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Endoskopowe metody leczenia złośliwych guzów wnęki wątroby

Endoscopic Treatment of Malignant Hilar Biliary Obstruction

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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1. Słowa kluczowe

Złośliwe guzy wnęki wątroby; Rak dróg żółciowych; Złośliwa niedrożność dróg żółciowych; Endoskopowy drenaż dróg żółciowych; Endoskopowa cholangiopankreatografia wsteczna; Protezowanie dróg żółciowych

Malignant hilar biliary obstruction; Cholangiocarcinoma; Malignant biliary obstruction; Endoscopic biliary drainage; Endoscopic retrograde cholangiopancreatography; Biliary stent

2. Nota informacyjna oraz wykaz publikacji stanowiących rozprawę doktorską

Niniejsza rozprawa doktorska została przygotowana na podstawie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych, na podstawie art. 192 ust. 2 i 3 oraz art. 221 ust. 14 ustawy z dnia 20 lipca 2018 r. – Prawo o szkolnictwie wyższym i nauce (tekst jednolity: Dz.U. z 2024 r., poz. 1571, z późn. zm.), a także Statutu Warszawskiego Uniwersytetu Medycznego.

Łączny IF prac cyklu 8.3 MEiN 280

- **Pietrzak J**, Przybyłkowski A. Endoscopic Treatment of Malignant Hilar Biliary Obstruction. Cancers (Basel). 2023 Dec 13;15(24):5819. doi: 10.3390/cancers15245819. PMID: 38136363; PMCID: PMC10741735. **IF = 4.5 MEiN 200**

- **Pietrzak J**, Przybyłkowski A. Managing Occluded Uncovered Self-expanding Metal Stents in Patients with Malignant Hilar Biliary Obstruction: A Retrospective Cohort Study. J Gastrointestin Liver Dis. 2025 Sep 26;34(3):339-342. doi: 10.15403/jgld-6215. PMID: 41004819. **IF = 2.0 MEiN 40**

- **Pietrzak J**, Pertkiewicz J, Kozieł S, Babski P, Ligocka J, Przybyłkowski A. Endoscopic treatment of malignant hilar biliary obstruction: A retrospective cohort study. World J Gastrointest Endosc 2025; 17(12): 110432 [PMID: 41479936 DOI: 10.4253/wjge.v17.i12.110432]. **IF = 1.8 MEiN 40**

Spis treści

3. Wykaz stosowanych skrótów

Skrót	Rozwinięcie w j. angielskim	Rozwinięcie w j. polskim
MHBO	malignant hilar biliary obstruction	złośliwe guzy wnęki wątroby
PTBD	percutaneous transhepatic biliary drainage	przezskórny przezwątrobowy drenaż dróg żółciowych
ERCP/ECPW	endoscopic retrograde cholangiopancreatography	endoskopowa cholangiopankreatografia wsteczna
EUS-BD	endosonography-guided biliary drainage	endoskopowy drenaż dróg żółciowych pod kontrolą EUS
CCC	cholangiocarcinoma cancer	rak dróg żółciowych
FCSEMS	full covered self-expandable metal stents	całkowicie powlekana samorozprężalna proteza metalowa
UCSEMS	uncovered self-expandable metal stents	niepowlekana samorozprężalna proteza metalowa
OS	overall survival	całkowity czas przeżycia
RBO	recurrent biliary obstruction	nawrót niedrożności dróg żółciowych
RFA	radiofrequency ablation	ablacja prądem o częstotliwości radiowej
ESGE	European Society of Gastrointestinal Endoscopy	Europejskie Towarzystwo Endoskopii
ASGE	American Society for Gastrointestinal Endoscopy	Amerykańskie Towarzystwo Endoskopii

