Malignant biliary obstruction caused by metastatic gastric cancer

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Purpose

Malignant biliary obstruction frequently is caused by metastatic disease from the stomach, colon, lung, uterus, and breast (1, 2). In case of metastatic gastric cancer, the incidence of malignant biliary obstruction is reported to be 1.3-2.3 \% (3-5). There have been sporadic reports on the radiologic findings of malignant biliary obstruction caused by metastatic gastric cancer (2, 6). In those reports, however, radiologic features were described simply. Furthermore, there have been no reports on the clinical and imaging characteristics of metastatic biliary obstruction according to histology of the primary gastric cancer, and statistical relationship between clinical and imaging characteristics.

Percutaneous or endoscopic placement of self-expandable metallic stents has become an established palliative treatment in the relief of malignant biliary obstructions. However, endoscopic approach is usually difficult in patients who have previously undergone gastric operation. To our knowledge, articles concerning the clinical outcome of patients who underwent percutaneous metallic stent placement for malignant biliary obstruction caused by metastatic gastric cancer are few and limited. Limited studies have reported that potential predictors of survival for patients with malignant biliary obstruction caused by metastatic gastric cancer.

Therefore, the objectives of this study were to investigate the characteristics of malignant biliary obstruction caused by metastatic gastric cancer and to assess the outcome of percutaneous transhepatic biliary drainage and metallic stent placement.
Methods and Materials

Patient Population

From January 2005 to December 2009, 117 consecutive patients with malignant biliary obstruction caused by metastatic gastric cancer were retrospectively studied. Demographic, clinical, and laboratory data were collected from the patients’ medical records or from the electronic patient information database. The protocol of this study was approved by the Institutional Review Board of our Institution and informed consent was waived. All patients had histologically proven primary gastric cancer. World Health Organization criteria for histological typing of gastric tumors were used, where signet ring cell carcinoma is defined as an adenocarcinoma in which a predominant component (more than 50% of the tumor) is made up of isolated or small groups of malignant cells containing intracytoplasmic mucin. [Watanabe H, Jass JR, Sobin LH, Ota K. Histological Typing of esophageal and gastric tumors. WHO International histological Classification of Tumors (2nd edn). Springer:Berlin, 1990.] The characteristics of the primary gastric cancer in 117 patients with malignant biliary obstruction are presented in Table 1.

Imaging Diagnosis

Contrast-enhanced CT scans were performed using a 4-channel (Lightspeed QX/I or Lightspeed plus: GE Medical Systems, Milwaukee, Wis) multidetector CT scanner or a 16-channel multidetector CT scanner (Somatom sensation 16; Siemens). 120-150 mL of iopromide (Ultravist 300 or Ultravist 370; Schering, Berlin, Germany) was administered intravenously at a rate of 3 mL/sec with an automatic power injector. Scan parameters for 4-channel multidetector row CT scanner were $4 \times 2.5$ collimation, a table speed of 15 mm per gantry rotation, 120 kVp, 200 effective mAs, slice thickness of 5-mm, and 5-mm reconstruction interval. CT parameters for 16-channel multidetector CT scanner were $16 \times 1.5$-mm detector collimation, a table speed of 24-mm per gantry rotation, 120 kVp, 200 maximal effective mAs with the use of automatic dose modulation technique (Care Dose; Siemens Medical Solutions, Forchheim, Germany), slice thickness of 5-mm, and 5-mm reconstruction interval.

The level of biliary obstruction was evaluated with CT and cholangiography and classified into two lesions: biliary hilum and biliary non-hilum. The hilar lesions were subclassified according to the Bismuth classification. The non-hilar lesions were divided into three segments: common hepatic duct (CHD) from the biliary hilum to the level of the cystic duct, upper half of common bile duct (CBD), and lower half of CBD. The cause of biliary obstruction demonstrated on CT was classified into six types as follows. Intraductal metastasis (enhancing ductal wall thickening or mass), periductal lymph node enlargement, periductal seeding mass, extrinsic compression by a metastatic liver mass, direct invasion by primary or recurred cancer, and no demonstrable lesion (Fig. 1-5).
PTBD and Stent Placement

No patients underwent endoscopic drainage because it was usually difficult for patients who had undergone gastric operation. Therefore, we used PTBD and metallic stent placement as the first-line treatment for patients with malignant biliary obstruction caused by metastatic gastric cancer.

