Surgical Interest Group
Monash University Malaysia

CRITICAL ANALYSIS

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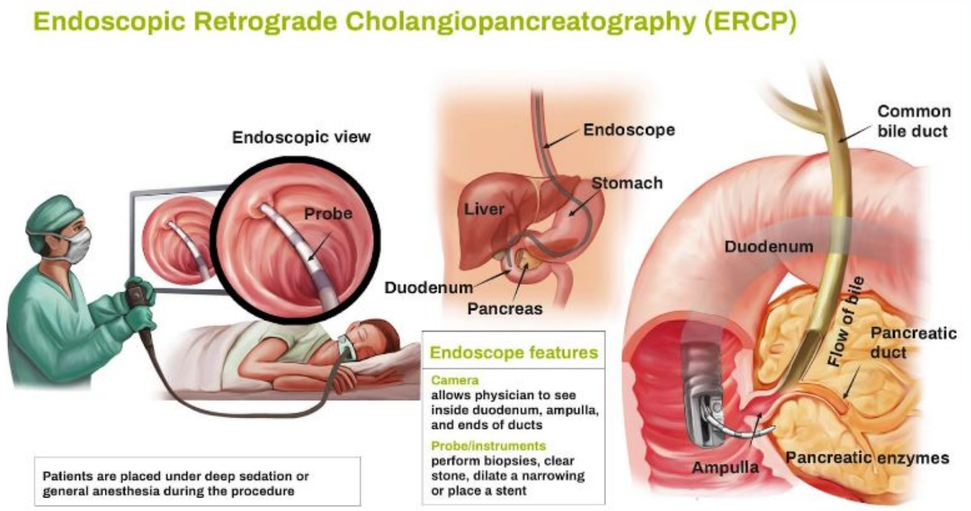
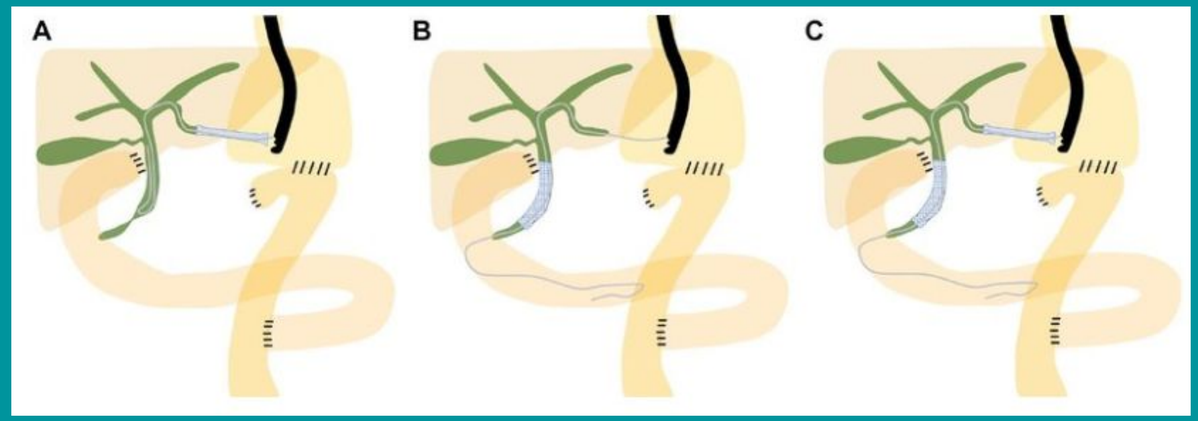
01 Background Information

Transpapillary stenting with ERCP



Placement of long plastic / metal stents from gallbladder into small intestine using body's natural cavities through use of ERCP assisted by a video camera

