

Review Article

Plastic Versus Metal Stents for Hilar Cholangiocarcinoma: a Meta-Analysis and Systematic Review

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Abstract

Background: Metallic or plastic stents are used for palliating inoperable malignant hilar obstruction. It is unclear if there is a difference between metallic versus plastic stenting in these patients.

Aim: To compare metallic and plastic stents for malignant hilar obstruction.

Method:

Study Selection Criteria: Studies using metallic or plastic stents for stenting of malignant hilar obstruction were selected.

Data collection & extraction: Articles were searched in Medline, Pubmed, Ovid journals, CINAHL, International pharmaceutical abstracts, old Medline, Medline non indexed citations, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews. Two reviewers independently searched and extracted data. Any differences were resolved by mutual agreement.

Statistical Method: Pooled proportions were calculated using both Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model).

Results: 1630 reference was identified, of which 159 relevant articles were selected and reviewed. 8 studies (N=575) for unilateral metallic stents, 7 studies (N=850) for unilateral plastic stents, 13 studies (N=340) for bilateral metallic stents and 8 studies (N=367) for bilateral plastic stents which met the inclusion criteria were included in this analysis. Pooled data are shown in Table 1 and 2. The pooled estimates calculated by fixed and random effect models were similar. The p for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10.

Conclusion: For unilateral stenting, metallic stents have lower complication rate and cholangitis when compared to plastic stents. Metallic stents have a higher mean survival, patency rate, and 30 day mortality. For unilateral stenting in malignant hilar obstruction, metallic stents are superior to plastic stents. For bilateral stenting, metallic stents have lower complication rate and early cholangitis when compared to plastic stents. Metallic stents have a higher mean survival, patency rate, and 30 day mortality. For bilateral stenting in hilar malignant obstruction, metal stents are superior to plastic stents.

Keywords: Plastic Stent; Metal Stent; Cholangiocarcinoma; Hilar; Meta-analysis; Systematic Review

Introduction

This meta-analysis and systematic review was written in accordance with the proposal for reporting by the QUOROM (Quality of Reporting of Meta-analyses) statement [1]. The study design for this meta-analysis and systematic review conformed to the guidelines of Standards for Reporting of Diagnostic Accuracy (STARD) initiative [2].

Hilar Cholangiocarcinoma (Klatskin tumor) is a malignant neoplasm arising from the epithelial lining of the biliary tree, near the confluence of the right and left hepatic duct. The tumor histology is

that of adenocarcinoma in > 90% of the confirmed cases. The overall incidence is about 3000 new cases each year in the United States as noted in the data base registries Surveillance Epidemiology End Results, SEER [3]. The incidence for extra hepatic cholangiocarcinoma has remained unchanged over the last few years despite the increase in the incidence of intra hepatic cholangiocarcinomas [4,3].

Clinical presentation of hilar obstruction includes painless jaundice with purities, dark urine and stools. The risk factors for cholangiocarcinoma include conditions that predispose to chronic biliary inflammation and cholestasis, which eventually promote malignant transformation. In the US and Europe, primary sclerosing

cholangitis (PSC) is the major risk factor followed by congenital biliary disorders such as choledochal cysts and biliary atresia. The cumulative prevalence of cholangiocarcinoma among patients with PSC ranges between 5-15% among various series [5] and is independent to the duration of the illness with the highest incidence within the first 2 years of diagnosis. Elsewhere, in the Far East Asia (Thailand) Liver flukes namely *Opisthorchis viverrini* and *Clonorchis sinensis* are associated with cholangiocarcinoma. The relative risk of Cholangiocarcinoma is 4.8 when it is associated with liver flukes [6]. Thorotrast, a 25 % colloid solution of thorium dioxide (ThO₂), which was used as contrast agent, is also strongly associated with cholangiocarcinoma. It has radio nucleotide property with half-life of 14 billion years. It deposits in various tissues resulting in prolonged Alfa radiation exposure resulting in cirrhosis and cholangiocarcinoma [7]. Despite many known risk factors, a specific identifiable risk factor may not be known in many individuals at diagnosis.

Cholangiocarcinoma has grave prognosis and surgical resection with or without liver transplantation offers the only long-term clear survival benefit when detected at an early stage. Predictors of long-term survival include lower tumor stage, clear margins, absent lymph node disease, no loco-regional invasion or distant metastasis [8]. Palliation in late or unresectable stage is to minimize symptoms related to cholestasis (intense jaundice and prurities), minimizing cholangitis and relief of pain with or without additional adjuvant chemotherapy and radiotherapy.

