Percutaneous stenting in malignant biliary obstruction caused by metastatic disease: clinical outcome and prediction of survival according to tumor type and further therapeutic options

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Abstract

Background and study aims : **Obstructive jaundice caused by metastatic disease leads to deterioration of general condition and short survival time. Successful decompression can offer symptom control and enable further treatment with chemotherapy, which can improve survival.**

Patients and methods : **Ninety-nine percutaneous transhepatic cholangiography (PTC) procedures with metallic stent placement were performed in 93 patients between 2007 and 2013.**

Files were retrospectively studied and a review of patients' demographics, clinical and laboratory parameters, treatment and survival was performed. Kaplan-Meier survival analysis with log-rank test was done in function of bilirubin level, tumor type and treatment with chemotherapy.

Results : **Hyperbilirubinemia resolved in 73% of procedures. Median survival time after the procedure was 48 (95%CI 34.8 - 61.1) days. If additional chemotherapy was possible, a median survival of 170 (95%CI 88.5 - 251.4) days was noted versus 32 (95%CI 22.4 - 41.5) days without chemotherapy ($p < 0.01$).**

Survival rates greatly differed between primary tumor type, with the largest benefit of PTC in colorectal cancer.

In 35 % of the procedures minor or more severe complications were noted. The 30-day mortality was 33%, with 3 procedure related deaths.

Conclusions : **PTC with metallic stenting can bring symptom relief and enable further treatment with chemotherapy, which can lead to a longer survival time, especially in colorectal cancer.**

However, in patients in whom palliative stenting failed to resolve the hyperbilirubinemia survival is short. (Acta gastroenterol. belg., **2017**, 80, **249-255**).

Keywords : Extrahepatic cholestasis ; neoplasm metastasis ; interven diology ; cholangiography ; mortality ; chemotherapy.

Introduction

When jaundice is caused by a pancreatic carcinoma or a cholangiocarcinoma, potentially curative surgery may be possible. Few patients with biliary obstruction secondary to metastasis are suitable for curative resection and therefore they are treated in a palliative setting. Hyperbilirubinemia can cause jaundice, pruritus, renal impairment, immune dysfunction, anorexia and weight loss and thus quality of life is impaired. This can lead to rapid deterioration of the general condition and a shorter survival. Successful decompression of the biliary obstruction is crucial for symptom control, but also for enabling further treatment with chemotherapy.

Biliary obstruction can be solved by endoscopic stent placement or by a percutaneous transhepatic approach. The last approach can be the first choice for technical reasons or is applied after failure of endoscopy.

Although drainage and stenting of the biliary tree is minimally invasive, there are known risks (pain, bleeding, biliary leak, cholangitis, and sepsis) linked to this procedure.

Thus, the benefits and risks of this treatment must be considered in view of the prognosis of these patients.

Few data are available on the clinical benefit of this palliative treatment (1). In particular the effect on subsequent administration of chemotherapeutic agents and how this impacts survival, especially when second or third line agents are available, is of interest.

This is a retrospective study of consecutive patients who underwent percutaneous stenting for malignant obstruction secondary to metastases from carcinomas of different origins.

The aim of the study was to determine morbidity and mortality associated with this palliative treatment, but also to identify which goal was set for the intervention (pure palliative treatment or bridge to further treatment with palliative chemotherapy), whether this goal was achieved and to determine the effect on survival.

Material and Methods

Patients

Patients referred for percutaneous transhepatic cholangiography (PTC) and bile duct stenting for secondary malignant biliary obstruction were eligible for inclusion. Indications for PTC were failed endoscopic retrograde cholangiopancreatography (ERCP) or the presence of a biliodigestive anastomosis. Excluded were patients with an obstruction caused by a primary tumor of the bile duct or pancreas. All malignancies with obstruction caused by metastatic disease were included. The indication for bile duct recanalization was either intention to re-start chemotherapy, cholangitis or palliative symptom relief.

