Endoscopic palliative treatment versus surgical bypass in malignant low bile duct obstruction: A systematic review and meta-analysis

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ABSTRACT

Aims: Despite technological advances, only about 20% of periampullary tumors are found to be resectable at the time of presentation. Biliary tree obstruction and consequent jaundice occur in 70–90% of those patients and has important consequences for a patient’s quality of life. Relief of biliary tree obstruction is the main goal for treatment, and few options for palliative therapy of biliary tree obstruction can be performed, including surgical bypass, percutaneous stenting, and endoscopic stenting. Objective: The aim of the present study was to acquire and analyze data to compare the success of procedures, procedure-related complication, mortality in 30 days, recurrent-jaundice rates in endoscopic, and surgical palliative techniques. Methods: Two independent reviewers searched the following electronic databases: Medline, EMBASE, Cochrane, LILACS, BVS, SCOPE, and CINAHL (EBSCO). Inclusion criteria included studies involving patients with distal biliary obstruction due to periampullary tumors who underwent endoscopic therapy or a surgical procedure for palliation. Results: No differences were observed for success of procedures; differences were observed with better outcomes for endoscopy therapy with regards to mortality associated with procedure, complication associated with procedure, and mortality in 30 days. Also, differences were observed with better outcomes for surgery therapy for recurrent-jaundice. Conclusion: Endoscopic palliative drainage is associated with a lower rate in complication, mortality associated with procedure, and mortality in 30 days. Recurrent-jaundice analysis demonstrated an overall lower rate in surgical bypass procedures. No differences were found for the success of procedures.

Keywords: Periampullary tumors, Bile duct cancer, Cholangiocarcinoma, Pancreatic carcinoma, Endoscopy, Gastrointestinal, Surgical procedures

How to cite this article

INTRODUCTION

Jaundice due to biliary obstruction is usually the main symptom at the time of diagnostic in periampullary cancers. Despite technological advances, only about 20% of periampullary tumors are found to be resectable at the time of presentation. Biliary tree obstruction and consequent jaundice occur in 70–90% of those patients and has important consequences for a patient’s quality of life. Palliation remains the principal management in such patients because of this dismal natural history, and relief of biliary tree obstruction is a prime concern [1, 2]. Few options for palliative therapy of biliary tree obstruction can be performed, including surgical bypass, percutaneous stenting, and endoscopic stenting. Although initial results with surgical bypass demonstrated low rates of recurrent jaundice (2–5%), the surgery itself carries an appreciable risk of post-operative morbidity and mortality, up to 24% in some trials [3, 4]. Surgical decompression has been advocated in patients who at the time of laparotomy for planned tumor resection are found to have unresectable disease as well as in occasional patients with longer projected survival [5, 6]. Advances in minimally invasive therapy have led to the development of luminal stents whose insertion can relieve jaundice and hence avoid the need for surgery [7–9].

Early biliary stents came in the form of a plastic prosthesis that was inserted across the obstructing mass to provide drainage of the biliary tree; however, bilioduodenal reflux and food fibers result in stent blockage. Various changes in plastic stent design and adjunctive therapy such as antibiotics have failed to significantly improve their patency [10]. With a wider bore than plastic stents, several studies have shown that they exhibit superior patency to plastic stents [11–13]. Obstructive jaundice due to malignant distal biliary obstruction can thus be relieved by surgery or endoscopic metal or plastic stents [14, 15]. A number of randomized controlled trials (RCTs) have compared various combinations of these interventions [16, 17]. Endoscopic stents appear to offer a less invasive option, but the many designs and stent types available have made selecting the ideal stent for individual patients complicated. This paper reviews the outcomes associated with surgery and endoscopic therapies.

OBJECTIVES

The aim of the present study is to acquire and analyze data to compare success of procedure, procedure-related complication, mortality in 30 days, and recurrent-jaundice rates in endoscopic surgical procedures in patients with distal biliary obstruction due to periampullary tumors (i.e., pancreatic neoplasms or low bile duct carcinoma).

