (11 jours vs. 10 jours, P=0.042). La fistule biliaire post-opératoire était corrélée à la largeur et la longueur de la tranche d'hépatectomie.

Conclusion : Cet essai clinique prospectif randomisé multicentrique ne démontre pas la supériorité du drainage biliaire transcystique. L'utilisation d'un drainage biliaire transcystique lors des hépatectomies pour prévenir l'apparition d'une fistule biliaire post-opératoire ne doit pas être recommandée.

TITRE EN ANGLAIS : RANDOMIZED CLINICAL TRIAL OF BILIARY FISTULA PREVENTION AFTER HEPATECTOMY BY TRANSCYSTIC BILIARY DRAINAGE

DISCIPLINE ADMINISTRATIVE : Médecine spécialisée clinique

MOTS-CLÉS : Fistule biliaire - Hépatectomie - Chirurgie hépatique - Drain transcystique - Essai randomisé - Multicentrique - Prospectif - Morbi-mortalité

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