The options of optimal palliation for obstructive jaundice depend on the local expertise and can include surgical bypass and stenting either endoscopic or percutaneous. Head to head comparison of surgical bypass versus endoscopic stenting showed significantly lower early major complications and procedure related mortality, though there was no clear long term survival advantage favoring endoscopic palliation [9]. When percutaneous stenting is compared to endoscopic bile duct decompression, the evidence is conflicting with discordant results with one showing benefit from endoscopic approach [10] and the other favoring percutaneous approach [11]. In general, most centers resort to percutaneous biliary decompression with stenting second only to endoscopic stenting due to quality of life issues.

There are many variables that are considered in optimizing endoscopic palliation taking into account the disease stage and extension, type of stent (plastic or metal) and unilateral versus bilateral stenting is better. However, negotiating hilar obstruction is quite challenging when compared to distal biliary obstruction and should ideally be performed by endoscopists with significant case volume and expertise to achieve acceptable results [5]. There is still no consensus regarding the issue of plastic or metal and also whether unilateral or bilateral stenting offer superior palliation for malignant hilar obstruction.

The aim of this meta-analysis is to systematically review the medical literature and compare the efficacy of metal versus plastic stents whether placed unilateral or bilateral in achieving acceptable palliation from symptoms related to obstructive jaundice. Also to look for early and late procedure related complication. We also looked at sustained and durable stent patency.

Methods

Study selection criteria

Studies using metallic or plastic stents for stenting malignant hilar obstruction were selected.

Data collection & extraction

Articles were searched in medline (through PubMed, an electronic search engine for published articles and Ovid), Pubmed, Ovid Journals, embase, Cumulative Index for Nursing & Allied Health Literature, ACP Journal Club, dare, old Medline, Medline non-indexed citations, ovid Healthstar, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews(central). The search was performed from January 1966 to January 2014. Abstracts were manually searched in the major Gastroenterology journals for the past 3 years. Study authors were contacted when the required data could not be determined from the publications. The search terms used were Plastic Stent, Metal Stent, Cholangiocarcinoma, Hilar, Meta-analysis, and Systematic Review. Two authors (SRP and NRK) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement. The agreement between reviewers for the collected data was quantified using the Cohen's κ [12].

Quality of Studies

Clinical trials designed with a control and treatment arms can be assessed for quality of the study. A number of criteria have been used to assess this quality of a study (e.g. randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome) [13,14]. There is no consensus on how to assess studies designed without a control arm. Hence, these criteria do not apply to studies without a control arm [13]. Therefore, for this meta-analysis and systematic review, studies were selected based on completeness of data and inclusion criteria.

Outcome measures

The studies that reported specific outcomes including successful stenting, improvement in bilirubin, procedure complications, ascending cholangitis and 30 day mortality. We defined success of stenting as placement of stent across the stricture with flow of either contrast or bile through the stent. Improvement of jaundice is defined as reduction in the total bilirubin by 75% in 1 month. Cholangitis was defined as presence of fever or evidence of increase in bilirubin. Procedure related complication was further defined as early (< 30 days) and late (> 30 days).

Statistical methods

This meta-analysis was performed by calculating pooled proportions. First the individual study was transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. This was done to give a weight to each individual proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model [15,16]. Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. More

width means more weight was give to a study. Larger studies get more weight and small studies get less weight. The heterogeneity among studies was tested using Cochran’s Q test based upon inverse variance weights [17]. If p value is > 0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by both Egger bias indicator [18] and Begg-Mazumdar bias indicator [18]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio [12,19-21].

Results

Unilateral Stenting

1630 reference were identified, of which 159 relevant articles were selected and reviewed. 8 studies (N=575) for unilateral metallic stents [22-29] and 7 studies (N=850) for unilateral plastic stents [24,30-35], which met the inclusion criteria, were included in this meta-analysis. Pooled data are shown in Table 1. The pooled estimated by fixed and random effect models were similar. Figure 1 shows the success of unilateral metal stent placement in a for rest plot. The p for chi-

Table 1: Pooled proportion of unilateral metallic and unilateral plastic stents with 95% CI for malignant hilar obstruction.