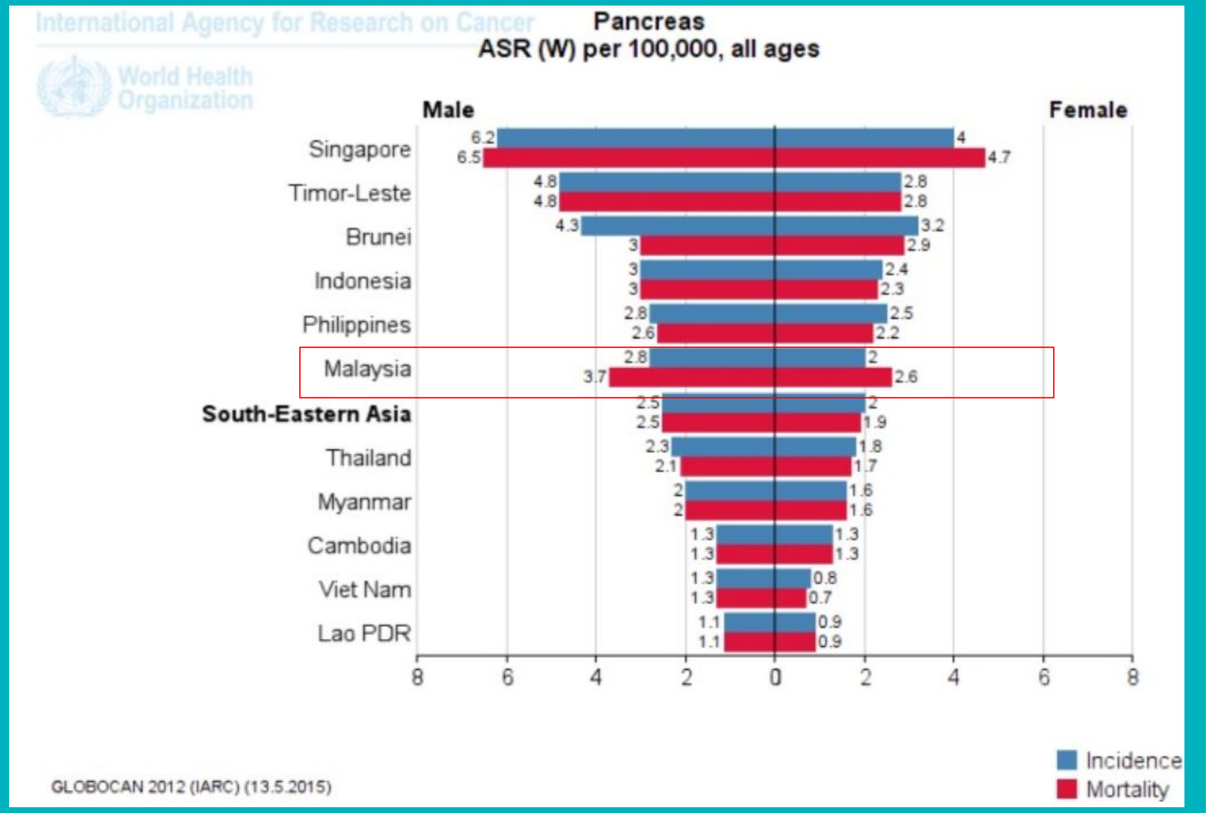
Endoscopic ultrasound guided biliary drainage (EUS-BD)



Biliary duct is accessed under EUS guidance followed by guidewire placement and fistula dilation.

A **stent** is deployed between biliary duct and intestine --> create permanent fistula for biliary drainage.

In this study, it is performed as choledochoduodenostomy (CDS) and hepaticogastrostomy (HGS)



02. Epidemiology

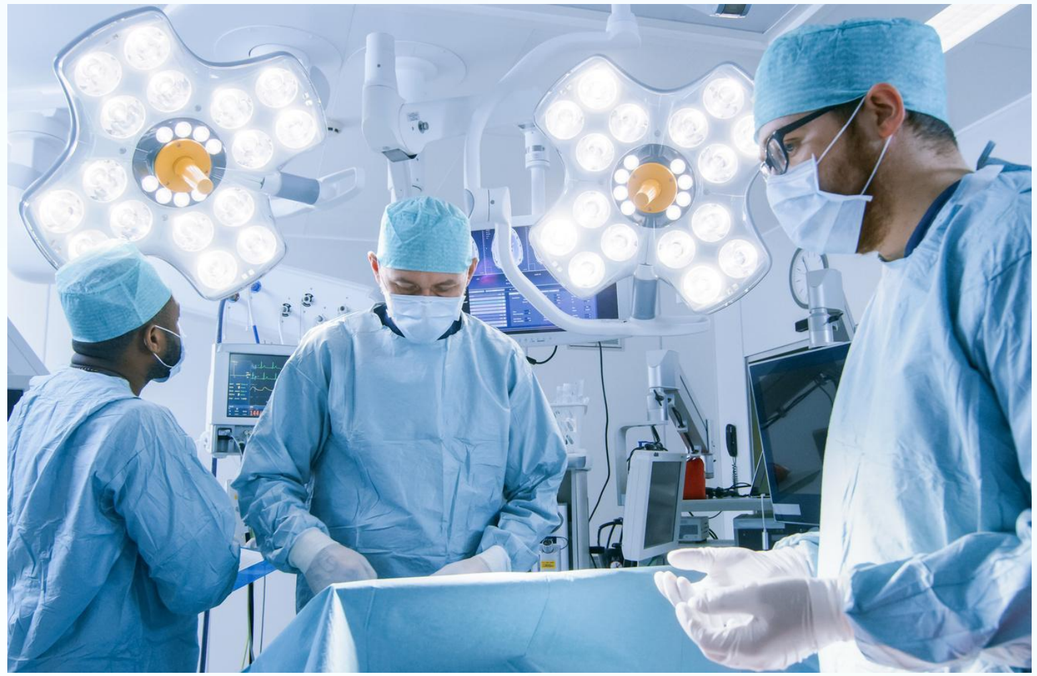
- Most common causes of malignant biliary obstruction (MBO): **pancreatic adenocarcinoma**, cholangiocarcinoma, ampullary/duodenal adenocarcinoma, gallbladder adenocarcinoma, lymphoma, and compressive metastatic proximal lymph nodes
- Pancreatic cancer (highly aggressive)
  - **12th most common cancer in the world**
  - 7th most frequent cause of cancer death worldwide in 2012
- Malaysia:
  - Uncommon → The National Cancer Registry reported 1829 cases of pancreatic cancer in 2011
  - Sex ratio: **1.32:1 (M: F)**
  - **Chinese** → 50% higher incidence rate