PTBD and metallic stent placement were performed under conscious sedation using intravenous pethidine hydrochloride (Demerol, Keukdong Pharmaceutics, Seoul, Korea) and local anesthesia using intramuscular lidocaine (Jeil Pharmaceuticals, Taegu, Korea). Antibiotics were administered intravenously 24 hours before the procedures and for at least 48 hours afterwards. Intrahepatic bile duct was punctured with a 21-gauge Chibaneedle (Cook, Bloomington, IN) under the guidance of fluoroscopy or ultrasound (US). Based on the standard biliary drainage procedures, an 8.5-10-F biliary drainage catheter (Cook) was initially placed in intrahepatic bile duct.

A total of 66 metallic stents of four types were placed transhepatically in 54 patients, 0-39 days after the PTBD (median, 10 days). The remaining 63 patients did not have any biliary stents placed because of an unsuccessful drainage after PTBD, poor general health status (Eastern Cooperative Oncology Group [ECOG] performance status grade 3-4), or extensive extrabiliary metastases. All stent placements were performed using commercially available uncovered (Zilver, Cook;Sentinol, Boston Scientific, Galway, Ireland) or polytetrafluoroethylene-covered (Hercules, S&G Biotech, Seoungnam, Gyunggi, Korea; double biliary stent, TaeWoong Medical, Kimpo, Korea) metallic stents in Korea.

The type of stent to be used was made by the physician operators according to their availability and personal preference. Covered stents were used in 30 patients, whereas uncovered stents were used in 24 patients. Stent deployments were arranged in one of the following configurations: unilateral stenting through a single percutaneous site via single stent insertion; bilateral stenting through a single percutaneous site via stent-in-stent deployment with a T-configuration.

After stent placement, an 8.5-10-F biliary drainage catheter was left in place for 3-5 days to flush and maintain access to the biliary system. Correct stent position, expansion, and function were confirmed by cholangiography performed through the catheter. The catheter was subsequently removed if free contrast flow through the stent into the duodenum was documented and if serum bilirubin level was successfully decreased or normalized.

Endpoints of PTBD and Stent Placement

Successful drainage was defined as a decrease in serum bilirubin level of #20% relative to baseline within 1 week after PTBD. Technical success for stent placement was defined as the successful deployment of the stent in the appropriate position resulting in drainage
of the stented bile duct. Successful internal drainage for stent placement was defined as a decrease in serum bilirubin level to <75% of the pretreatment value within 1 month following stent placement. Patients with stents that remained patent were assumed to have no increase in serum bilirubin levels and no dilatation of the intrahepatic bile ducts, as shown by US or CT during follow-up. Stent patency was defined as the time interval between initial stent placement and recurrence of obstruction. If obstruction was not evident during a patient’s life, stent patency was considered equal to patient survival. A stent was assumed to be patent at the time of patient death if serum bilirubin levels were normal or only mildly increased (<3 mg/dl). If the patient was obviously jaundiced or had higher bilirubin levels, the stent was assumed to be obstructed. Patient survival was defined as the time interval between initial stent placement and patient death or last follow-up. If the patient was alive at the last follow-up, survival was considered equal to follow-up duration. Complications were classified as major and minor according to the guidelines of the Society of Interventional Radiology Standards of Practice Committee (ref). Major complications were defined as those necessitating major therapy, an unplanned increase in the level of care or prolonged hospitalization (>48 hours), or permanent adverse sequelae or death. Minor complications were defined as those requiring no or nominal therapy, including overnight admission for observation only.

**Statistical Analysis**

Mann-Whitney U test was used to compare pairs of independent, continuous variable between the groups. Student’s t test was used to compare categorical variables between the groups. Paired-sample t test was used to compare the pre- and post-biliary intervention (PTBD and stenting) serum bilirubin levels. Patient survival after PTBD, stent patency, and patient survival rates after stent placement were calculated according to the Kaplan-Meier method, and differences between curves were analyzed by the log-rank test. The following variables were included in this analysis: age; sex; histology, serosal invasion, and lymph node metastasis of primary gastric cancer; history of previous gastrectomy, type of metastasis, level of biliary obstruction, serum bilirubin levels after PTBD, metallic stenting after PTBD, and chemotherapy after PTBD. The serum bilirubin levels after PTBD were dichotomized and their cut-off point was based on statistical significance (a decrease to 0.5-2 mg/dl post-PTBD versus a decrease to 4.1 mg/dl or more). Variables found to be significant by univariate long rank analysis (p < .2) were considered as candidate variables for multivariate analysis to determine the most significant factors. Multivariate analysis was performed using the Cox proportional hazard model. All statistical analysis was performed using an SPSS package (version 14.0; SPSS, Chicago, IL). A two-sided P value of less than .05 was considered to indicate statistical significance.
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**Table 1:** Table 1. Characteristics of primary gastric cancer.