4. Streszczenie

Złośliwe guzy wnęki wątroby (ang. malignant hilar biliary obstructions) mogą być spowodowane przez raka dróg żółciowych, raka pęcherzyka żółciowego, raka wątrobowokomórkowego, raka trzustki lub przez przerzuty do węzłów chłonnych wnęki wątroby. Endoskopowe protezowanie dróg żółciowych jest metodą z wyboru w leczeniu paliatywnym, jak i pomostowym pacjentów z niedrożnością dróg żółciowych na tle nowotworowym. Wśród ekspertów panuje pogląd, że konieczne jest odprowadzenie żółci z ponad 50% objętości wątroby, aby drenaż dróg żółciowych był skuteczny, co nierzadko wymaga drenażu obu płatów wątroby. Badacze wskazują na istotny brak jednoznacznych oraz zgodnych wytycznych dotyczących optymalnej strategii terapeutycznej w protezowaniu dróg żółciowych oraz brak precyzyjnych wskazań do stosowania dodatkowej techniki terapeutycznej - ablacji prądem o częstotliwości radiowej (RFA). Niniejszy cykl publikacji dokumentuje przegląd systematyczny dostępnych metod i aktualnych wytycznych oraz porównanie wyników leczenia endoskopowego przy użyciu różnych rodzajów protez z dodatkowym użyciem ablacji prądem o częstotliwości radiowej (RFA). Prezentowane badania oryginalne zostały przeprowadzone w macierzystym ośrodku autora, co zapewnia spójność ocenianych metod leczniczych i ciągłość obserwacji klinicznej.

5. Summary

Malignant hilar biliary obstructions may be caused by cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, pancreatic cancer, or metastases to lymph nodes located in the hepatic hilum. Endoscopic biliary stenting is the treatment of choice for both palliative and bridging therapy in patients with malignant biliary obstruction. There is a general consensus among experts that effective biliary drainage requires decompression of more than 50% of the liver volume, which often requires bilateral hepatic drainage. Available evidence indicates a notable lack of clear guidelines regarding the optimal therapeutic strategy for biliary stenting, as well as the absence of precise recommendations for the use of adjunctive therapeutic techniques such as radiofrequency ablation (RFA). This series of publications presents a systematic review of available treatment modalities and current guidelines, along with a comparison of clinical outcomes achieved using different types of stents, with and without the adjunctive application of radiofrequency ablation (RFA). All original studies included in this series were conducted at the author's home institution, ensuring consistency of the evaluated therapeutic approaches and continuity of clinical follow-up.