03

AIMS of study

To determine whether endoscopic ultrasound (EUS)-guided biliary drainage (**EUS-BD**) is comparable to conventional transpapillary stenting with endoscopic retrograde cholangiopancreatography (**ERCP**) as **primary palliation method for malignant distal biliary obstruction.**

04 PICO



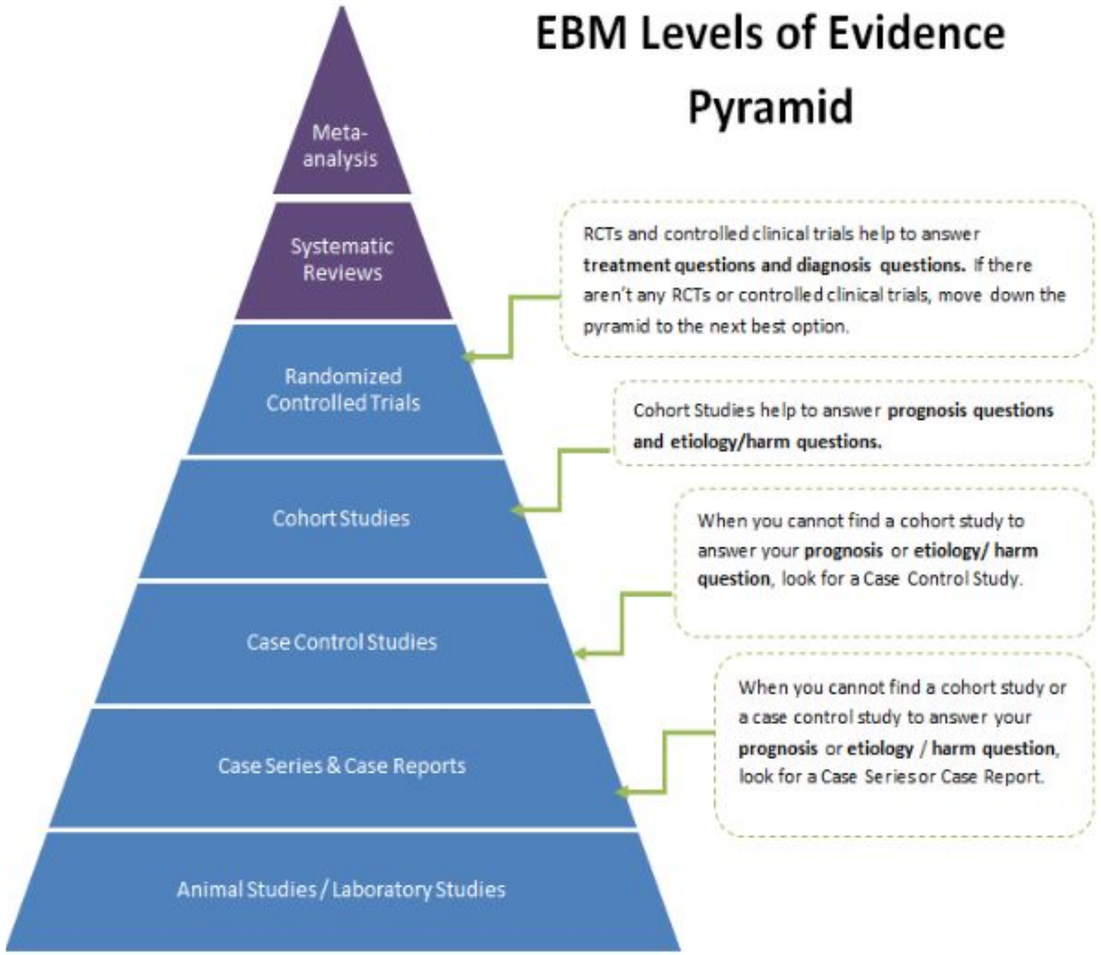
P	Patients with unresectable malignant distal biliary obstruction
I	Endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD)
C	Transpapillary stenting with endoscopic retrograde cholangiopancreatography (ERCP)
O	The noninferiority of EUS-BD as a primary palliation method in relieving malignant distal biliary obstruction

