*Gastroenterology Report*, 2023, **11(0)**, goad048
https://doi.org/10.1093/gastro/goad048
**Review Article**

## Review Article

# Efficacy and complications of inoperable malignant distal biliary obstruction treatment by metallic stents: fully covered or uncovered?

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## Abstract

Obstructive jaundice caused by malignant distal biliary obstruction is a common clinical symptom in patients with inoperable biliary–pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP)-guided stent implantation is an effective treatment for obstructive jaundice. Internal stent drainage is more physiologic and associated with a better quality of life than external stent drainage methods such as percutaneous transhepatic gallbladder drainage or percutaneous transhepatic cholangiodrainage. Self-expanding metallic stents, which may be covered and uncovered, are commonly used. However, some uncertainties remain regarding the selection of metallic stents, including drainage patency time, clinical effect, stent migration, and post-operative complications such as pancreatitis, bleeding, and cholecystitis. This review aims to summarize the current progress and controversies surrounding the use of covered or uncovered metallic stents in inoperable common biliary obstruction via ERCP.

**Keywords:** malignant distal biliary obstruction; ERCP; metallic stents; USEMS; CSEMS

## Background

Malignant distal biliary obstruction (MDBO) usually appears in advanced stages of some cancers, such as cholangiocarcinoma, pancreatic ductal adenocarcinoma, and carcinoma of Vater's ampulla [1]. Consequently, obstructive jaundice frequently develops in cases of outflow obstruction. Thus, palliative biliary drainage plays an important role in alleviating clinical symptoms, improving quality of life, and prolonging overall survival [2, 3]. For malignant tumor-induced distal biliary obstruction, effective drainage and improvement of liver function are prerequisites for subsequent treatment, such as neoadjuvant chemotherapy, targeted therapy, and immunotherapy. External drainage methods, such as percutaneous transhepatic gallbladder drainage (PTCD) and percutaneous transhepatic cholangiodrainage (PTGD), are easy to implement and inexpensive. However, complete external drainage usually results in a series of digestion and absorption problems. Long-term external drainage, in contrast, has a significant impact on quality of life. In addition, because patients with obstructive jaundice frequently have coagulopathy, transhepatic puncture is considered a high-risk procedure.

Currently, the most common technique in clinical practice is biliary stent implantation via endoscopic retrograde cholangiopancreatography (ERCP) [3]. Compared with external stent drainage methods such as PTGD and PTCD, internal stent drainage is physiologically more compatible and promotes better quality of life for patients [4, 5]. Owing to the advancements in endoscopic technology, the implantation of a permanent metallic stent under ERCP has become the preferred option for improving patients' quality of life [3].

Plastic and metallic stents are the most commonly used types of stents for internal stent drainage [6]; however, plastic stents, which are applied for temporary drainage, are more susceptible to blockages due to their narrow diameter and sludge formation [6]. Metallic stents are self-expandable; they can be an uncovered self-expandable metal stent (USEMS) or a covered self-expandable metal stent (CSEMS) and have been considered the best option for permanent drainage [6, 7] (Figure 1). However, the advantages and disadvantages of USEMS and CSEMS for MDBO drainage are controversial. There are several unanswered questions regarding survival, stent patency time, drainage effect, and post-operative