6. Wstęp

Złośliwe guzy wnęki wątroby (MHBO) to wyzwanie diagnostyczne i terapeutyczne. Najczęstszą ich przyczyną jest zewnątrzwątrobowy rak dróg żółciowych, znacznie rzadziej rak pęcherzyka żółciowego, rak wątrobowokomórkowy, rak trzustki lub przerzutowe zajęcie węzłów chłonnych we wnęce wątroby. Częstość występowania MHBO jest zróżnicowana geograficznie, w Europie wynosi od 0,5 do 3,4 przypadków na 100 000 osób [1]. Początkowy przebieg choroby jest najczęściej bezobjawowy. Dopiero wystąpienie żółtaczki, świądu skóry, bólu brzucha czy zapalenia dróg żółciowych prowadzi do rozpoznania, które w większości przypadków dotyczy już zaawansowanego, nieresekcyjnego stadium guza. Mediana przeżycia chorych w nieoperacyjnym MHBO wynosi zaledwie 7–16 miesięcy [2]. Do klasyfikacji anatomicznej lokalizacji zwężeń stosuje się klasyfikację Bismutha-Corlette'a [3]. Guzy typu I–II, choć formalnie zaliczane do zmian wnęki wątroby, w praktyce mogą być skutecznie leczone endoskopowo poprzez implantację pojedynczej protezy żółciowej. Zdecydowanie większe wyzwanie stanowią guzy typu III–IV, wymagające złożonych strategii endoskopowych i najczęściej obustronnego drenażu. Wokół tej grupy pacjentów koncentruje się niniejszy cykl publikacji. Skuteczność techniczna drenażu w MHBO (80–90%) jest niższa niż w przypadku dystalnych zwężeń dróg żółciowych (95–98%), co odzwierciedla złożoność procedury [4-5]. W licznych badaniach wykazano, że protezowanie dróg żółciowych w MHBO nie tylko łagodzi objawy niedrożności, ale także poprawia jakość życia i wydłuża czas przeżycia pacjentów [6-8]. Obecnie dostępne są trzy główne metody odbarczenia dróg żółciowych: endoskopowy drenaż dróg żółciowych wykonywany podczas cholangiopankreatografii wstecznej (ECPW), przezskórny przezwątrobowy drenaż dróg żółciowych (PTBD) oraz najrzadziej wykonywany drenaż endoskopowy dróg żółciowych pod kontrolą endosonografii (EUS-BD). Wybór metody zależy od lokalizacji niedrożności, stanu ogólnego chorego, stopnia zaawansowania choroby podstawowej (np. obecność wodobrzusza, zwężeń przewodu pokarmowego) oraz doświadczenia zespołu zabiegowego w danym ośrodku. W praktyce klinicznej ECPW jest wykorzystywany znacznie częściej niż PTBD w leczeniu MHBO, głównie ze względu na mniejszą inwazyjność, większą dostępność i większy komfort pacjenta, co ma szczególne znaczenie w leczeniu paliatywnym. Rozwój metod obrazowania, technik endoskopowych i narzędzi, a także rosnące doświadczenie operatorów sprawiają, że rola drenażu endoskopowego w leczeniu MHBO stale się zwiększa. Istotnym elementem postępowania jest dobór rodzaju protez. Obecnie stosuje się trzy główne typy: plastikowe protezy, samorozprężalne metalowe protezy niepokrywane (UCSEMS) oraz samorozprężalne metalowe protezy pokrywane (FCSEMS). Wybór rodzaju protezy zależy od przewidywanego czasu przeżycia pacjenta, możliwości technicznych oraz przyjętej strategii terapeutycznej. Zgodnie z aktualnymi zaleceniami, w większości ośrodków – w tym również w macierzystym ośrodku autora – metodą pierwszego wyboru w leczeniu paliatywnym MHBO pozostaje ECPW z implantacją odpowiednio dobranych protez. Analiza optymalnego doboru typu protezy stanowi jeden z głównych celów niniejszej rozprawy doktorskiej [9-11].

7. Cele pracy

- Przegląd systematyczny oraz analiza aktualnych wytycznych towarzystw gastroenterologicznych (ESGE, ASGE, Asia-Pacific consensus).

- Porównanie czasu ogólnego przeżycia (overall survival, OS), czasu do nawrotu niedrożności dróg żółciowych (recurrent biliary obstruction, RBO), liczby reinterwencji oraz częstości powikłań u pacjentów leczonych protezami plastikowymi, UCSEMS, FCSEMS oraz pacjentów, którym wykonywano jednostronny lub obustronny drenaż dróg żółciowych.

- Ocena wpływu RFA oraz chemioterapii na czas drożności protez (RBO) oraz ogólne przeżycie chorych (OS).

- Analiza metod postępowania w przypadku wystąpienia wtórnej niedrożności UCSEMS oraz porównanie ich skuteczności.

8. Materiał i metody

Przeprowadzono przegląd systematyczny piśmiennictwa dotyczącego endoskopowego leczenia złośliwej niedrożności dróg żółciowych okolicy wnęki wątroby. Przeszukiwanie bazy PubMed obejmowało okres od początku jej istnienia do maja 2023 roku i skutkowało identyfikacją 671 publikacji. Po analizie tytułów, streszczeń oraz pełnych tekstów, zgodnie z wytycznymi PRISMA, do ostatecznej analizy włączono 48 badań spełniających kryteria włączenia. Na podstawie uzyskanych danych opracowano artykuł przeglądowy z elementami przeglądu systematycznego.