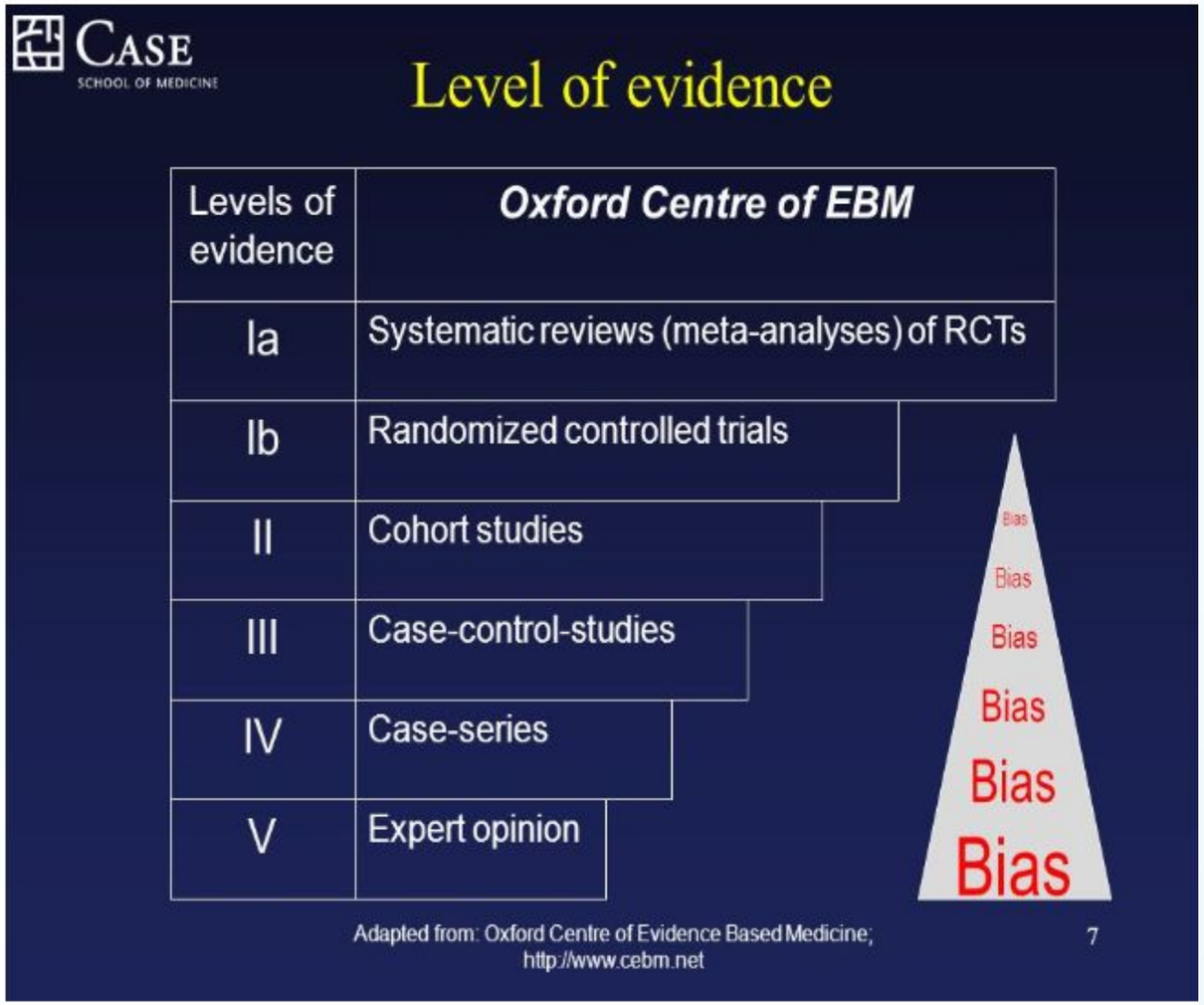
- Null hypothesis: Not stated

05 Study Design

Level of evidence according to using CEBM levels:

Level 1b





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Is the study design appropriate?