**Received:** 22 December 2022. **Revised:** 09 July 2023. **Accepted:** 30 July 2023

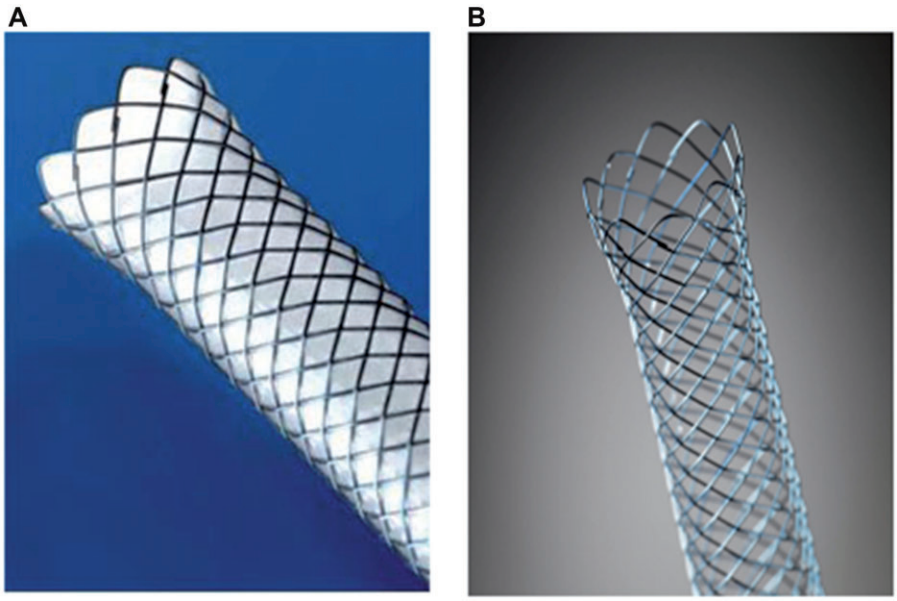


**Figure 1.** Wallflex biliary metallic stents from Boston Scientific. (A) Fully covered metallic stent. (B) Uncovered metallic stent. These pictures were downloaded from the website https://www.bostonscientific.com/en-US/products/stents–gastrointestinal/wallflex-biliary-rx-stents.html.

complications such as cholecystitis, stent occlusion, and pancreatitis. This review aims to summarize the drainage efficiency and post-operative complications of the application of USEMS and CSEMS in MDBO by searching the latest studies using the key words "ERCP," "MDBO," "metal stents/," "CSEMS," "USEMS," and "complications," and combining our own experience.

## Stent drainage effect

The effect of stent drainage is commonly used to evaluate whether stent implantation has successfully relieved biliary obstruction and symptoms, primarily by examining the overall survival time after stent implantation, stent patency time, and drainage efficiency.

### Overall survival time

The studies included in this review reported varied sample sizes and spanned a long period of time. Nonetheless, overall survival outcomes have been noticeably consistent with the use of CSEMS and USEMS with no significant difference in survival time between these surgical methods [8–17]. It has been suggested that the survival time after effective drainage with stent implantation as a palliative treatment is more dependent on the biological behavior of the tumors than on the type of stent used. However, we discovered that the survival time both in the CSEMS and USEMS groups varied greatly across studies (from 112 to 359 days). In addition to the effect of sample size, we found that the proportion of causative diseases contributed to the high heterogeneity [16, 17]. For example, the subgroup analysis in the study by Isayama *et al.* [8] revealed that patients with metastatic pancreatic cancer had a worse prognosis than patients with other types of cancer. The overall survival time reported by studies included in this review is shown in Table 1.

### Stent patency time

The time of stent patency determines the duration of effective drainage, which may influence patient survival in some cases. The most common causes of USEMS occlusion include tumor ingrowth or outgrowth, which eventually blocks the stent lumen. Mechanical force extrusion caused by tumor proliferation has also been reported as a cause of stent occlusion, which is common in pancreatic malignancies [8]. Owing to the characteristics of CSEMS, tumor growth into the lumen can be prevented; thus, CSEMS could theoretically better sustain patency. Accordingly, most studies have confirmed that CSEMS outperforms USEMS in terms of patency maintenance [11, 15, 18, 19]. However, some studies reported no significant difference between methods [8, 10, 12–14, 20, 21] and the randomized–controlled trial (RCT) by Lee *et al.* [9] demonstrated that patency was better maintained with USEMS than with CSEMS (413.3 vs 207.5 days, $P = 0.041$). Of note, these outcomes may have been influenced by the small sample size ($n = 40$). The lack of detailed subgroup analysis and varied disease types among studies may also be factors leading to the equivocal conclusion.

Mechanistically, stent dysfunction could occur for different reasons. For example, stent migration and tumor ingrowth and overgrowth could lead to stent dysfunction and ultimately have a negative impact on stent patency. Two available meta-analyses showed that CSEMS outperformed USEMS in terms of biliary patency maintenance; the subgroup analysis indicated that the benefits of CSEMS were more apparent for pancreatic malignant tumors and cholangiocarcinoma, while there was no significant difference between stent types in patients with duodenal papilla cancer and gallbladder cancer [18, 19]. The meta-analysis conducted by Tringali *et al.* [22] involved 11 RCTs and indicated that the USEMS and CSEMS groups were comparable in terms of stent patency; however, CSEMS was associated with more frequent stent migration, a lower rate of tumor ingrowth, and a higher rate of tumor overgrowth. These authors also identified many confounding factors that are correlated with stent patency, suggesting that further systematic subgroup analyses are needed in future RCTs [22].

