



# Statistical analysis of photodynamic therapy and stent drainage for unresectable cholangiocarcinoma

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## HIGHLIGHTS

- **Methods:** Databases including PubMed, Medline, Embase and Cochrane Central Database were systematically searched from inception to December 2017 for clinical trials that compared photodynamic therapy with biliary stenting. Mortality, survival period, serum bilirubin levels, successful biliary drainage rate and incidence of cholangitis were pooled analysis.
- **Results:** Overall, 8 studies met inclusion criteria were included for pooling ( $n = 509$ ). The PDT group had lower mortality (RR = 0.91, 95% CI: 0.83–1.01,  $p = 0.07$ ) and longer survival periods (MD = 202.75, 95% CI: 128.64–276.86,  $p < 0.00001$ ) at follow-up compared with the biliary stenting group. There were no differences in serum bilirubin (MD =  $-1.19$ , 95% CI:  $-3.20$ – $0.82$ ,  $p = 0.25$ ) and the incidence of cholangitis (OR = 1.09, 95% CI: 0.63–1.86,  $p = 0.77$ ) between the two groups, whereas the PDT group showed a higher successful biliary drainage rate (OR = 4.08, 95% CI: 2.32–7.18,  $p < 0.00001$ ).
- **Conclusion:** PDT is effective and has significant survival benefits for unresectable CC patients compared with stenting only. PDT could be a promising palliative treatment for patients diagnosed with advanced CC.

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## ABSTRACT

**Background:** Photodynamic therapy (PDT) combined with biliary stent showed therapeutic effects in the palliative treatment of unresectable cholangiocarcinoma (CC). We aimed to evaluate the survival outcomes and procedure-related complications of PDT compared to conventional stenting for CC patients.

**Methods:** Databases including PubMed, Medline, Embase and Cochrane Central Database were systematically searched from inception to December 2017 for clinical trials that compared photodynamic therapy with biliary stenting. Mortality, survival period, serum bilirubin levels, successful biliary drainage rate and incidence of cholangitis were pooled analysis. The relative risk and odds ratio for dichotomous outcomes and mean difference for continuous outcomes were calculated using random-effects model. Heterogeneity was quantified using  $I^2$  statistics. The publication bias was ascertained by visual examination of funnel plots.

**Results:** Overall, 8 studies met inclusion criteria were included for pooling ( $n = 509$ ). The PDT group had lower mortality (RR = 0.91, 95% CI: 0.83–1.01,  $p = 0.07$ ) and longer survival periods (MD = 202.75, 95% CI: 128.64–276.86,  $p < 0.00001$ ) at follow-up compared with the biliary stenting group. There were no differences in serum bilirubin (MD =  $-1.19$ , 95% CI:  $-3.20$ – $0.82$ ,  $p = 0.25$ ) and the incidence of cholangitis (OR = 1.09, 95% CI: 0.63–1.86,  $p = 0.77$ ) between the two groups, whereas the PDT group showed a higher successful biliary drainage rate (OR = 4.08, 95% CI: 2.32–7.18,  $p < 0.00001$ ).

**Conclusion:** PDT is effective and has significant survival benefits for unresectable CC patients compared with stenting only. PDT could be a promising palliative treatment for patients diagnosed with advanced CC.

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## 1. Introduction

Cholangiocarcinoma (CC) is a primary malignancy originating from the bile duct epithelia. CC can be classified based on location as intrahepatic, extrahepatic, or perihilar [1]. Perihilar CC accounts for 60% to 70% of all cholangiocarcinoma [2]. CC is a rare cancer

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with high mortality, but its incidence has been increasing in the past decade [3,4]. It is often clinically silent and difficult to diagnose until the tumour is at an advanced stage. Therefore, according to the 2013 Asia-Pacific Consensus, surgical resection is the only recommended curative intervention, with only 20% to 30% of patients having potentially resectable tumours [5]. Overall 5-year survival rates for those patients who are able to achieve complete resection range from 10% to 40% [6].

The usual possible therapeutic strategy for unresectable CC is to relieve obstructive jaundice by endoscopic or percutaneous palliative management. Although palliative therapies such as stenting, radiotherapy and chemotherapy, generally provide relief of cholangitis and improve quality of life, randomized trials showing that these therapies prolong survival time are lacking [7]. Several studies have reported median survival for patients undergoing biliary stent placement of 88 to 270 days [8]. In addition, these palliative procedures carry some risk for procedure-related morbidity and mortality. Early morbidity and mortality are significantly higher after surgical procedures, whereas long-term complications occur more frequently with endoscopic treatment [9]. Even after successful stent insertion, patients may suffer from tumour progression and ultimately die from liver failure or cholangitis within a few months because the stents cannot decompress the affected segments or remodel malignant tissues [8,10]. Although endoscopic biliary stenting remains the mainstay of palliative treatment for patients with unresectable CC [11], tumour growth and the duration of stent patency are major problems. Much work is required to optimize stent replacement and evaluate the outcome of palliative therapies.