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**Fig. 1:** Fig. 1. A case of intraductal metastasis. A 54 years old female underwent subtotal gastrectomy due to signet ring cell carcinoma. CT scan shows enhancing wall thickening of the hilar bile duct, GB neck and cystic duct. Cholangiography demonstrates dilatation of the intrahepatic bile duct with obstruction at the level of biliary hilum.

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**Fig. 2:** Fig. 2. A case of biliary obstruction due to periductal lymph node enlargement. A 50 years old male with history of subtotal gastrectomy for adenocarcinoma. CT scan shows extrinsic compression by a large metastatic lymph node at the level of upper half of the common bile duct. Tight stricture is also noted on the cholangiography at the proximal CBD. Unilateral stening was successful performed across the lesion and ampulla.

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**Fig. 3:** Fig. 3. A case of biliary obstruction due to periductal seeding mass. A 77 years old male underwent total gastrectomy for adenocarcinoma. There is intrahepatic biliary dilatation and obstruction at proximal extrahepatic bile duct level. Cholangiography shows good contrast passage through the bile duct after stent graft placement.

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**Fig. 4:** Fig. 4. A case of extrinsic compression by a metastatic liver mass. A 72 years old female with gastric adenocarcinoma. Multiple metastatic masses in the liver causing biliary obstruction at the level of hilum. Good contrast passage through the stent graft is noted on the immediate cholangiography after bilateral stenting through a single percutaneous site via stent-in-stent deployment with a T-configuration.

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Fig. 5: A case of biliary obstruction due to recurred cancer invasion. A 66 years old male with distal gastrectomy for adenocarcinoma. CT scan shows a enhancing recurred mass near the surgical material causing biliary obstruction at the level of distal common bile duct. Stent placement was successfully performed across the lesion.

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Results

Biliary obstruction: Characteristics

The imaging characteristics are summarized in Table 2. Seventy-eight (67%) patients had previously undergone gastrectomy for their primary gastric cancer. In these patients, the interval between previous gastrectomy and onset of biliary obstruction ranged from 1 to 126 months, with a median duration of 26 months. Thirty-nine (33%) patients had not undergone gastrectomy due to advanced tumor stage and extragastric metastases. In these patients, the interval between diagnosis of primary gastric cancer and onset of biliary obstruction ranged from 0.5 to 28.5 months, with a median duration of 6.2 months.

Most of biliary obstruction was caused by intraductal metastasis indistinguishable from primary biliary malignancies in 63 (54%) patients and metastatic lymph node in 25 (21%) patients. All intraductal metastasis in the 63 patients manifested themselves as pure enhancing wall thickening (n = 60) or intraductal mass (n = 3). Forty-one (65%) of the 63 patients with intraductal metastasis had cystic ductal lesions contiguous with the intraductal lesion. The relationship between type of metastasis (only including intraductal metastasis and metastatic lymph node group) and clinicopathologic characteristics is summarized in Table 3. Among the variables, type of metastasis was significantly associated with histology of primary gastric cancer (p = .001) and level of obstruction (p < .001). The lymph node metastasis was significantly associated with differentiated histology of primary gastric cancer and also significantly associated with non-hilar biliary obstruction.

The relationship between histologic type of primary gastric cancer and clinical characteristics is summarized in Table 4. Among the variables, histologic type was significantly associated with age (p = .015), sex (p = .010), and type of metastasis (p < .001). Age of patients with malignant biliary obstruction which associated with signet ring cell histology of primary gastric cancer was significantly younger than that of patients associated with differentiated histology. Moreover, signet ring cell histology was significantly associated with female gender and intraductal metastasis.

PTBD: Technical Outcomes

Mean serum bilirubin levels before PTBD were 10.1 ± 7.1 mg/dl and 1 week after PTBD were 5.1 ± 4.9 mg/dl. There was a significant difference in the pre- and post-PTBD serum bilirubin levels (p < .001). Successful drainage was achieved in 105 (90%) of 117 patients. Among the 12 patients who did not show successful internal drainage, post-stenting serum bilirubin levels increased in 7 patients and minimally decreased in 5 patient. Age, sex, histology of primary gastric cancer, type of metastasis, level of obstruction, and serum bilirubin levels before stenting showed no association with the rate of successful internal drainage.
Minor complications occurred in eight (7%) patients. These patients had self-limiting hemobilia that completely resolved 2-6 days after PTBD and without transfusion. A major complication occurred in one (1%) patient. The patient had severe hemobilia secondary to a pseudoaneurysm of a right intrahepatic artery that was treated successfully by selective transarterial embolization.