- **Gold standard** for effectiveness research
- **Straightforward** investigation of cause–effect relationships with **minimal bias and confounding factors**
- **Randomization** balances participant characteristics between the groups allowing **attribution** of any differences in outcome to the study intervention

06 Methodology

Recruitment process:

- Conducted by 4 tertiary academic centres in South Korea
  Patients were enrolled between May 2015 and January 2017
- Before the start of the procedure, informed consent was obtained
- All patients who presented with unresectable malignant distal biliary obstruction initially underwent endoscopic drainage procedure for biliary decompression.
- Unresectability was determined by radiologist and surgeon based on CT criteria and/or MRI with or without EUS
- Randomised in a 1:1 ratio using computer-generated random numbers

Randomisation:

DOUBLE BLINDING has been done

The process of randomisation was consistent across both groups with no difference apart from the exposure

Both groups were given prophylactic antibiotics before the start of the intervention. Sedation was also performed.

All these measures thus reduce the risk of selection, performance and detection biases.

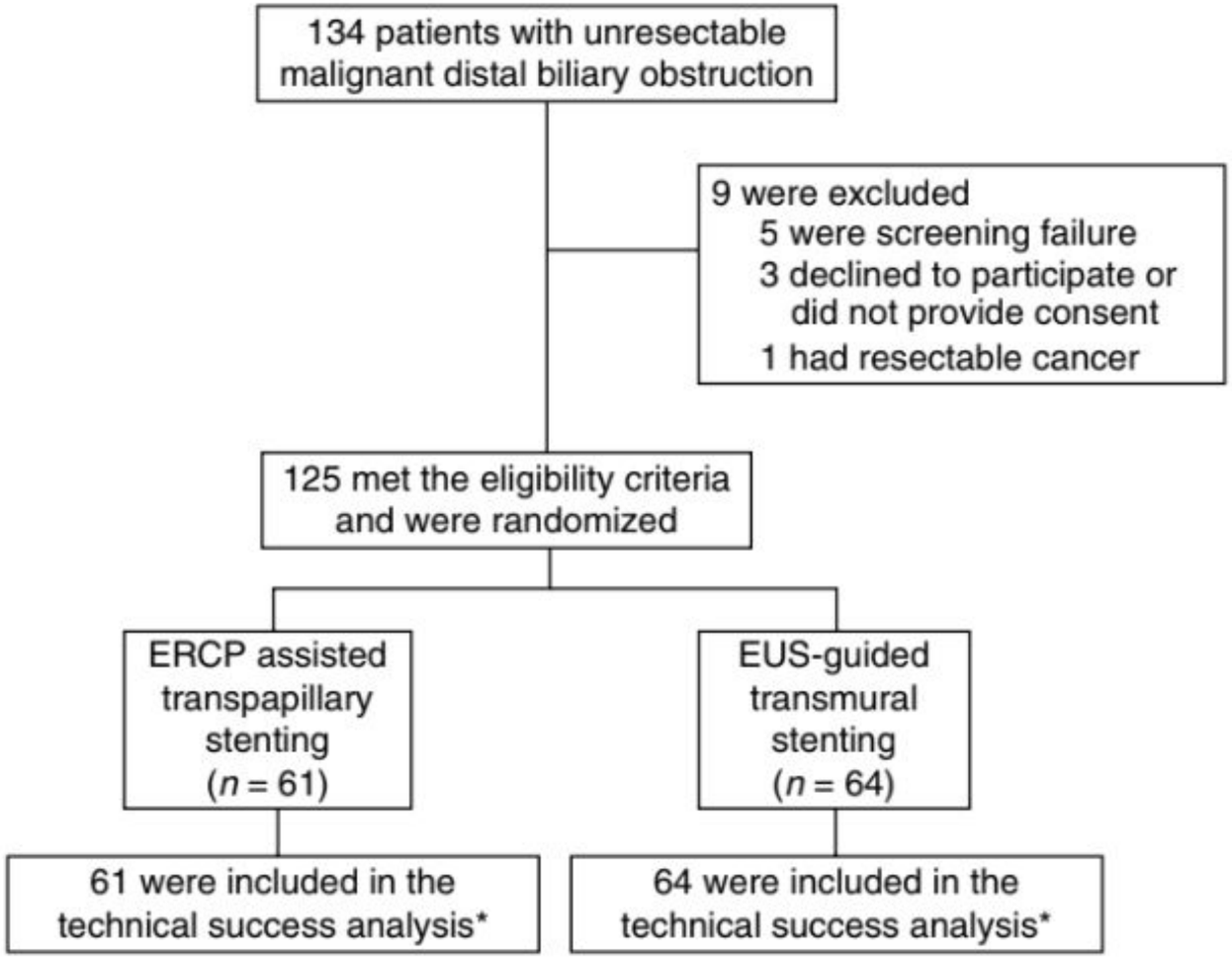


Fig. 1 Flow diagram of enrolled patients.
*Technical success rates were calculated by intention-to-treat analysis