Patients' demographics, clinical and laboratory parameters, treatment and survival data were retrieved

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retrospectively from hospital files and by questionnaires (written and per telephone) sent to the referring hospitals and the general practitioners. Patients' general condition was estimated by a retrospective assignment of a WHO status. The type of primary tumor was noted and classified in major groups : colorectal cancer, pancreas, bile duct, gastric, esophageal tumors and other tumors (miscellaneous group) (Table 1). The time interval from disease onset to biliary obstruction was calculated. Data related to the chemotherapeutic options and treatment before and after PTC were collected.

Table 1**. — Patients characteristics**

Patients	
Total number	93
Gender male/female	56/37
Mean age (time of PTC), year	62.8 (SD 12)
Median level of bilirubin before PTC	11,45 mg/dl (range 6.9 -16.7 mg/dl)
Tumor	
Cholangiocarcinoma	7 (8%)
Pancreas	20 (23%)
Colorectal (rectal 9 pt)	28 (30%)
Stomach	15 (16%)
Esophagus	5 (5%)
Other (breast, pharynx, multiple myeloma, prostate, gall bladder, lung, ovary, bladder, hypernephroma, NET)	18 (18%)
Number of procedures	99
1 procedure	89
2 procedures	2
3 procedures	2
WHO performance status	
0	4
1	35
2	30
3	18
4	0
Unknown	6

PTC and stenting was performed under general anesthesia and X-ray fluoroscopy. Unilateral cholangiography with a 21G needle and Ultravist 240 (Bayer) contrast medium was sufficient to visualize an occlusion below the hilum. Hilar obstruction required a bilateral cholangiography. In case of an infrahilar occlusion, the occluded choledochus was recanalized in a coaxial way and a 10mm self-expandable stent was placed, usually covering the papilla. In case of a hilar obstruction, Y-stenting of the hilum approaching from the right and left hepatic duct was chosen whenever both liver lobes contained functional parenchyma. If the procedure had been technically challenging, a temporary external/internal biliary drain was left in place to decompress the biliary system. Prophylactic antibiotics were administered and bile was sampled for bacteriology.

Technical and biochemical success of the PTC procedure was measured by recanalization of the bile duct system and by the reduction of the bilirubin level below 5 mg/dL (85.5 μmol/L).

Postoperative morbidity within 30 days was subdivided in major (bleeding requiring intervention, cholangitis requiring intensive care, sepsis) and minor complications. PTC related mortality was registered at 30 days or in-hospital. Predictors of 30-day mortality were identified using multivariate analysis. This was performed in function of type of tumor (colorectal cancer versus a group of other tumors with comparable survival : pancreas, bile duct, gastric and esophageal tumors. The miscellaneous group was excluded because of variability in prognosis), performance status (WHO 0, 1 and 2 versus 3) and bilirubin higher than 17,5 mg/dL (299.25 μmol/L) before PTC. This cut-off was based on the study of Tapping *et al* (2), where this level was identified as independent predictor for early complications (1-30 days).

We investigated whether patients in whom (re-)start of chemotherapy was intended, actually received chemotherapy after PTC. Reasons why patients were precluded from further chemotherapy were noted : failure to lower bilirubin serum level, procedural complications, and deterioration of general condition or early death.

Survival analysis was performed in function of level of bilirubin, type of tumor and treatment with chemotherapy. Approval of the local ethical committee was obtained.

Statistical analysis

Statistical analysis was performed using SPSS statistics data editor 22. Kaplan-Meier survival analysis with log-rank test was used to plot and compare survival and logistic regression analysis was used for multivariate analysis.

If patients had more than one procedure, survival analysis was performed with the data of the first procedure. In other data analysis the whole group was considered.

Statistical significance was taken as $p < 0.05$.

Results

Patients

Between October 2007 and March 2013, 200 consecutive PTC with metallic stent placement were performed for malignant biliary obstruction. Ninety-nine procedures in 93 patients were performed for metastatic disease.

The characteristics of the patients are summarized in table 1. Sixty percent of the patients were male (56 patients) with a mean age at the time of the procedure of 62.8 years.