In addition, some studies analysed different stent materials and discovered that the patency time of CSEMS covered with Wallflex material is better than that of non-Wallflex [18], indicating that further research on the material used for covering self-expandable metal stents is warranted. Detailed information regarding patency is reported in Table 2.

**Table 1.** Overall survival time after stent implantation

| Study | Reference | Type of study | Number of patients | USEMS | CSEMS | P-value |
|---|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 112 | 255 (12–810) days ($n = 55$) | 237 (11–1,155) days ($n = 57$) | ns |
| Lee *et al.* (2014) | [9] | RCT | 40 | 359 (95% CI, 239–480) days ($n = 20$) | 350 (95% CI, 264–436) days ($n = 20$) | 0.271 |
| Jang *et al.* (2018) | [26] | Retrospective study | 645 | 161 (65.0–328.0) days ($n = 431$) | 164 (54.0–315.0) days ($n = 214$) | 0.76 |
| Sakai *et al.* (2021) | [11] | RCT | 92 | 223 (95% CI, 101–338) days ($n = 48$) | 213 (95% CI, 111–323) days ($n = 44$) | 0.238 |
| Lee *et al.* (2013) | [12] | Retrospective study | 749 | 11.8 (95% CI, 10.5–13.2) months ($n = 578$) | 10.4 (95% CI, 8.7–12.1) months ($n = 171$) | 0.84 |
| Kullman *et al.* (2010) | [13] | RCT | 400 | 174 days ($n = 200$) | 116 days ($n = 200$) | 0.32 |
| Yoon *et al.* (2006) | [14] | Retrospective study | 77 | 308 ± 42 days ($n = 41$) | 392 ± 60 days ($n = 36$) | 0.952 |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 65 | 190 (11–439) days ($n = 21$) | 291 (6–724) days ($n = 44$) | ns |
| Kitano *et al.* (2013) | [16] | RCT | 120 | 222 days ($n = 60$) | 285 days ($n = 60$) | 0.68 |
| Conio *et al.* (2018) | [17] | RCT | 158 | 112 (95% CI, 65.9–158.1) days ($n = 80$) | 134 (95% CI, 97.8–170.2) days ($n = 78$) | 0.23 |
| Saleem *et al.* (2011) | [19] | META | 203 | WMD (CSEMS vs USEMS) = 51.18 days | | 0.01 |
| Moole *et al.*(2016) | [21] | META | 2,239 | OR (CSEMS vs USEMS) = 1.29 | | ns |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; 95% CI, 95% confidence interval; WMD, weighted mean difference; OR, odds ratio; ns, not significant.

**Table 2.** Stent patency after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | P-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 193 days | 225 days | ns |
| Lee *et al.* (2014) | [9] | RCT | 413 day | 207 days | 0.041 |
| Jang *et al.* (2018) | [26] | Retrospective study | 557.9 days | 546.7 days | 0.14 |
| Sakai *et al.* (2021) | [11] | RCT | 301 (95% CI, 188–421) days | 455 (95% CI, 312–568) days | 0.0112 |
| Lee *et al.* (2013) | [12] | Retrospective study | 26.3 (95%CI, 15.9–NA) months | 15.4 (95% CI, 12.3–71.5) months | 0.61 |
| Kullman *et al.* (2010) | [13] | RCT | 199 days | 154 days | 0.326 |
| Yoon *et al.* (2006) | [14] | Retrospective study | 202 ± 29 days | 245 ± 48 days | 0.736 |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 164 (11–285) days | 226 (1–724) days | 0.02 |
| Kitano *et al.* (2013) | [16] | RCT | 166.9 ± 124.9 days | 219.3 ± 159.1 days | 0.047 |
| Yamashita *et al.* (2022) | [18] | META | MD(CSEMS vs USEMS) = 45.51 days | | $p = 0.02$, $I^2$=64% |
| Conio *et al.* (2018) | [17] | RCT | 541 (95% CI, 175.6–304.4) days | 240 (95%CI, 319.9–762.1) days | 0.031 |
| Saleem *et al.* (2011) | [19] | META | WMD(CSEMS vs USEMS) = 60.56 days | | $p = 0.001$, $I^2$=0% |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; 95% CI, 95% confidence interval; WMD, weighted mean difference; MD, mean difference; ns, not significant.