Groups were defined precisely:

As stated in both inclusion and exclusion criterias

Baseline characteristics:

Baseline characteristics of the two study groups were **similar**
(e.g age, etiology of biliary obstruction, ASA class) with the **exception of sex**

Table 1 Baseline characteristics[a]

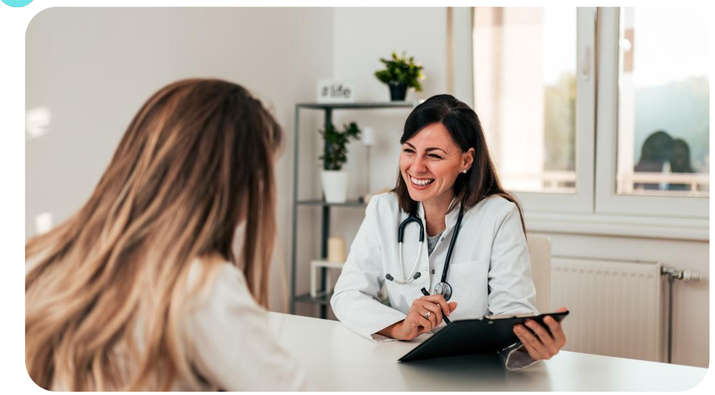
Variables	ERCP ($n=61$)	EUS-BD ($n=64$)	All patients ($n=125$)
Age – mean (range), yr	68.4 (46, 88)	64.8 (40, 90)	66.6 (40, 90)
Sex (male: female)	26:35	41:23	67:58
ASA class[b]			
I	5	5	10
II	52	54	106
III	4	5	9
Etiology of biliary obstruction			
Pancreatic cancer	40	38	78
Cholangiocarcinoma	8	3	11
Gallbladder cancer	4	4	8
Ampulla of Vater cancer	3	5	8
Stomach cancer	2	4	6
Duodenal cancer	1	2	3
Hepatocellular carcinoma	1	0	1
Others	2	8	10
Common bile duct diameter (mm)	15.0±3.9	15.7±4.0	15.4±3.9
Intrahepatic duct diameter (mm)	—	5.57±2.49[c]	—
Total bilirubin (mg/dL)			
Initial	7.7±6.4	8.3±7.2	8.0±6.8
1 week	2.8±4.5	3.0±3.2	2.9±3.8
4 weeks	1.5±2.9	1.5±2.4	1.5±2.7
Alkaline phosphatase (U/L)			
Initial	497.4±272.8	527.4±331.3	512.8±303.3
1 weeks	296.8±171.7	343.3±394.5	321.2±309.1
4 weeks	172.4±118.8	204.9±324.5	189.2±247.2
Surgically altered anatomy			
Billroth-II	0	1	1
Roux-en-Y	1	3	4
Duodenal invasion			
Type 1	8	7	15
Type 2	2	4	6
Type 3	5	7	12
[d]Systemic chemotherapy – no. (%)	26 (42.6)	37 (57.8)	63 (50.4)

[a]Plus-minus values are means ± SD. There were no significant differences between the two groups in any baseline characteristics except sex ($P=0.02$)
[b]The ASA physical status classification system is a system for assessing the fitness of patients before surgery: I. normal healthy patient, II. a patient with mild systemic disease, and III. A patient with severe systemic disease
[c]EUS-HGS group
[d]Systemic chemotherapy was performed at least 2 sessions after biliary drainage

Sample size collected was justified:

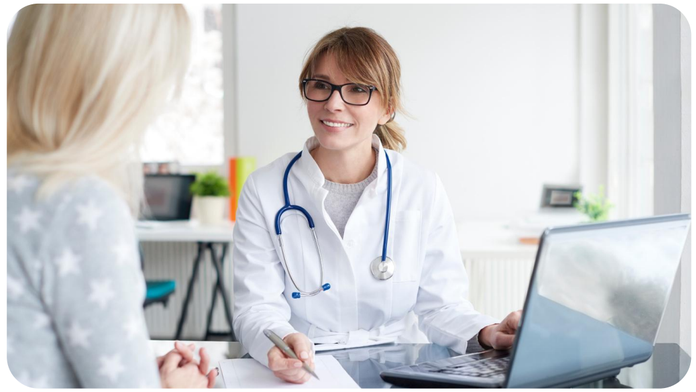
- To achieve a statistical power of 80% with the assumption of a type I error rate of 5%, a total of 118 (59 per group) was required.
- Considering a 5% drop-out rate, a final sample size of 124 patients (62 per group) was calculated. This study has included a total of 125 patients for analysis.