PTBD: Survival analysis

Cutoff date for data analysis was 31 December 2010. During the median follow-up period of 185 days (range, 7-1266 days), 110 patients died and seven patients were still alive. The causes of deaths were disease progression (n = 97) and sepsis (n = 3). The 30-day mortality rate was 11% (13 of 117 patients). The median survival after PTBD was 104 days (95% CI, 84-123 days).

On the basis of univariate log rank analyses, five of the 11 variables (p < .2) were considered as candidate variables for multivariate analysis to determine the most independent predictors for patient survival. The variables were histology of primary gastric cancer (p = .119), level of biliary obstruction (p = .074), metallic stenting after PTBD (p = .001), serum bilirubin level after PTBD (p < .001), and chemotherapy after PTBD (p < .001) and were entered into multivariate analysis model. On the basis of multivariate Cox regression analysis, histology of primary gastric cancer (p = .011), serum bilirubin level after PTBD (p = .002), and chemotherapy after PTBD (p < .001) were the independent predictors of patient survival (Table 5).

The median survival of 115 days (95% CI, 64-166 days) in patients whose had differentiated histology of primary gastric cancer was significantly longer than that of 80 days (95% CI, 44-116 days) in patients whose had signet ring cell histology of primary gastric cancer (Fig. 6). The median survival was significantly longer in patients whose serum bilirubin levels #2 mg/dl after PTBD (172 days; 95% CI, 122-222 days) than in patients whose serum bilirubin levels >2 mg/dl (48 days; 95% CI, 31-65 days). In addition, the patients who received chemotherapy after PTBD had a significant longer median survival of 172 days (95% CI, 111-233 days) compared with that of 55 days (95% CI, 36-74 days) for the patients who did not receive chemotherapy after PTBD (Fig. 7).

Metallic Stent Placement: Outcomes and Stent Patency Analysis

The technical success rate of the stent placement was 100%. Mean serum bilirubin levels before stent placement were 5 ± 4.5 mg/dl and 1 week after stent placement were 1.8 ± 2.4 mg/dl. There was a significant difference in the pre- and post-stenting serum bilirubin levels (p < .001). Successful internal drainage was achieved in 49 (91%) of 54 patients. Seven patients (6%) experienced minor complications including self-limiting hemobilia and pancreatitis. Three patients had self-limiting hemobilia that completely resolved within 3 days after stent placement and without transfusion. Four patients who
presented with acute pancreatitis were treated successfully conservatively for 3-7 days (mean, 4 days). However, none experienced major complications.

According to the Kaplan-Meier analysis, the median stent patency time was 351 days (95% CI, 219-483 days). Cumulative stent patency rates at 3, 6, 9, and 12 months were 95%, 77%, 70%, and 50%, respectively. Stent occlusion was observed in 13 (24%) patients after a mean interval of 231 days. Stent occlusions were caused by tumor ingrowth in all 7 (13%) patients who underwent uncovered stent placement. Of the 7 patients, tumor ingrowths were caused by intraductal metastasis in 6 patients and periductal metastasis in 1 patient. Stent occlusions were caused by tumor overgrowth in 4 (7%) or sludge incrustation in 2 (4%) patients who underwent covered stent placement. Of the 6 patients, tumor overgrowths were caused by progression of lymph node metastasis in 4 patients and sludge incrustations were observe in 2 patients with biliary obstruction caused by intraductal metastasis. Four of these 13 patients with stent occlusion were managed by insertion of more than one additional stent, whereas 9 patients were managed by internal or external drainage catheter due to their rapidly progressing disease and poor general condition. Age, sex, histology of primary gastric cancer, type of metastasis, level of obstruction, serum bilirubin level before stenting, chemotherapy after stenting, and stent type showed no association with the stent patency rates and successful internal drainage.

**Metallic Stent Placement: Survival Analysis**

On the basis of univariate log rank analyses, two of the nine variables (\( p < .2 \)) were considered as candidate variables for multivariate analysis to determine the most independent predictors for patient survival. The variables were serum bilirubin level after stenting (\( p < .001 \)) and chemotherapy after stenting (\( p = .001 \)) and were entered into multivariate analysis model. On the basis of multivariate Cox regression analysis, serum bilirubin level after stenting (\( p = .017 \)) and chemotherapy after stenting (\( p = .033 \)) were the independent predictors of patient survival (Table 6).