## Drainage efficiency

Recent studies have demonstrated no significant difference in the implantation success rate between the USEMS and CSEMS groups [18, 20]. A non-inferiority study compared the efficacy of USEMS and CSEMS for preoperative biliary drainage of pancreatic cancer after neoadjuvant chemotherapy and the results showed that USEMS and CSEMS had similar clinical effects in terms of biliary drainage, chemotherapy completion rate, and surgery completion rate [20].

## Medical costs

There is a paucity of studies that have evaluated the medical costs of self-expandable metal stents. A recent retrospective study by Bor *et al.* [23] compared treatment costs between self-expandable metal stents and plastic stents for the management of malignant biliary obstruction. The results indicated that the cumulative treatment costs for patients with different survival times did not significantly differ; however, among patients with a survival time of 2–4 months, treatment costs were higher for plastic stents than for self-expandable metal stents. Unfortunately, this study did not compare the costs of different types of metallic stents [23]. According to another study [8], the cost of CSEMS was lower than that of USEMS (USD 3,901.3 vs 5,129.1), but there was no significant difference in overall survival. It is noteworthy that the covered stents were handcrafted by the researchers; thus, the cost of the CSEMS was lowered relative to that of commercial stents. Based on our experience, the medical cost depends on two key aspects. The first is the source of the stents and materials, such as imported or domestic, and the structure of coated materials. For example, the cost of CSEMS was significantly higher than that of USEMS (CNY 4,650 vs 3,500) from Micro-Tech (Nanjing) Co., Ltd, a domestic company in China. However, the cost was comparable between CSEMS and USEMS from Boston Scientific (CNY 18,000). Second, the condition of the patient, such as the accompanying chronic disease, tumor burden,

or post-operative complications, influences the total cost of medical treatment.

## Post-operative complications

### Cholecystitis

Since patients undergoing ERCP treatment and stent implantation are usually complicated by obstructive jaundice, biliary hypertension itself is also a high risk factor for biliary infection. Anatomically, the use of a contrast medium, guide wires, and other instruments during the operation may induce cholecystitis, whereas complete mesh coverage by CSEMS results in inadequate bile drainage in the gall bladder. Thus, patients receiving CSEMS are more likely to develop post-operative cholecystitis, whereas USEMS implantation may reduce this complication due to the mesh [24, 25]. However, this viewpoint neglects the plasticity of the soft tissue because the compression of the opening of the cystic duct by the USEMS may also result in gall bladder dysfunction, which eventually leads to cholecystitis [20].

Reportedly, the average onset time of post-operative cholecystitis is ~4.6 days. Most studies, including the meta-analysis, reported that there were no significant differences in the incidence of acute cholecystitis between the USEMS and CSEMS groups [8, 11–15, 17–19]. However, one study with a large sample size of 645 patients (431 receiving USEMS vs 214 receiving CSEMS) showed that the CSEMS group had a higher incidence of post-operative cholecystitis (7.8% vs 1.2%) [26]. Importantly, this study also revealed significant differences between the two groups in the proportion of patients who had undergone cholecystectomy before stent implantation, the proportion of patients with hepatic involvement, and the length of stent implanted [26]. However, since this study was conducted retrospectively, selection bias may have existed [26].

Based on these results, the risk factors for cholecystitis following ERCP stent implantation were analysed. Except for the study that acknowledged that the type of stent in itself was a risk factor [26], other studies indicated that the occurrence of cholecystitis was significantly associated with the contrast medium flowing into the gallbladder, tumor involving the cystic duct, and cholecystolithiasis, which were considered independent risk factors for post-operative cholecystitis [24, 27–31].

The incidence of post-operative cholecystitis is presented in Table 3. Antibiotic therapy and gallbladder drainage are the most common treatments for post-operative cholecystitis, although emergency cholecystectomy has also been reported. Ultrasound-guided gallbladder puncture was recommended for patients with high risk factors, such as cystic duct tumors and gallstones [24, 32, 33].