Wykonano retrospektywną analizę wyników leczenia kohorty pacjentów chorych na MHBO leczonych endoskopowo w latach 2016-2024 w Pracowni Endoskopowej Kliniki Gastroenterologii i Chorób Wewnętrznych CSK UCK WUM. Wyniki opublikowano w dwóch artykułach oryginalnych.

Badanie przeprowadzono zgodnie z instytucjonalnymi i krajowymi standardami etycznymi oraz z Deklaracją Helsińską z 1964 roku wraz z jej późniejszymi poprawkami.

Kryteria włączenia do badania obejmowały: rozpoznanie MHBO w stopniu III–IV według klasyfikacji Bismutha-Corlette'a ; rozpoznanie nowotworu na podstawie badania histopatologicznego lub – w przypadku raka wątrobowokomórkowego (HCC) – typowymi kryteriami radiologicznymi zgodnie z wytycznymi EASL Barcelona 2001 [12]; prowadzenie leczenia endoskopowego wyłącznie w macierzystym ośrodku autora; dostępność pełnej dokumentacji medycznej oraz danych dotyczących obserwacji pacjentów. Pierwszorzędowym punktem końcowym było całkowite przeżycie (liczone od daty pierwszego zabiegu ECPW do daty zgonu). Punkty końcowe drugorzędowe obejmowały: częstość występowania zapalenia dróg żółciowych po ECPW, odsetek niepowodzeń, inne powikłania pozabiegowe, łączną liczbę procedur oraz średni czas drożności protez [13]. Do wykonywania zabiegów ECPW używano duodenoskopów firmy Olympus Medical Systems Corp., Tokio, Japonia. Stosowane protezy obejmowały: plastikowe (o średnicy 7–10 Fr i długości 10–15 cm, głównie protezy proste Boston Scientific), niepowlekane SEMS (6–10 mm średnicy i 8–12 cm długości; Boston Scientific, Cook Medical, MicroTech) oraz w pełni powlekane SEMS (6–10 mm średnicy i 8–12 cm długości; Boston Scientific). Wszystkie protezy wprowadzano drogą przezbrodawkową. Ablację prądem o częstotliwości radiowej (RFA) wykonywano za pomocą cewnika Habib™ EndoHPB (EMcision Ltd, Londyn, Wielka Brytania).

9. Wyniki

Według wytycznych ASGE w leczeniu MHBO dopuszczalne jest zastosowanie zarówno protez plastikowych, jak i metalowych, przy czym w celu ograniczenia liczby zabiegów u chorych z przewidywanym krótkim czasem przeżycia preferowane jest zastosowanie niepokrytych protez metalowych, natomiast w sytuacjach, gdy dalsze postępowanie terapeutyczne pozostaje niepewne, dopuszcza się protezy plastikowe. ASGE rekomenduje drenaż obustronny, formułując to zalecenie jako warunkowe, oparte na niskiej jakości dowodów. ESGE rekomenduje stosowanie niepokrywanych protez metalowych oraz strategię drenażu obejmującego ≥50% objętości wątroby, przedstawiając silne zalecenia oparte na dowodach umiarkowanej jakości. Zaktualizowany konsensus Asia-Pacific różnicuje strategię protezowania w zależności od możliwości leczenia systemowego: u pacjentów z dobrą odpowiedzią na chemioterapię zaleca wielokrotne protezowanie protezami plastikowymi z planową wymianą protez, natomiast u chorych niezakwalifikowanych do leczenia systemowego lub po jego niepowodzeniu, zaleca obustronne protezowanie protezami metalowymi, opierając się na dowodach umiarkowanej jakości i wysokim poziomie konsensusu ekspertów. Analizując 48 publikacji uwzględnionych w przeglądzie systematycznym, autor wnioskuje, że zastosowanie niepokrywanych protez metalowych wiąże się z dłuższą drożnością protez oraz mniejszą częstością nawrotowej niedrożności dróg żółciowych w porównaniu z leczeniem protezami plastikowymi. Ponadto drenaż obejmujący ≥50% objętości wątroby był związany z lepszą skutecznością kliniczną i mniejszym ryzykiem zapalenia dróg żółciowych (Tabela 1).