As an evolving therapy, photodynamic therapy (PDT) combined with biliary stenting have been evaluated for the treatment of cancers. PDT involves the intravenous administration of photosensitizing agent, followed by exposure to a specific wavelength of light to destroy cancerous tissues and neovascular cells [12]. Activation of the photosensitizer by light illumination generates highly reactive oxygen species, resulting in cellular injury and may improve bile duct patency [13]. Several clinical trials have shown significant therapeutic effects of PDT for unresectable hilar cholangiocarcinoma [10,14]. It has been confirmed that PDT improves survival, jaundice, and quality of life and is well tolerated. PDT therefore appears to be a promising therapeutic approach for patients with CC, and a large number of clinical studies have been reported. We conducted an updated systematic review and meta-analysis to evaluate the effectiveness of PDT compared with conventional stenting for unresectable CC [15–20]. We also summarized the procedure-related complications and adverse events associated with PDT.

## 2. Methods

### 2.1. Search strategy

We conducted a systematic search of PubMed, Medline, Embase, Web of Science and Cochrane Central Database from inception to December 2017. The medical subject heading (MeSH) search terms were “photodynamic therapy”, “PDT”, “photochemotherapy”, “cholangiocarcinoma”, “hilar malignancy”, “malignant biliary obstruction”, “bile duct cancer/neoplasm”, “percutaneous trans-hepatic biliary drainage”, and “biliary drainage”. The searches were not limited by date or language. We also screened the references from the related literatures, including identified original studies and reviews [21–25].

### 2.2. Study selection criteria

Prospective studies, retrospective studies and randomized controlled trials (RCTs) comparing PDT with placement of either plastic or metal biliary stents for palliation of unresectable CC were included. Study outcomes included survival, quality of life, and successful biliary drainage. Exclusion criteria were as follows: (1) non-human research; (2) non-primary studies such as letters, editorials, reviews, meta-analyses and systematic reviews; and (3) studies from which obtain original data could not be extracted (abstracts, preview articles). If there were multiple studies from the same centre, only the most complete and recent study was included. Two investigators independently screened the abstracts and full text. Newcastle-Ottawa Scale [15] was applied to assess the quality of the studies [26–30].

### 2.3. Data extraction

We used a standardized data collection form and recorded the descriptive data from the selected studies. The following data were extracted: name and year of study, type of study, number of patients included, male/female distribution, median age, Bismuth staging, dose of photosensitizer, stent type, outcomes data (i.e. survival number at the end of observation, median survival in days, serum bilirubin level, successful biliary drainage rate, median stent patency in days), and overall adverse events (i.e., cholangitis, abscess and photosensitivity) in both groups. Successful biliary drainage was defined as a > 50% decrease in bilirubin levels after successful stenting [31–37].

### 2.4. Statistical analysis

Meta-analysis of the selected trials was performed using Review Manager V5.3 software. We estimated the relative risk (RR) or odds ratio (OR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes. We evaluated the heterogeneity among studies using the Cochrane Q statistic and  $I^2$  statistic. The random-effects model was applied if the heterogeneity was statistically significant ( $I^2 > 50\%$ ), and the fixed-effects model was used when heterogeneity was non-significant. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. We ascertained the potential publication bias by visual examination of funnel plots.

## 3. Results

### 3.1. Search results

The literature search yielded 709 references, of which a total of 58 records were considered relevant for this analysis after screening of abstracts and titles. The full texts of these 58 articles were assessed, and 50 articles were excluded for having no full text or no control experiment. Eight studies that met the inclusion criteria were finally included for extraction of data [8,10,14,17–21]. Fig. 1 shows a diagram of the screening and selection processes.

### 3.2. Study characteristics

The baseline characteristics and descriptive data of the included studies are summarized in Table 1. There were only two randomized trials, whereas the rest were non-randomized studies including historical controls and controlled cohorts. These studies were published from 2003 to 2016, and there were two studies from Asia. A total of 509 patients are included in this meta-analysis, including 254 patients who received PDT and 255 who received only biliary stent placement as the control group. The median age

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