Proportion	Unilateral Metallic Stents (95% CI)	Unilateral Plastic Stents (95% CI)
Success of Placement	95.00% (91.90 to 97.38)	88.34% (77.91 to 95.74)
Decrease in Bilirubin	81.95% (71.96 to 90.14)	60.96% (44.93 to 75.85)
Overall Complications	24.53% (14.67 to 35.98)	35.14% (13.39 to 60.80)
Early Complications	11.27% (5.25 to 19.22)	18.82% (14.39 to 23.68)
Late Complications	21.15% (16.06 to 26.74)	39.33% (32.12 to 46.77)
Mean Survival	145.04 days (121.64 to 168.44)	127.22 days (84.51 to 169.92)
Mean Stent Patency	158.75 days (114.09 to 203.42)	18.97 days (5.40 to 32.54)
Overall Cholangitis	18.11% (10.38 to 27.42)	20.81% (10.18 to 34.01)
Early Cholangitis	7.90% (3.99 to 12.98)	11.92% (7.42 to 17.32)
Late Cholangitis	15.66% (10.18 to 22.08)	18.44% (8.86 to 30.54)
30 Day Mortality	1.44% (0.38 to 3.19)	14.23% (4.78 to 27.62)

Compared to unilateral plastic stenting, metallic biliary stents showed favorable outcome including lower complication rate and cholangitis and higher mean survival, patency rate, and 30 day mortality.

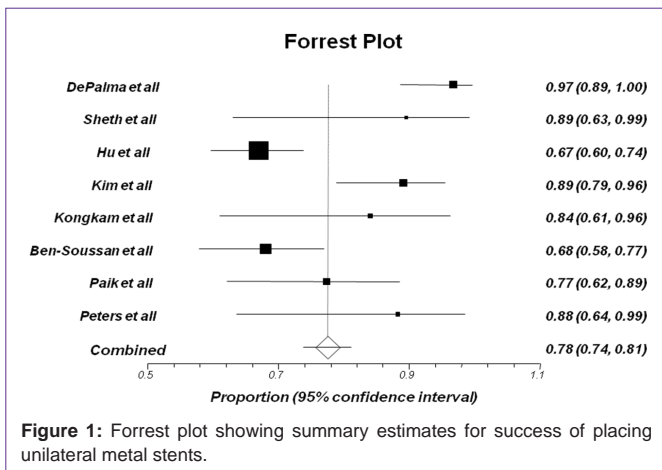


Figure 1: Forrest plot showing summary estimates for success of placing unilateral metal stents.

squared heterogeneity for all the pooled accuracy estimates was > 0.10. For unilateral metal stenting, Begg-Mazumdar bias indicator gave a Kendall’s tau = 0.071 (p = 0.91) and Egger bias was 1.32 (95% CI = -7.79 to 5.14, p = 0.63). Begg-Mazumdar bias calculations for the unilateral plastic stenting gave a Kendall’s tau = -0.07 (p = 0.72) and Egger bias for unilateral plastic stents gave a value of -5.81 (95% CI = -10.85 to -0.78, p = 0.03). These indicate that there was no clear publications bias. Funnel plot to look at publication also showed no bias. Figure 2, shows the funnel plot for unilateral metal stent.

Table 1: Pooled proportion of unilateral metallic and unilateral plastic stents with 95% CI for malignant hilar obstruction.

Bilateral Stenting

1640 reference articles were identified, of which 169 relevant articles were selected and reviewed. 13 studies (N=340) for bilateral metallic stents [28,36-47] and 8 studies (N=367) for bilateral plastic stents [31,32,35,37,45,46,48,49], which met the inclusion criteria, were included in this analysis. Pooled data are shown in table 2. The pooled estimated by fixed and random effect models were similar. The p for chi-squared heterogeneity for all the pooled accuracy estimates

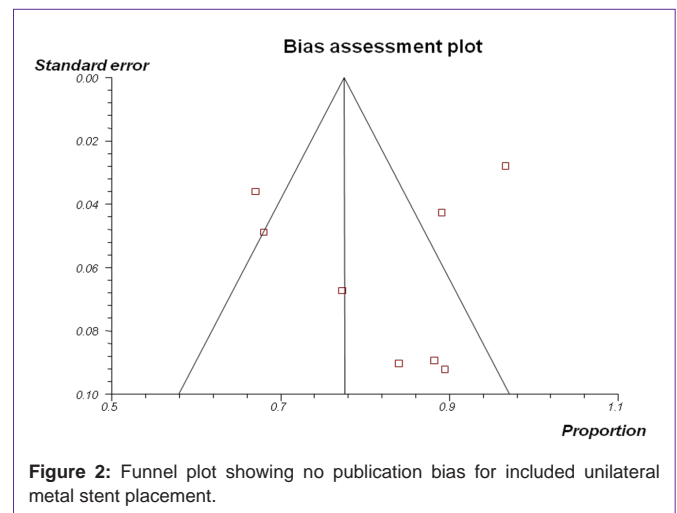


Figure 2: Funnel plot showing no publication bias for included unilateral metal stent placement.