Thirty % of patients (28 patients) suffered from colorectal cancer. Other causes were metastatic disease of pancreatic adenocarcinoma, of gastric cancer, of cholangiocarcinoma, of cancer of the esophagus and a miscellaneous group (bladder, multiple myeloma, breast, prostate, gall bladder, lung, neuroendocrine tumor of the pancreas, renal cell cancer, ovary, duodenal and pharynx).

The median level of bilirubin before the procedure was 11.45 mg/dl (195.8 μmol/L), the highest level was 37 mg/dl (632.7 μmol/L) (IQR 6.9-16.7 mg/dl ,117-285.5 μmol/L, mean 13.5 mg/dl, 230.85 μmol/L).

Seventy-one percent of patients had already been treated with chemotherapy before biliary obstruction caused by metastases occurred. Approximately half of them had been treated with more than one line of chemotherapy.

Technical success and complications (within 30 days)

Nighty-nine percutaneous bile duct stentings were performed in N=93 patients with a technical success of 100%. Four patients underwent another PTC procedure for recurrent biliary obstruction with a time interval varying from 2 to 10 months.

In 35 % of procedures complications were reported (table 2), among which infectious problems, such as cholangitis, were the most frequent.

Bleeding (defined as drop in hemoglobin of more than 2g/dL and the need for transfusion or technical intervention) occurred in 8 percent of the procedures. Three deaths occurred within 7 days post procedure and were linked to complications following the PTC (cholangitis with septic shock, respiratory failure). In-hospital mortality was 28% and 30-day mortality was 33% and disease related.

Table 2. — **Characteristics of procedure (absolute number)**

Hospitalisation (median days)	6 (SD 15.2)
Complication PTC	
None	64
Bleeding	8
Pain	5
Cholangitis	16
Biliary Leak	5
Death	3
Other (pneumonia, pancreatitis, liver abscess, renal failure, subcutaneous abscess)	10
External drain	
Yes	16
No	83
Stent	
Right	5
Left	6
Bilateral (Y-stent)	30
Distal	44
Combination	14

Most of the time a one-step procedure was performed, with stent placement at the time of the drainage. In 16 patients an external drain was left ; this was followed by a second look to verify function of the stent and removal of the drain.

The median post-procedure hospital stay (including days in the referring hospital) was 6 days (IQR 3-14 days).

Biochemical success

Seventy-three% of procedures (70/95) were biochemically successful showing a reduction of the bilirubin level below 5 mg/dl (85.5 μmol/L), this is the threshold for chemotherapy. In 36 percent of the procedures (34/95) the bilirubin value decreased below 2 mg/dl (34.2 μmol/L). In 25 cases the level of bilirubin remained above 5 mg/dl (85.5 μmol/L). In 4 patients no data on bilirubinemia after the procedure could be found.

Clinical success

In 22 procedures (22%) only symptomatic relief was pursued. Cholangitis was the main reason for PTC in 12 other procedures (12%). In two patients, the cholangitis could not be resolved and the patients died of septic shock. There were missing data on goal of treatment in 2 procedures.