### Stent occlusion

Stent occlusion is one of the most common long-term complications and a major factor in stent patency, with tumor ingrowth being one of the major causes [9]. CSEMS could prevent tumor growth into the lumen, resulting in a lower incidence of occlusion than that of USEMS [8, 11, 15, 18, 22]. However, in addition to tumor ingrowth obstructing the lumen, tumor overgrowth resulting in the “cap effect” and sludge formation can also induce stent occlusion. In this regard, there was no significant difference between the USEMS and CSEMS groups [13]. Stent occlusion was rarely caused by mechanical tumor extrusion, but this was reported in patients with pancreatic cancer [12]. Thus, stent occlusion is not caused by a single factor, but most likely occurs due to the interaction and common effects of multiple factors. As a result, most studies have concluded that CSEMS has a lower rate of occlusion than that of USEMS, while others have proposed that there was no significant difference between the two [10, 13, 17].

In terms of stent occlusion risk factors, patients with hepatic hilum involvement and implanted stent of longer length were more likely to experience stent occlusion. Interestingly, a retrospective study showed that taking aspirin delayed the incidence of stent occlusion, which may be related to the decreased production of bile mucin [26]. Excess mucin secretion raises the viscosity of bile, which promotes the accumulation of clogs [26]. Some stents with newly developed materials, such as drug-eluting coverage, have been steadily applied in the clinical field, but their effects still need to be demonstrated by further clinical trials [34–36]. The existing data pertaining to stent occlusion are displayed in Table 4.

### Stent migration

Stent migration is a common cause of unplanned reintervention, resulting in increased medical costs and complications. Stent migration and stent occlusion sometimes appear to be contrary. Stent occlusion may be caused by tumor ingrowth, which creates an inverse “grasping force” for the stent, and strong friction keeps the stent firmly in place, whereas CSEMS is exactly the opposite. In agreement, previous research found that the patients receiving USEMS had a lower incidence of stent migration than those receiving CSEMS [12, 13, 17–20, 22, 26]. In this regard, some trials have attempted to improve the types of stents in recent years, such as partially covered and half-covered stents, to balance the

**Table 3.** Post-operative cholecystitis after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | P-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 0/55 (0.0%) | 2/57 (3.5%) | ns |
| Seo *et al.* (2019) | [20] | RCT | 4/43 (9.3%) | 2/42 (4.8%) | 0.68 |
| Jang *et al.* (2018) | [26] | Retrospective study | 4/328 (1.2%) | 10/129 (7.8%) | <0.001 |
| Isayama *et al.* (2006) | [28] | Retrospective study | 3/75 (4.0%) | 10/171 (5.8%) | 0.76 |
| Sakai *et al.* (2021) | [11] | RCT | 0/48 (0.0%) | 1/44 (2.3%) | 0.489 |
| Lee *et al.* (2013) | [12] | Retrospective study | 3/477 (0.6%) | 0/99 (0.0%) | 0.59 |
| Kullman *et al.* (2010) | [13] | RCT | 2/200 (1.0%) | 2/200 (1.0%) | >0.5 |
| Yoon *et al.* (2006) | [14] | Retrospective study | 0/41 (0.0%) | 1/36 (2.8%) | ns |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 1/21 (4.8%) | 0/44 (0.0%) | ns |
| Kitano *et al.* (2013) | [16] | RCT | 2/60 (3.3%) | 1/60 (1.7%) | ns |
| Conio *et al.* (2018) | [17] | RCT | 0/90 (0.0%) | 2/78 (2.6%) | 0.23 |
| Yamashita *et al.* (2022) | [18] | META | OR (CSEMS vs USEMS) = 1.78 | | $P = 0.39$, $I^2 = 6\%$ |
| Saleem *et al.* (2011) | [19] | META | RR (CSEMS vs USEMS) = 1.27 | | $P = 0.67$, $I^2 = 0\%$ |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; OR, odds ratio; RR, relative risk; ns, not significant.

**Table 4.** Stent occlusion after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | *P*-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 21/55 (38.2%) | 8/57 (14.0%) | <0.001 |
| Jang *et al.* (2018) | [26] | Retrospective study | 93/431 (21.6%) | 34/214 (15.9%) | 0.87 |
| Sakai *et al.* (2021) | [11] | RCT | 21/48 (43.8%) | 10/44 (22.7%) | 0.0467 |
| Kullman *et al.* (2010) | [13] | RCT | 45/200 (22.5%) | 47/200 (23.5%) | >0.5 |
| Yoon *et al.* (2006) | [14] | Retrospective study | 15/41 (36.6%) | 9/36 (25%) | 0.273 |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 8/21 (38.1%) | 5/44 (11.4%) | 0.015 |
| Conio *et al.* (2018) | [17] | RCT | 10/80 (12.5%) | 12/78 (15.4%) | 0.65 |
| Kitano *et al.* (2013) | [16] | Retrospective study | 22/60 (36.7%) | 14/60 (23.3%) | 0.081 |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; OR, odds ratio; RR, relative risk; ns, not significant.