The median survival was significantly longer in patients whose serum bilirubin levels \#2 mg/dl after stenting (182 days; 95% CI, 122-242 days) than in patients whose serum bilirubin levels >2 mg/dl (54 days; 95% CI, 20-88 days) (Fig. 8). In addition, the patients who received chemotherapy after stenting had a significant longer median survival of 224 days (95% CI, 138-310 days) compared with that of 148 days (95% CI, 133-163 days) for the patients who did not receive chemotherapy after stenting.
Table 2: Table 2. Imaging characteristics of 117 patients with malignant biliary obstruction caused by metastatic gastric cancer. CBD = common bile duct, CHD = common hepatic duct

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Table 3: Table 3. Comparison of characteristics according to type of metastasis in patients with metastatic biliary obstruction. CBD = common bile duct

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**Table 4:** Table 4. Comparison of characteristics according to histology of primary gastric cancer in patients with metastatic biliary obstruction CBD = common bile duct

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Table 5: Table 5. Results of multivariate Cox regression analysis in patients following PTBD. PTBD = percutaneous transhepatic biliary drainage

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Table 6: Table 6. Results of multivariate Cox regression analysis in patients following stent placement.

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Fig. 6: Figure 6. Kaplan-Meier curves show significant difference in survival between in patients who had differentiated histology of primary gastric cancer and had signet ring cell histology of primary gastric cancer.
Fig. 7: Figure 7. Kaplan-Meier curves show significant difference in survival between in the patients who received chemotherapy after PTBD and the patients who did not receive chemotherapy after.
Fig. 8: Figure 8. The median survival was significantly longer in patients whose serum bilirubin levels ≤2 mg/dl after stenting than in patients whose serum bilirubin levels >2 mg/dl.

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Conclusion

In this study, we found that upper CBD (33%) and hilum (33%) were the most frequent levels of biliary obstruction, and intraductal metastasis (54%) and lymph node metastasis (21%) were the most frequent types of metastasis. The most frequent site of obstruction caused by metastatic gastric cancer was the common bile duct (CBD) because the cause of obstruction was predominantly lymph node metastasis along the hepatoduodenal ligament. In addition, we found that lymph node metastasis was significantly associated with differentiated histology of primary gastric cancer and non-hilar biliary obstruction. All 25 patients with lymph node metastasis had non-hilar bile duct (upper CBD and whole CBD) obstruction. In four cases, we found no obstructing lesion with CT and the obstruction level was the lower CBD. The cause of this pattern is probably the small metastatic lymph node around CBD or small intraductal metastasis. On the histologic bases of primary gastric cancer, we found that signet ring cell histology was significantly associated with women and intraductal metastasis. Therefore, we could postulate that, during a follow-up period after gastrectomy in patients with signet ring cell histology of primary gastric cancer, close imaging observation of biliary system may be necessary for early detection and subsequent treatment such as chemotherapy.

In this study, we found that histology of primary gastric cancer, serum bilirubin level after PTBD, and chemotherapy after PTBD were the independent predictors of survival in patients who underwent PTBD. Our results also suggest that chemotherapy after PTBD could prolong the patient survival. However, the patients who received chemotherapy had lower serum bilirubin level and better general condition than the patients who did not receive chemotherapy. These clinical background imbalances might influence the survival difference.

In this study, serum bilirubin level and chemotherapy after stenting were the independent predictors of survival in patients underwent metallic stent placement. Unlike the survival analysis of the patients underwent PTBD, the histologic type of primary gastric cancer was not independent predictor of survival in patients underwent metallic stent placement. Because many patients with signet ring cell histology did not undergo metallic stent placement due to contraindication of metallic stent placement, this might influence no significant difference in survival rates between the histologic types of the patients underwent metallic stent placement. Therefore, our results suggest that patients with differentiated histology of primary gastric cancer can be candidates for treatment with a combination of PTBD with subsequent metallic stent placement and chemotherapy.

In conclusion, intraductal metastasis was the common type of metastasis in patients with malignant biliary obstruction caused by metastatic gastric cancer. Because signet ring cell histology of primary gastric cancer was significantly associated with intraductal metastasis, close imaging observation of biliary system may be necessary for early detection of metastasis and subsequent treatment such as chemotherapy. PTBD with
metallic stent placement provides good palliation for patients with malignant biliary obstruction caused by metastatic gastric cancer. The survival period in patients with differentiated histology was significantly longer than that in patients with signet ring cell histology after PTBD. In addition, serum bilirubin level and chemotherapy after biliary intervention were independent factors for predicting survival. Therefore, patients with differentiated histology of primary gastric cancer and serum bilirubin level #2 mg/dl after PTBD are probably best candidates for treatment with combination of metallic stent placement and chemotherapy.
References


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