Table 2: Pooled proportion with 95% CI for Bilateral Metallic and Bilateral Plastic Stents for Malignant Hilar Obstruction.

Proportion	Bilateral Metallic Stents (95% CI)	Bilateral Plastic Stents (95% CI)
Success of Placement	91.06% (83.92 to 96.26)	87.57% (77.89 to 94.75)
Decrease in Bilirubin	90.42% (83.02 to 95.88)	73.92% (65.48 to 81.54)
Overall Complications	12.51% (4.46 to 23.84)	41.83% (25.43 to 59.21)
Early Complications	16.17% (5.86 to 30.30)	27.71% (21.15 to 34.79)
Mean Survival	204.49 days (181.77 to 227.22)	151.92 days (128.79 to 175.04)
Mean Stent Patency	114.64 days (23.12 to 72.94)	8.09 days (7.19 to 9.00)
Overall Cholangitis	20.54% (10.69 to 32.58)	25.49% (18.43 to 33.26)
Early Cholangitis	8.06% (1.19 to 20.20)	17.49% (6.30 to 32.74)
Late Cholangitis	13.93% (4.39 to 27.68)	18.15% (0.40 to 65.55)
30 Day Mortality	3.92% (0.51 to 10.34)	13.64% (9.27 to 18.69)

Compared to bilateral plastic stenting, metallic stenting showed favorable outcomes including lower cholangitis rates and higher patency rates, mean survival and 30 day mortality.

was > 0.10 . Figure 3 shows for rest plot for bilaterally placed metal stents. For bilateral metal stenting, Begg-Mazumdar bias indicator gave a Kendall's tau = -0.02 ($p = 0.86$) and Egger bias was -1.25 (95% CI = -4.23 to 1.74 , $p = 0.36$). Begg-Mazumdar bias calculations for the bilateral plastic stenting gave a Kendall's tau = -0.24 ($p = 0.38$) and Egger bias for bilateral plastic stents gave a value of -3.42 (95% CI = -7.42 to 0.58 , $p = 0.1$). These indicate that there was no clear publications bias. Funnel plot to look at publication bias also showed no bias. Figure4, shows the funnel plot for bilateral metal stent. The change adjusted agreement analysis between the reviewers for data collected separately gave a kappa value of 1.0 (Table 2).

Discussion

For unilateral stenting, metal stents have a higher success rate of placement (95%) when compared to unilateral plastic stent placement (88%). This might be due to the smaller deployment system of the metal stents compared to plastic stents, making it easier to maneuver through tight strictures. It is not clear from the included papers if dilation of the stricture was performed to improve success of plastic stent placement. When it comes to patency of a stent, unilateral metal stents showed a markedly longer period of patency

(159 days) when compared to plastic stents (19 days). This prevents repeat endoscopic treatments to exchange stents in these patients. The overall complication rate of unilateral metal stents was lower than unilateral plastic stents. This difference was seen both in early and late complications. More specifically, the percentage of patients with cholangitis was lower with unilateral metal stents (18%) when compared to plastic stents (21%). A closer look into early or late cholangitis, unilateral metal stents seem to be better than unilateral plastic stents. The 30 day mortalities was markedly lower for unilateral metal stent (1 day) compared to unilateral plastic stents (14 days). These differences might be due to the larger size of the metal stents. The overall survival was better with unilateral metal stents (145 days) compared to unilateral plastic stents (127 days). From this data it is not clear if placing two plastic stents unilaterally is better than one unilateral metal stent.