**Table 5.** Stent migration after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | *P*-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 0/55 (0.0%) | 1/57 (1.8%) | ns |
| Seo *et al.* (2019) | [20] | RCT | 0/60 (0.0%) | 5/59 (8.5%) | 0.03 |
| Jang *et al.* (2018) | [26] | Retrospective study | 6/431 (1.4%) | 23/214 (10.7%) | <0.001 |
| Sakai *et al.* (2021) | [11] | RCT | 0/48 (0.0%) | 1/44 (2.3%) | 0.478 |
| Lee *et al.* (2013) | [12] | Retrospective study | 3/578 (0.5%) | 12/171 (7.0%) | <0.001 |
| Kullman *et al.* (2010) | [13] | RCT | 0/200 (0.0%) | 6/200 (3.0%) | 0.03 |
| Yoon *et al.* (2006) | [14] | Retrospective study | 0/41 (0.0%) | 1/36 (2.8%) | ns |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 0/21 (0.0%) | 2/44 (4.5%) | ns |
| Conio *et al.* (2018) | [17] | RCT | 0/80 (0.0%) | 5/78 (6.4%) | 0.025 |
| Yamashita *et al.* (2022) | [18] | META | OR (CSEMS vs USEMS) = 7.92 | | $P = 0.95$, $I^2 = 0\%$ |
| Saleem *et al.* (2011) | [19] | META | RR (CSEMS vs USEMS) = 8.11 | | $P = 0.02$, $I^2 = 0\%$ |
| Tringali *et al.* (2018) | [22] | META | OR (CSEMS vs USEMS) = 4.54 | | $I^2 = 0\%$ |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; OR, odds ratio; RR, relative risk; ns, not significant.

**Table 6.** Post-operative hemorrhage after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | *P*-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 2/55 (3.6%) | 0/57 (0.0%) | ns |
| Seo *et al.* (2019) | [20] | RCT | 0/60 (0.0%) | 1/59 (1.7%) | 0.5 |
| Kullman *et al.* (2010) | [13] | RCT | 1/200 (0.5%) | 0/200 (0.0%) | >0.5 |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 0/21 (0.0%) | 1/44 (2.3%) | ns |
| Yamashita *et al.* (2022) | [18] | META | OR (CSEMS vs USEMS) = 0.80 | | ns |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; OR, odds ratio; ns, not significant.

long drainage patency of CSEMS and the strong fixation of USEMS; however, clinical studies to date have not demonstrated their superiority [37–39]. The incidence of reported stent migration is shown in Table 5.

## Post-operative bleeding

Theoretically, CSEMS may be more effective in relieving hemobilia due to the compression of bleeding sites [8]. However, clinical studies and meta-analyses have suggested that there were no significant differences in post-operative bleeding between the CSEMS and USEMS groups [8, 13, 15, 18, 20]. We speculate that, while hemobilia is common during the ERCP procedure, few patients require invasive reintervention and the occurrence of hemobilia is more dependent on the operator's experience than the type of stent. Furthermore, post-operative bleeding includes not only hemobilia, but also secondary organ injury caused by the operation and duodenal wall injury after stent migration [40]. Nonetheless, no systematic study has yet been conducted on this aspect. Table 6 presents the currently available data on the post-operative bleeding rate.

## Post-operative pancreatitis

Pancreatitis is one of the most common complications of ERCP, regardless of its leading cause. Metallic stents are usually larger in diameter (>8 mm) than the plastic stents and endoscopic sphincterotomy (EST) is rarely performed to increase stent stability, resulting in a stronger compression of the common opening of the biliary–pancreatic duct [41, 42]. As biliary cannulation is difficult owing to its anatomical structure and invasion of the tumor [43, 44], not all patients can receive pancreatic duct intubation for pancreatitis prevention.