MATERIALS AND METHODS

Protocol and Registration

PROSPERO 2015 CRD42015017792 [18]

Eligibility Criteria

a) Types of studies: Randomized clinical trials, controlled clinical trial, and cohort studies.

b) Types of participants: Patients with distal biliary obstruction due to periampullary tumors (i.e., pancreatic neoplasms or low bile duct carcinoma).

c) Types of intervention: Comparison between endoscopic palliative stents and surgical palliative procedures.

d) Types of outcome measures: The main outcome measures were the following: success of procedure, procedure-related complication, mortality in 30 days, and recurrent-jaundice rates.

In this literature search, we do not limit ourselves by year of publication or by language.

Information sources include MEDLINE as well as the Cochrane Controlled Trials Register, EMBASE, EBSCO, LILACS, Library University of Sao Paulo, Research website BVS, and SCOPE.

Search

Medline:

P: “(Periampullary Tumors OR Biliary Tract Neoplasms OR Biliary Tract Cancer OR Biliary tract tumors OR Bile Duct Cancer OR Pancreatic Neoplasms OR Cholangiocarcinoma OR Pancreatic Carcinoma) AND I: (Endoscopy OR Endoscopy, Gastrointestinal) AND C: (Surgery OR Surgical Procedures, Operative)".

Embase:

P: Pancreatic neoplasms OR bile duct neoplasms AND I: endoscopy AND C: surgery AND (‘clinical trial’ OR ‘controlled study’ OR ‘major clinical study’ OR ‘prospective study’ OR ‘retrospective study’)").

Cochrane, LILACS, Scopus and CINAHL:

P: pancreatic neoplasms OR bile duct neoplasms AND I: endoscopy AND C: surgery
Study Selection
Eligibility assessment was performed independently in an unblinded, standardized manner by two reviewers. Assessment included a thorough reading of the abstract to identify studies that compare endoscopic with surgical techniques. Studies selected were read in their entirety and excluded according criteria JADAD [19], NEWCASTLE OTTAWA [20] and Methodology Check List SIGN [21]. Studies that did not report the results in absolute numbers and those not written in English, Spanish, or Portuguese were excluded. Disagreements between reviewers were resolved by consensus.

Data Collection Process and Items
We extracted data by a detailed reading of the results of each study. This included information on the success of the procedure, procedure-related complication, mortality in 30 days, and recurrent-jaundice rates. We only included absolute numbers reported in the text of the article or with the analysis of graphs. We excluded an article for not reporting the results in absolute numbers. One review author extracted the following data from included studies, and the second author checked the extracted data. Disagreements were resolved by discussion between the two reviewers; we did not contact authors for further information.

Data items
The following information was extracted from each included study: Characteristics of population (type and location of tumors); type of intervention, considering different modalities of techniques in endoscopic treatment (plastic stents, metallic stents, covered or uncovered stents) versus surgical approach (hepaticojejunostomy, cholecystojejunostomy, choledocojejunostomy and gastrojejunostomy associated); type of outcome measure including complications, success of procedure, morbidity, mortality, survival in 30 days, recurrent-jaundice, and hospitalization rates.

Risk of Bias In Individual Studies
Since both cohort and randomized studies were included, the risk of bias in individual studies was assessed using the Newcastle-Ottawa Quality Assessment for cohort studies [20] and JADAD Scale for randomized trials [19] as well as the Methodology Check List: SIGN for both [21, 22].

We extracted data into a table of all studies with the following: experiment events rate (EER), control event rate (CER), number needed to treat (NNT), and absolute risk (ARR).

Synthesis of Results
We performed a meta-analysis with the software RevMan5 [23] using the following characteristics: dichotomous data type, statistical method of Mantel-Haenszel, fixed effect model analysis, effect measure risk difference, study confidence interval 95%, total confidence interval 95%, and year of study.