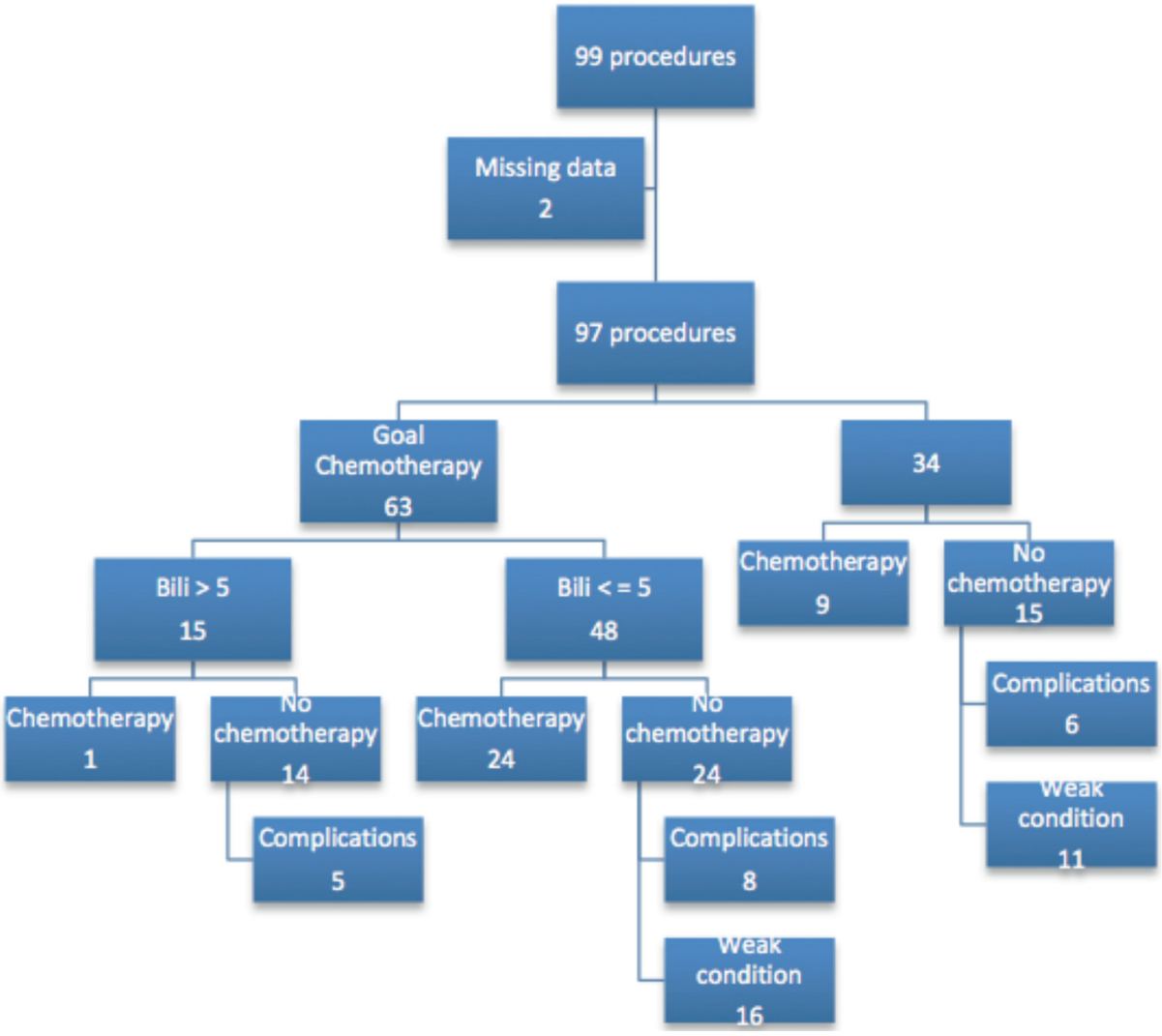
In 64% of procedures (63/99), the intervention was intended to allow treatment with chemotherapy. In 76% of these 63 procedures (48/63), a level of bilirubin allowing administration of chemotherapy was reached (below 5 mg/dl or 85.5 μmol/L). Nevertheless, only 40 % actually started treatment (25/63 achievement of goal) (See flow-chart).

Most of the patients who did not receive chemotherapy had a weak general condition. Eight patients could not be treated with chemotherapy due to procedure related complications (cholangitis n = 2, abscess n = 1, kidney failure n= 1, infection n = 4).

Although it was not the primary goal of the intervention, in another 9 procedures chemotherapy could be administered (See flow-chart, CRC n =4 , pancreatic cancer n = 2, cholangiocarcinoma n = 1, lung cancer n = 1 and carcinoma of the prostate n=1)

Independently of the initial goal of the PTC, 34 procedures on 28 patients (35 % of all procedures) were followed by treatment with chemotherapy.

Only patients with colorectal cancer could receive multiple lines of chemotherapy after PTC, even when they had already been treated with different lines of chemotherapy.