Prospective studies have reported no significant difference in post-operative pancreatitis between the USEMS and CSEMS groups [8, 11, 13, 20, 22]. Only two retrospective studies found that the CSEMS group had a higher incidence of post-operative pancreatitis than the USEMS group (13.6% vs 0%, $P = 0.026$ [15] and 5.8% vs 1%, $P < 0.001$ [12]). All patients were treated conservatively; the study by Kawakubo *et al.* [15] was mainly focused on 65 cases of biliary obstruction caused by lymph node metastasis, rather than primary biliary and pancreatic system diseases.

The multivariate analysis showed that contrast medium flowing into the pancreatic duct [odds ratio (OR), 3.17; 95% confidence

**Table 7.** Post-operative pancreatitis after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | *P*-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 1/55 (1.8%) | 5/57 (8.8%) | ns |
| Seo *et al.* (2019) | [20] | RCT | 0/60 (0.0%) | 1/59 (1.7%) | 0.5 |
| Jang *et al.* (2018) | [26] | Retrospective study | 21/431 (4.9%) | 11/214 (5.1%) | 0.88 |
| Sakai *et al.* (2021) | [11] | RCT | 2/48 (4.2%) | 0/44 (0.0%) | 0.496 |
| Lee *et al.* (2013) | [12] | Retrospective study | 6/578 (1.0%) | 10/171 (5.8%) | <0.001 |
| Kullman *et al.* (2010) | [13] | RCT | 4/200 (2.0%) | 3/200 (1.5%) | >0.5 |
| Kawakubo *et al.* (2011) | [15] | Retrospective study | 0/21 (0.0%) | 6/44 (13.6%) | 0.026 |
| Yamashita *et al.* (2022) | [18] | META | OR (CSEMS vs USEMS) = 1.22 | | ns |
| Saleem *et al.* (2011) | [19] | META | RR (CSEMS vs USEMS) = 1.27 | | $P = 0.77$, $I^2 = 42\%$ |
| Tringali *et al.* (2018) | [22] | META | OR (CSEMS vs USEMS) = 1.22 | | ns |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; OR, odds ratio; RR, relative risk; ns, not significant.

**Table 8.** Post-operative reintervention rate after stent implantation

| Study | Reference | Type of study | USEMS | CSEMS | *P*-value |
|---|---|---|---|---|---|
| Omata *et al.* (2004) | [8] | RCT | 72.0% | 32.0% | <0.05 |
| Seo *et al.* (2019) | [20] | RCT | 1.9% | 3.6% | 0.99 |
| Lee *et al.* (2013) | [12] | Retrospective study | 27.7% | 27.5% | ns |
| Yamashita *et al.* (2022) | [18] | META | 22.3% | 19.8% | $P < 0.01$, $I^2 = 58\%$ |

USEMS, uncovered self-expanding metal stent; CSEMS, covered self-expanding metal stent; RCT, randomized–controlled trial; META, meta-analysis; ns, not significant.

interval (CI), 1.32–9.29; $P = 0.015$] and non-pancreatic cancer patients (OR, 3.43; 95% CI, 1.44–10.05; $P = 0.010$) were risk factors for pancreatitis [31]. This could be related to the obvious dilatation of the pancreatic duct in patients with cancer of the head of the pancreas who had a long disease course. The incidence of post-operative pancreatitis is listed in Table 7.

## Other complications

Other post-operative complications that have not been thoroughly investigated include stomachache, cholangitis, and liver abscess [20]. However, most of the studies that investigated these complications did not show a significant difference between the CSEMS and USEMS groups [45]. Adverse events may ultimately lead to reintervention. In this case, three primary studies and one meta-analysis compared the reintervention rates between the CSEMS and USEMS groups but failed to reach an agreement (Table 8).

Hamada *et al.* [46] reported that long-term recurrent bacteria and food debris accumulation from duodenal reflux after stent implantation can obstruct the stent and induce cholangitis. To improve stent performance, researchers have designed new stents by changing the shape, material, and coverage, such as anti-reflux and drug-eluting stents, although current studies have not indicated obvious benefits [45–48]. Therefore, additional clinical trials are needed to clarify the benefits and limitations of different stents.