Risk of bias across studies.
To identify true heterogeneity and cause for publication bias between studies, we conducted both a graphic funnel plot and a 12 analysis. We noted a value of 12 greater than 50% as having high heterogeneity. If the study was outside the funnel plot it was regarded as publication bias, but if it was inside the funnel plot it was considered as having true heterogeneity.

RESULTS

Study Selection
We identified 8238 studies through MEDLINE, We identified 1941 studies through COCHRANE, LILACS, SCOPUS, and CINAHL. Eliminating repeated studies, we found 9179 studies in total. We excluded studies that did not have information about periampullary cancers. We chose eight studies that we reviewed with JADAD [19], NEWCASTLE OTTAWA [20], and the methodology check list: Cohort and clinical trial studies SIGN [21]. We excluded a study that was written in French. We included seven studies for qualitative analysis and five studies for quantitative analysis (Figure 1).

![Figure 1: Flow Diagram.](image-url)
Study Characteristics

The characteristics of the studies are summarized in Table 1. Table 2 describes the oncologic diagnosis analyzed, the number of interventions for each treatment group, and the report in absolute numbers for each outcome of interest extracted. The survival and hospital stay was expressed in mean without standard error, was no topic under analysis [24–29].

Risk of Bias Within Studies

We identify biases selected for qualitative analysis studies and evaluate them according criteria from the JADAD, Methodology check list: SIGN, and NEWCASTLE OTTAWA [19–21] (Table 2).

Summary Measures

Individual analysis for each study included the following: experiment events rate (EER), control event rate (CER), number needed to treat (NNT), and absolute risk (ARR) (Table 3).

Results of Individual Studies and Synthesis of

Table 1: Study Characteristics.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
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<th>Mor proc</th>
<th>Mor 30d</th>
<th>Comp</th>
<th>Surv</th>
<th>Re-jaund</th>
<th>Hos-stay</th>
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<td>mo</td>
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<td>0</td>
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<td>mo</td>
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<td>2</td>
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<td></td>
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<td>0</td>
<td>0</td>
<td>6.5</td>
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<td>1</td>
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<td>9</td>
<td>6.6</td>
<td>mo</td>
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<td>mo</td>
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<td></td>
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<td>mo</td>
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<td>Bypass N25</td>
<td>23</td>
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<td>Stent N23</td>
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<td>2</td>
<td>7</td>
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<td>mo</td>
<td>8</td>
<td>18</td>
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<td>5</td>
<td>8</td>
<td>3.7</td>
<td>mo</td>
<td>3</td>
<td>24</td>
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HJ Hepatojejunostomoty
HCJ Hepatocholedocojejunostomy
ADPH Pancreatic adenocarcinoma head
TB Biliary Tree
Succ Success
Mor proc Mortality procedure
Mor 30d Mortality in 30 days
Comp complication
Surv survival
Re-jaund recurrent-jaundice
hstay hospital Stay
mo month
Table 2: Risk of bias within studies.

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<th>WORK</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
<th>Other bies</th>
<th>NEW CASTEL</th>
<th>JADAD</th>
<th>SIGN</th>
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<td>63y</td>
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<td>M Stent 15</td>
<td>64.2y, success reduction 50% B</td>
<td>3</td>
<td>accept</td>
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<td></td>
<td></td>
<td>HJ HCJ Bypass 15</td>
<td>61.4y Don't lost</td>
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<td>Maosheng 2001 Cohort Study 83-99 [25]</td>
<td>Obst Jaudance Palliative ADPH N60</td>
<td>M Stent 19</td>
<td>67.5y, MS = 10mm 6-8cm, B13.7 (1.2), success reduction B 2 week 16 preprocedure drainage B P Stent Hstlay 12</td>
<td>8</td>
<td>accept</td>
<td></td>
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<tr>
<td></td>
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<td>HJ HCJ CJ + or - Bypass 41</td>
<td>66.0y, B8.8 (1), success reduction B 2 week 34 preoperative drainage 3 P Stent Hstlay 32.</td>
<td></td>
<td></td>
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<tr>
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<td>Obst Jaudance Palliative ADPH-TB-AM- VA N201</td>
<td>P Stent N101</td>
<td>70y B270, TS 3, Percucellosio CPRE fail, PS10FR, Intention to treat success reduction 20% B 5 day, 19 RENDEUSOUZ, 4.5m mean exchange</td>
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<td>70y B 311, TS 3.6, intention to treat, success reduction 20% B 5 day LOST 3%</td>
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<td>Obst Jaudance Palliative ADPH-TB N50</td>
<td>P Stent N25</td>
<td>77y, success reduction 50% B, 7-10FR OS,</td>
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<td>67y, 19 treated according to randomisation, 10% lost.</td>
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<td>61y</td>
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HJ Hepatopojejunostomy ADPH Pancreatic adenocarcinoma head TB Biliary Tree