Follow up



Clinical symptoms and laboratory examinations were recorded at baseline and at 1, 7, and 28 days after the procedures

Patients were followed up for at least 6 months after the procedures or until death, with a median follow-up of 155 days → sufficient for all the outcomes to be measured.



Seems to be completed → However, statement for completion and loss to follow up was not mentioned in the study.

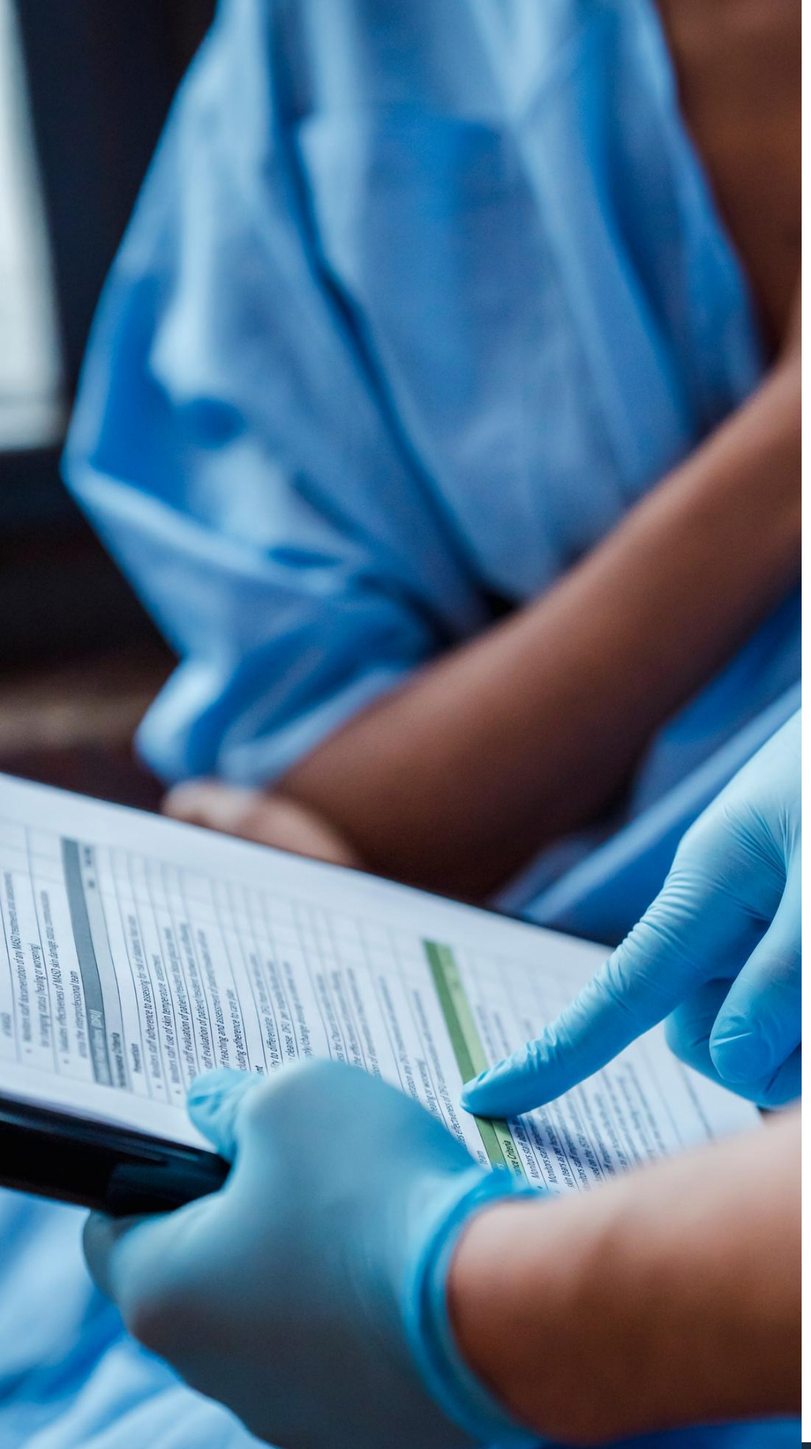
Statistical Methods

Types of statistical analysis	Outcomes Measured
One-sided Z-test	To assess primary outcome: difference in the technical success rate and the margin of noninferiority of 10%
(a) Student t-test **(b) Fisher exact test/ Pearson chi-square test**	To compare characteristics of the study groups: (a) Continuous variables (b) Categorical variables
Kaplan-Meier method with use of log-rank test	To calculate the overall survival and stent patency
Mann-Whitney test	To compare the changes in QOL scores which was calculated as the difference from baseline to the 4 or 12 weeks

Statistical analyses were performed using SAS version 9.4 (SAS Institute).