# Discussion

In this review, we examined studies on the two most used metallic stents: USEMS and CSEMS. Even though several clinical trials have already been conducted, many questions remain unanswered. First, there was no significant difference in the overall survival time between the USEMS and CSEMS groups, which may be considered a result of several factors that influence this outcome. Since metallic stents are mostly used for palliative biliary drainage in patients with unresectable malignant tumors, the impact of the tumor itself on survival must be far greater than the stent type itself. However, in terms of stent patency, most researchers found that CSEMS has a lower probability of occlusion since the covering material prevents tumor growth into the lumen. Nonetheless, this also leads to easy migration of the tumors from the biliary tract, suggesting that stent occlusion and migration are opposite processes. In this case, the stent is fixed in the biliary tract by two forces: one is caused by the compression of the narrow segment and the other by the restraint of the papillary sphincter. Although tumor ingrowth occludes the duct, it also provides a “grasping force” for the stent fixation. Therefore, the incidence of stent migration in the USEMS group was lower than that in the CSEMS group. However, no research has been conducted to investigate the relationship between EST and stent migration. It is well established that the situation for patients undergoing stent implantation via ERCP is usually not ideal. Many factors, such as tumor ingrowth, tumor growth beyond the coverage of the stent, biliary sludge occlusion, tumor mechanical extrusion, and stent length, affect stent patency. These factors occasionally interact with each other, eventually leading to stent occlusion. The timing and extent of occlusion demonstrated by different studies often varied, which depends on various factors and the mechanisms of stent occlusion. This finding could explain why some studies are inconsistent in these conclusions. Researchers should consider that stent patency, occlusion, and migration are based on the predicted survival of the primary disease. For example, in a study comparing CSEMS and USEMS [8], the researchers hypothesized that cumulative stent patency was affected by the type of disease. Locally advanced pancreatic cancer had higher cumulative patency than other cancers, but there was no significant difference in metastatic pancreatic cancer due to its shorter prognosis [8].

Second, the findings on the incidence of post-stent cholecystitis are the most controversial among the current studies. We assume that CSEMS are more likely to induce cholecystitis due to blockage of the cystic duct opening, while USEMS can maintain continuous gallbladder drainage. However, we neglect the

plasticity of soft tissues by compression. Most studies have suggested that the type of stent is not an independent risk factor for post-operative cholecystitis, but excess contrast medium into the gallbladder and tumors involving the cystic duct are the main causes. This prompts us to realize that clinical treatment should not be overly idealized. In terms of pancreatitis, pancreatic duct stent implantation is one of the most reliable preventive approaches; however, the operation becomes more difficult in the presence of tumor invasion, which may have contributed to the heterogeneity between studies. All patients who had pancreatitis could be cured using conservative treatment.

There are some limitations of our review. First, although ERCP was first conducted in the 1970s, it is still a delicate procedure that is variably applied. Thus, only a few studies regarding this topic have been conducted. Next, the lack of high-quality RCTs resulted in ambiguous conclusions, including those relating to stent patency and post-operative cholecystitis [24]. Consequently, in clinical practice, the selection of self-expanding metal stents is based on the endoscopist's subjective decision. Finally, not all of important parameters, such as medical costs, were examined in the trials included in this review. Accordingly, further RCTs are required.

In conclusion, ERCP itself is a variable procedure and patients with late-stage malignancies present with additional variables, such as poor condition, a history of abdominal surgery, and tumor invasion into the duodenum. Since all types of stents have benefits and drawbacks, we must consider the actual situation before and during the operation, such as the estimated survival time, subsequent treatment plan, and existence of cholecystitis prior to the operation. With the progression of medical technology and material advances, more types of stents will be developed and optimized by researchers, such as half-covered, drug-eluting, anti-reflux, and anti-migration stents. However, these are still in the early stages of clinical application and more high-quality trials are required.

## Authors' Contributions

J.N.G. contributed to the design of the review and the revision of the manuscript; X.Y.G. is responsible for drafting the manuscript and the revision of the manuscript; Y.S., B.F., H.R.L., and T.L. contributed to the data collection; H.F.L., J.L., and F.G. are responsible for the revision of the manuscript. G.T., Y.G., X.M.L., and Z.Y. contributed to the design of the review, the data collection, and the revision of the manuscript. All authors read and approved the final manuscript.

## Funding

This work was supported by the National Nature Science Foundation of China [no. 81902382 to J.N.G.] and the General Project of Natural Science Foundation of Liaoning Province [No. 2022-MS-318 to J.N.G.].

## Acknowledgements

We are grateful for the support of the Scientific Research Office of the First Affiliated Hospital of Dalian Medical University.

## Conflict of Interest

The authors declare that they have no conflicts of interest with respect to in this review.

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