Table 3: Summary Measures

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<tr>
<th>WORK</th>
<th>population</th>
<th>succ.</th>
<th>CER</th>
<th>ARR NNT</th>
<th>Mor proc</th>
<th>CER</th>
<th>ARR NNT</th>
<th>mirt 30d</th>
<th>CER</th>
<th>ARR NNT</th>
<th>com</th>
<th>CER</th>
<th>ARR NNT</th>
<th>r- joun</th>
<th>CER</th>
<th>ARR NNT</th>
<th>ARR TNN</th>
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<td>12</td>
<td>0.14</td>
<td>0.06</td>
<td>0.2</td>
<td>-5</td>
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<td>0.07</td>
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<td>Bypass N25</td>
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<td>0.14</td>
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<td>0.07</td>
<td>0.4</td>
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</tbody>
</table>

Succ Success Mor proc Mortality procedure Mor 30d Mortality in 30 days Comp complication Re-jaund recurrent-jaundice CER control event rate EER experimental event rate ARR Absolute risk reduction NNT Number needed to treat
Mortality associated with procedure: two clinical trials reported mortality associated with procedure; the heterogeneity test was not applicable. The fixed-effects model was adopted, and the risk ratio was 0.21 (95% CI: -0.16, –0.03) (Figure 3b). Analysis of the pooled data revealed differences in mortality associated with procedure that favored endoscopy therapy, with potential bias in this statement.

**Mortality 30 Days**

Mortality at 30 days: Five clinical trials reported mortality at 30 days; the heterogeneity test indicated a χ² of 1.44 and an I² of 0%, demonstrating homogeneity. The fixed-effects model was adopted, and the RD was -0.07 (95% CI: -0.13, 0.00) (Figure 4). Analysis of the pooled data revealed statistically significant differences in mortality at 30 days between the two therapies and favors endoscopy therapy.

**Complication associated with procedure**

Complication associated with procedure: five clinical trials reported complication associated with procedure; the heterogeneity test indicated a χ² of 12.10 and an I² of 67%, demonstrating high heterogeneity. The fixed-effects model was adopted, and the RD was -0.19 (95% CI: -0.28, –0.09) (Figure 5a). Analysis of the pooled data revealed differences in complication associated with procedure, with potential bias in this statement. In the funnel plot analysis, the study Andersen (1999) was identified as a source of heterogeneity for publication bias. By consensus of reviewers, we opted to withdraw this work from the meta-analysis complication associated with procedure (Figure 5b).

Complication associated with procedure for endoscopy and surgery therapies: four studies reported complication associated with procedure; the heterogeneity test indicated a χ² of 3.50 and an I² of 14%, demonstrating low heterogeneity. The fixed-effects model was adopted, and the RD was -0.24 (95% CI: -0.34, –0.24) (Figure 5b). Analysis of the pooled data revealed statistically significant differences in complication associated with procedure and showed better outcomes for endoscopy therapy.