07. Results

- **All** appropriate **outcomes** have been **considered**
- All of them are **reliable** (p values< 0.05) except for rates of clinical success.
- Both **ITT and per protocol analysis** have been done.
- Thus, both attrition bias and confounding factors could be prevented.



Primary Outcome	Statistically significant or not?
Technical success rate	Noninferiority shown for technical success was statistically significant with (P=0.003), which is less than 0.05.
Secondary Outcomes	**Statistically significant or not?**
Rates of clinical success	P= 0.49, Not statistically significant
Median procedure time	P<0.001, Statistically significant
Median length of hospital stay	P= 0.03, Statistically significant
Adverse events (Early and Late)	Early → P= 0.03, Statistically significant Late → P= 0.01, Statistically significant
Reintervention along with stent patency duration	P= 0.001, Statistically significant
Changes in Quality of life (QOL) score	Global → P=0.001 Parts of functional (emotional → P=0.001; cognitive → P=0.003) Symptom scale (fatigue → P=0.02; pain → P=0.01; financial difficulties → P=0.01) All statistically significant

Table 2 Safety profile and procedure-related outcomes of ERCP and EUS-BD

	Intention-to-treat analysis			Per-protocol analysis		
Outcome measures, *n* (%)	**ERCP (*n*=61)**	**EUS-BD (*n*=64)**	***P*-value**	**ERCP (*n*=55)**	**EUS-BD (*n*=60)**	***P*-value**
Procedure time, median (IQR), min[a]	11 (7–18)	5 (3–12)	<0.001	14 (8–20)	5 (3–9)	<0.001
Follow up period, median (IQR), days	165 (99–253)	144 (101–209)	0.45	165 (99–253)	142 (90–209)	0.41
Adverse events						
Early (≤2 weeks, procedure-related)	12 (19.7)[b]	4 (6.3)[b]	0.03	12 (21.8)	2 (3.3)	0.003
Late (>2 weeks)	12 (19.4)[c]	3 (4.7)[c]	0.01	12 (21.8)	3 (5.0)	0.008
Procedure-related pancreatitis	9 (14.8)	0	0.001	8 (14.5)	0	0.002
Mild/Moderate/Severe	16 (26.2)/8 (13.1)/0	4 (6.3)/3 (4.7)/0	0.001	16 (29.1)/7 (12.7)/0	4 (6.7)/2 (3.3)/0	<0.001
Mortality						
Procedure-related	0	0		0	0	
Disease progression	51(83.6)	46 (71.9)		46 (83.6)	43 (71.7)	
Cardiopulmonary complication	0	2 (3.1)		0	2 (3.3)	
Reintervention rate	26 (42.6)[d]	10 (15.6)[d]	0.001	24 (43.6)	9 (15.0)	0.001
Reintervention method			<0.001			<0.001
ERCP	22	0		20	0	
EUS-BD	3	9[e]		3	8[e]	
PTBD	1	1		1	1	
Hospital stay, median (IQR), days	5 (4–6)	4 (3–5)	0.03	5 (4–6)	4 (3–5)	0.008

Strength

First **RCT** comparing EUS-BD with ERCP **as a primary modality for the palliative treatment** of malignant biliary obstruction

Prove its noninferiority, including:

- **Lower rates** of overall **adverse events** without post-procedure pancreatitis
- **Higher rate of stent patency** with a less reintervention
- More **preserved quality of life**

Limitations

- **One step stent introducer** is **not widely available** → limit the applicability of study
- EUS-BD is performed in a small number of high-volume academic centres due to its **perceived procedural complexity** and the need for **dedicated devices**, further limiting its generalizability
- **Devices and accessories tailor-made specifically** needed for effective and safe EUS-BD
- Only a small number of expert endoscopists perform EUS-BD as the first-line treatment
- The **acceptance of EUS-BD as a viable alternative to ERCP has been slow**, in part because of the long track record of efficacy and safety with ERCP.

08 Discussion

Might **NOT be applicable to Malaysia** even though it can provide better outcomes and quality of life.

Malignant biliary obstruction is **not common in Malaysia.**

Barriers for implementation:

- **Cost**
  - E.g In Korea, the median total costs for the biliary intervention ($1,203.36 for EUS-BD) → around RM5400
- **Lack** of **resources**, especially surgical skills and tailor-made devices that are required for effective and safe EUS-BD by which its procedure is very complex as well.

Conclusion

EUS-BD and ERCP had **similar levels of efficacy for the primary palliation** of unresectable malignant distal biliary obstruction based on rates of technical and clinical success.

Superiority of EUS-BD:

- ❏ Lower adverse outcomes with no risk of pancreatitis
- ❏ Longer stent patency with less need of reintervention
- ❏ More preserved QOL

THANK YOU

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