Flow-Chart — Goal of procedure and administration of chemotherapy after PTC. Major complications that inhibit further treatment with chemotherapy are stated.
Bilirubin > 5mg/dL (85.5 μmol/L), bilirubin <= 5mg/dL (85.5 μmol/L)

Table 3. — **Multivariate analysis of risk factors for 30-day Mortality**

	Unadjusted Odds Ratio (95% CI) p-value	Adjusted Odds Ratio (95% CI) p-value
Tumor [a]	0,254 (0,076; 0,850) 0,026	0,360 (0,096; 1,356) 0,131
WHO score [b]	5,538 (1,545; 19,849) 0,009	4,752 (1,263; 17,881) 0,020
Bilirubin [c]	0,882 (0,272; 2,866) 0,835	1,080 (0,259; 4,568) 0,904

[a] Tumor: cholangiocarcinoma, pancreatic adenocarcinoma, gastric cancer and cancer of the esophagus versus colorectal adenocarcinoma
[b] WHO score: WHO 0,1 and 2 versus WHO 3
[c] Bilirubin pre-PTC: < 17,5 mg/dL versus > 17,5 mg/dL

Table 4. — **Median Survival post PTC in days (95% Confidence Interval) in function of tumor type and treatment with chemotherapy after PTC**

Tumor	Overall	Chemotherapy	No chemotherapy	Statistical significance
Overall	48 (n=92[a]) (34,8-61,1)	170 (n=28) (88,6-251,4)	32 (n=63) (22,5-41,5)	p < 0,01
Cholangiocarcinoma	78 (n=7) (18,9-137,0)	87 (n=3) (35,7-138,2)	14 (n=4) (0-79,6)	nss
Pancreatic carcinoma	31 (n=19) (20,3-41,6)	135 (n=4) (79,4-190,8)	29 (n=15) (20,3-37,7)	p < 0.05
Colorectal cancer	67 (n=28) (39,8-94,2)	316 (n=9) (0-760,1)	57 (n=19) (44,3-69,6)	p = 0.01
Stomach cancer	40 (n=15[b]) (30,8-49,1)	117 (n=4) (0-264)	32 (n=10) (8,7-55,3)	nss
Esophageal cancer	9 (n=5) (4,7-13,3)		9 (n=5) (4,7-13,3)	
Other cancers	39 (n=18) (0-101,3)	127 (n=8) (92,3-161,6)	14 (n=10) (7,8-20,2)	p < 0.01

Nss = no statistical significance

[a]1 patient with NET is still alive, [b]1 patient unknown status of chemotherapy

No patients (n = 5) with esophageal cancer received chemotherapy after PTC, although this was the intention in 2 patients. All but one had already been treated with a platinum based regimen before PTC.

Survival

Only one patient in the cohort was still alive in August 2014, when the data collection was closed. This is a patient with a neuroendocrine tumor of the pancreas. The median survival time for the whole group was 48 days (95% CI 34.8-61.1 days).

The 30-day mortality of the whole group was 33%. In multivariate analysis, weak general condition (WHO 3) leads to a 4,7-fold increase in the 30-day mortality (Table 3). If in spite of PTC, the level of bilirubin remained above 5 mg/dL (85.5 μmol/L), a median survival of 24 days was noted (95%CI 6.4-41.6 days). If the level of bilirubin decreased between 2 and 5 mg/dl (34.4 μmol/L-85.5 μmol/L), median survival was 47 days (95% CI 31.7-62.3 days). A significantly longer median survival of 123 days was reached if the level of bilirubin could be reduced below 2 mg/dL (34.4 μmol/L) (95%CI 75.5-170.5 days).

If treatment with chemotherapy was possible, a longer median survival of 170 days or 5.5 months (95%CI 88.5-251.4 days) was attained. In the group without additional chemotherapy the median survival was only 32 days (95%CI 22.4-41.5 days). This difference in survival was statistically significant (p < 0.01).