**Recurrent-Jaundice**

Recurrent-Jaundice: five clinical trials reported Recurrent-Jaundice; the heterogeneity test indicated a χ² of 22.53 and an I² of 87%, demonstrating high heterogeneity. The fixed-effects model was adopted, and the RD was 0.25 (95% CI: 0.18, 0.32) (Figure 6a). Analysis of the pooled data revealed differences for Recurrent-Jaundice with significant risk of bias in does this affirmation. In the funnel plot analysis, the study Andersen (1989) was identified as a source of heterogeneity for publication bias. By consensus of

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**Procedure Success**

![Procedure Success](image)

Figure 2: Risk Difference in procedure success.
Figure 3: (a) Risk difference in mortality associated with procedure for endoscopy and surgery therapies. (b) Risk ratio in mortality associated with procedure for endoscopy and surgery therapies.

Figure 4: Risk Difference in mortality 30 days.
reviewers, we opted to withdraw this work from the meta-
alysis of Recurrent-Jaundice (Figure 6b).

Recurrent-Jaundice for endoscopy and surgery therapies: four clinical trials reported Recurrent-
Jaundice; the heterogeneity test indicated a $\chi^2$ of 1.47 and an $I^2$ of 0%, demonstrating homogeneity. The fixed-effects model was adopted, and the RD was 0.30 (95 % CI: 0.22, 0.38) (Figure 6b). Analysis of the pooled data revealed statistically significant differences for Recurrent-Jaundice and showed better outcomes for surgery therapy.

Risk of Bias Across Studies

Although the results of success of the procedure were homogeneous between the studies, and no difference was found between the procedures in clinical trials, there is substantial risk of bias because the concept of success is different for each study. Although all are based on a percentage of reduction of bilirubin, the percentages that determined a successful procedure were different.

Mortality at 30 days was homogeneous between the studies, and statistically significant differences were found between the two therapies that favored endoscopy.
therapy. We believe this result is one of the most solid because it was exposed in all studies in absolute numbers and because the concept of death is unlikely subject to interpretation bias.

With regard to complication associated with procedure, Andersen (1999) was identified as a source of heterogeneity for publication bias. Excluding this study, we analyzed four studies demonstrating low heterogeneity and found statistically significant differences (with low probability of bias) in complication associated with procedure that showed better outcomes for endoscopy therapy.

With regard to Recurrent-Jaundice, Andersen (1999) was identified as a source of heterogeneity for publication bias. Excluding this study, we analyzed four studies demonstrating homogeneity and revealed statistically significant differences (with low probability of bias) in Recurrent-Jaundice analysis that showed better outcomes for surgery therapy.

DISCUSSION

Summary of Evidence

About 70% of patients with periampullary tumors have evidence of obstructive jaundice at the time of presentation. Therefore, the main goal of palliative therapy in those patients is to resolve the biliary obstruction. Five randomized controlled trials comparing the outcomes of endoscopic stent placement versus surgical bypass for palliation therapy was analyzed.

No statistically significant differences were found in procedure success between the two therapies. Differences were found between mortality associated with procedure that favored the endoscopy therapy. There was significant risk of bias in this affirmation, and the risk ratio was 0.21. Statistically, significant differences (NNT 14) in mortality at 30 days between the two therapies favors endoscopy therapy. This is perhaps the most striking result unidentified in previous reviews. Also, statistically significant differences (NNT 4) in complication associated with procedure between the two therapies favors endoscopy therapy. Finally, statistically significant differences (NNH 3) were found for Recurrent-Jaundice and showed better outcomes for surgery therapy.

LIMITATIONS

Several limitations of the present study need to be considered. The characteristics of patients were not comparable in some studies. Although the studies were homogeneous in age, some studies had different average ages, which may lead to a significant bias in the results. Several endoscopic therapies including plastic stent and metallic stent (covered or uncovered) were used, and may be bias generator. The type of operation used was also different in all studies and may cause some biases. Finally, publication bias might exist when including published studies because positive results are more likely to be published than negative results.

CONCLUSION

Endoscopic palliative drainage is associated with a lower rate of complication as well as mortality associated with procedure and mortality within 30 days. Recurrent-jaundice analysis demonstrated an overall lower rate in surgical bypass procedures.

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Silvia Lucia Alves de Lima – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Fabio Alberto Castillo Bustamante – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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