When considering bilateral stents, metal stents again have a higher success rate of placement (91%) when compared to plastic stents (87%). As discussed earlier, this is probably due to the smaller deployment system of the metal stents compared to plastic stents. It is not clear from the included papers if dilation of the stricture was performed to improve success of plastic stent placement. Comparing the patency of bilateral stenting, metal stents showed a markedly longer period of patency (115 days) when compared to plastic stents (8 days). This prevents repeat endoscopic treatments to exchange stents in these patients. The overall complication rate of bilateral metal stents was lower (13%) than bilateral plastic stents (42%). This difference was seen both in early and late complications. Looking at cholangitis after placing bilateral stents: metal stents had a lower percentage (21%) compared to plastic stents (25%). A closer look into early or late cholangitis, bilateral metal stents seem to be better than bilateral plastic stents. The 30 day mortality was markedly lower for bilateral metal stent (4 day) compared to bilateral plastic stents (14 days). These differences might be due to the larger size of the metal stents. The overall survival was better with bilateral metal stents (204 days) compared to bilateral plastic stents (152 days).

Hilar malignancies are classified using Bismuth Classification. One of the draw backs of this meta-analysis is that subgroup analysis according to the Bismuth class cannot be done.

Studies with statistically significant results tend to be published and cited. Smaller studies may show larger treatment effects due to fewer case-mix differences (e.g. patients with only early or late disease) than larger trials. This publication and selection bias may affect the summary estimates. This bias can be estimated by Egger bias indicators and construction of Funnel plots. Bias among studies can affect the shape of the Funnel plot. In this meta-analysis and systematic review, bias calculations using both Egger bias indicator [18] and Begg-Mazumdar bias indicator [18] showed no statistically significant bias. Furthermore, analysis using Funnel plots showed no significant publication bias among the studies included in this analysis.

In conclusion, unilateral metal stents have lower complication rate and cholangitis when compared to plastic stents. Also, unilateral metallic stents have a higher mean survival, patency rate, and 30 day mortality. For bilateral stenting, metallic stents have lower complication rate and early cholangitis when compared to plastic

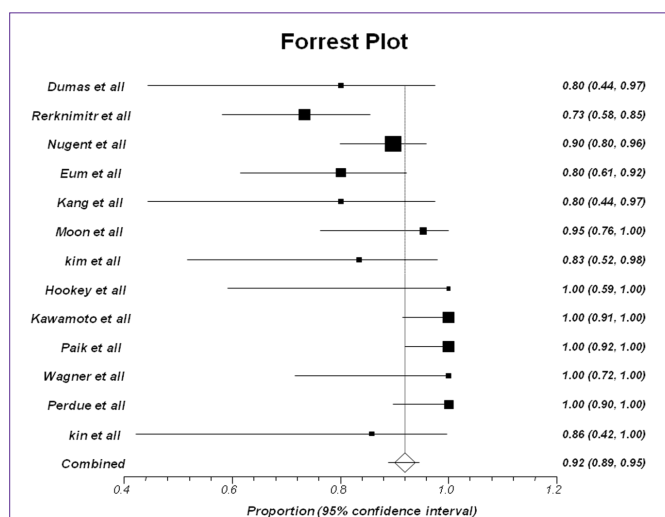


Figure 3: Forrest plot showing summary estimates for success of placing bilateral metal stents.

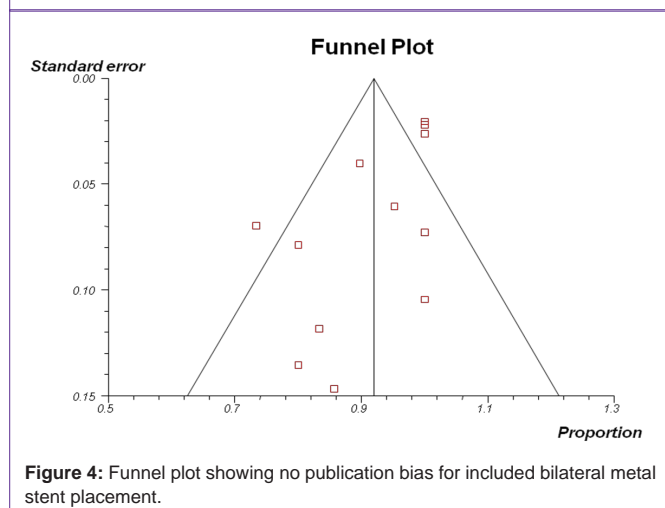


Figure 4: Funnel plot showing no publication bias for included bilateral metal stent placement.

stents. Metallic stents have a higher mean survival, patency rate, and 30 day mortality. Patient with unilateral or bilateral metal stents have a higher survival compared to plastic stents. When looking at unilateral or bilateral stenting for hilar malignancy, metal stents seem to be superior to plastic stents.

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