Table 4 shows that survival varied according the type of primary disease. Patients with colorectal cancer lived strikingly longer than patients in the other subgroups. With additional chemotherapy, they reached a survival of 10.4 months (316 days, 95% CI 77.3-480.6 days), compared with 1.8 months (57 days, 95% CI 44.3-69.6 days) without chemotherapy (p = 0.01). There was no difference in time between diagnosis and PTC, nor in number of treatment lines before PTC. The miscellaneous and the pancreas group also had a significantly better survival with additional chemotherapy (p < 0.01 respectively p < 0.05). The survival after PTC in patients with metastatic pancreatic carcinoma receiving additional chemotherapy was 135 days or 4.4 months (95% CI 79.4-190.8), as opposed to 29 days or 1 month (95% CI 20.3-37.7) in those who did not.

A non-significant trend towards survival benefit with chemotherapy after PTC was observed in the patients with cholangiocarcinoma (87 days, {95% CI 35.7-138.2 days} versus 14 days, {95% CI 0-79,6 days}) and patients with stomach cancer (117 days, {95% CI 0-264 days} versus 32 days, {95% CI 8.7-55.2 days}).

The survival of patients with cancer of the esophagus was the worst of all, with a median survival of 9 days (95% CI 4.7-13.2 days).

Discussion

Improving quality of life is a major goal in the palliative treatment of advanced carcinoma. Obstructive jaundice caused by metastatic disease leads to many symptoms, a rapid deterioration of the performance status and a shorsurvival. The few data available in literature suggest that symptom relief (especially pruritus) by stenting provides a considerable benefit for patients (1,3-8). Stent placement should be done in a minimally invasive way with a stent that has a good chance of remaining patent. ERCP is the preferred method, however endoscopic drainage is not always possible and thus the percutaneous route is often considered. Lately EUS-guided biliary drainage has shown to be technically feasible and has been studied as an alternative technique for PTC, showing less complications.

Reported rates of successful percutaneous drainage vary in literature from 57 to 98% (9-11). In our study, all procedures were technically successful and 73% of procedures were biochemically successful with a resolution of jaundice.

PTC can be performed for symptom control or treatment of cholangitis, but a more pertinent objective is further treatment with chemotherapy. In our series, 64% (63/99) of procedures was done with the intention to (re-)start chemotherapy. Although the desired decrease in bilirubin was reached in 78% (49/63) of patients, only 40% (25/63) actually received chemotherapy. Another 9/36 patients were treated with chemotherapy after PTC although this was not the initial goal. Overall, 34% (34/99) of patients received chemotherapy after PTC. This success rate is somewhat higher than the 22% reported elsewhere (12).

Moreover, our results showed that if decompression of metastatic biliary obstruction could lead to (re-)start of chemotherapy, survival was significantly improved from median 32 days to 170 days.

Two small numbered similar studies reported low median overall survival of 58 and 25 days respectively (11,12). Other investigators (3,13,14) demonstrated longer survival rates between 91 and 165 days (range 3-1430 days). Since there are no or limited data available on the use of chemotherapy after stenting in these studies, it is difficult to explain the difference with our results. In the study of Doctor *et al* (14), the longer survival can be explained by the inclusion of all patients with malignant distal bile duct obstruction, of which only 11% was caused by metastatic disease.

Another study comprising 35 patients (1), showed a median survival for the whole group of 4 months. In this study, median survival of the 17 patients who received additional chemotherapy was 10 months compared with 2 months in the others. This is higher than the survival time we noted. Since 80% of their patients could be treated endoscopically and only 20% required PTC, a selection bias of patients with less extensive disease might explain a better survival. This may also be the case in other studies (15,16) considering survival with endoscopically placed stents, mainly focusing on the use of different stent types and patency. One study also gives information on survival (mean 190 - 260 days, depending on stent type) and treatment with chemotherapy (more than half of patients), but there are no data on survival according to tumor type or further treatment. Studies with EUS guided biliary drainage mainly focus on technical aspects in distal obstruction, thus considering a different patient population. These studies do not give information on further treatment and survival.

The improved survival after PTC and chemotherapy is most striking in the group of colorectal cancer metastases, even if the obstructive jaundice occurs late in the disease. These patients have the best outcome with a median survival post PTC of 316 days or 10,4 months. Our findings on colorectal cancer are comparable with the median survival of the 16 patients with colorectal cancer in Van Laethems study (1), 1 year versus 2 months. This survival benefit is a reflection of the extensive treatment options with chemotherapy and targeted therapy for colorectal cancer. We therefore strongly suggest that both patients in the early and late stage of colorectal cancer should be referred for PTC.

In the miscellaneous group (e.g. breast cancer) and in pancreatic cancer the survival was also significantly increased with chemotherapy. But only a minority of patients with pancreatic cancer could be treated with chemotherapy after PTC.

In stomach cancer and cholangiocarcinoma a trend towards better survival was observed but this was not significant and no patients with esophageal cancer received chemotherapy after PTC, mostly because of the weak general condition of these patients.

The survival without consecutive chemotherapy is only 32 days. This is even worse for the more aggressive cancers like cholangiocarcinoma (14 days) and esophageal cancer (9 days). With a median hospital stay of 6 days, this means that the majority of these patients are unable to return home.

We recognized two main reasons for failure to start up chemotherapy : firstly, progressive deterioration of the general condition (33%, 16/48) leading to early death and secondly complications related to the procedure (N = 8/48, 16%) (see flow-chart). We found that weak general condition (WHO 3), increased the risk of 30-day mortality 4,7-fold, independently of tumor type or level of bilirubin. The complication risk associated with PTC (cholangitis and bleeding) is considerable and should be carefully weighed against the potential benefits of the procedure (1,9,10,13,14,17,18). Procedure-related mortality (within 7 days) was observed in 3%. In literature, the mortality range of the percutaneous biliary drainage varies from 0 to 3% (1,3,6,11,19) but this might be an underestimation of what happens in daily practice. A registration of PTC procedures in England showed an in-hospital mortality of 19.8 % in the malignant group (including non-metastatic disease) and 15.7 % in the benign group (18). We observed a 30-day mortality of 33 % and an in-hospital mortality of 28%. A similar result of 43% 30-day mortality is found in the study of Sut (20), and illustrates the advanced stage of the malignant disease and the severe co-morbidity of the patients.

Not reaching a sufficiently low serum bilirubin level is a minor reason (23% ; 14/63) for not restarting chemotherapy in patients in whom it was intended. Technical adjustments could improve biochemical results. We could have used covered or larger caliber biliary stents, and deliberately extend stents through the papilla. However, there is no evidence that this would have improved our results, in particular in hilar obstruction. Moreover, in almost 50% (25/49) of patients with a bilirubin below 5mg/dl (85.5 μmol/L), intended chemotherapy was not started.

The presented study is a retrospective survey, which inherently includes a patient selection bias. The number of patients in a weak condition was high. In daily practice, it might be that such patients would no longer be candidates for relief of obstructive jaundice in a hospital without an experienced interventional radiologist. We have no data on patients in whom a conservative approach without PTC was chosen. We could not compare the group of patients with a group relieved by endoscopical stenting. Although we included a large number of procedures, analysis of the individual tumor groups is limited due to small numbers.

Conclusion

PTC should be strongly considered in patients eligible for chemotherapy, as it can lead to a significant survival benefit. This is especially the case in colorectal cancer, both in early and late stage of the disease and in other cancers where multiple treatment lines are still possible.

Patients with malignant biliary obstruction and bad condition (WHO 3) have a high early mortality and a rapid decline in general condition, which can inhibit additional treatment with chemotherapy even though satisfactory biliary compression has been achieved.

If there are no chemotherapeutic options left, this invasive procedure should not be recommended lightly. The risks of PTC (complications, discomfort, external drainage and longer hospital stay) should be weighed against the possible benefit (small extension of survival, resolution of jaundice and accompanying symptoms).

It is crucial to openly discuss the benefits and disadvantages of PTC with our patients and to select the best candidates so therapeutic obstinacy can be avoided. We hope that the presented data can facilitate an informed discussion between patients, caregivers and clinicians prior to proceeding with PTC**.**

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