Tabela 1. Zestawienie zaleceń dotyczących protezowania w MHBO.

Towarzystwo (rok)	Zalecany rodzaj protez	Strategia drenażu i implantacji	Siła zaleceń i jakość dowodów
ASGE (2021)	protezy plastikowe lub niepowlekane protezy metalowe	preferowany drenaż obustronny; SEMS przy krótkim przewidywanym czasie przeżycia lub chęci ograniczenia reinterwencji; protezy plastikowe, gdy dalsze leczenie jest niepewne	zalecenia warunkowe, niska jakość dowodów
ESGE (2018)	niepowlekane protezy metalowe	drenaż obejmujący ≥50% objętości wątroby	silne zalecenia, umiarkowana jakość dowodów
Konsensus Asia-Pacific (2024)	protezy plastikowe lub niepowlekane protezy metalowe (w zależności od leczenia	wielokrotne protezowanie protezami plastikowymi z planową wymianą u chorych odpowiadających na chemioterapię; protezowanie niepowlekanymi protezami metalowymi techniką side-by-side lub stent-	umiarkowana jakość dowodów; wysoki poziom konsensusu

	systemowego)	in-stent u pacjentów niekwalifikujących się do leczenia systemowego lub po jego niepowodzeniu	ekspertów
Przegląd systematyczny autora (2023)	niepowlekane protezy metalowe	drenaż obejmujący ≥50% objętości miąższu wątroby	-

Do analizy wyników leczenia w macierzystym ośrodku autora włączono 164 pacjentów leczonych endoskopowym protezowaniem dróg żółciowych z powodu złośliwych zwężeń okolicy wnęki wątroby, u których wykonano łącznie 611 indywidualnych zabiegów endoskopowej wstecznej cholangiopankreatografii. W grupie badanej znalazło się 86 kobiet (52,4%) i 78 mężczyzn (47,6%), o medianie wieku 67 lat. Najczęstszą etiologią MHBO w badanej kohorcie był rak dróg żółciowych (62,2%), następnie rak pęcherzyka żółciowego (21,9%) i przerzuty raka jelita grubego (11,6%), natomiast inne nowotwory stwierdzono u 8 chorych (4,9%). Rozpoznanie histopatologiczne uzyskiwano najczęściej w badaniu wycinków lub cytologii szczoteczkowej pobranych podczas ECPW (54,9%), rzadziej w materiale operacyjnym (30,5%) lub biopsji celowanej pod kontrolą TK (10,4%). Średnia liczba wykonanych zabiegów ECPW przed rozpoznaniem wynosiła 1,2 (SD 1,0), a łączna średnia liczba zabiegów ECPW w całej kohorcie – 4,0 (SD 3,0). Przezskórny przezwątrobowy drenaż dróg żółciowych przed ECPW (pre-PTBD) wykonywano sporadycznie. Sukces techniczny definiowano jako pomyślne umieszczenie co najmniej jednej protezy w przewodzie wątrobowym prawym lub lewym. Naciekanie dwunastnicy stwierdzano najczęściej w grupie nowotworów przerzutowych (25,0%) oraz raka pęcherzyka żółciowego (17,1%), rzadziej w raku dróg żółciowych (7,8%), natomiast w przerzutowym raku jelita grubego nie obserwowano go wcale (Tabela 2).

Tabela 2. Charakterystyka ogólna grupy badanej.

Kryterium	Wartość
Płeć, liczba pacjentów (%)	Kobiety: 86 (52,4%) / Mężczyźni: 78 (47,6%)
Wiek w latach, mediana (zakres)	67 (65,6)
≤ 60 lat	n = 45 (27,4%)
> 60 lat	n = 119 (72,6%)
Etiologia, liczba pacjentów (%)	
Rak dróg żółciowych (CCC)	102 (62,2%)

Rak pęcherzyka żółciowego (GBC)	36 (21,9%)
Rak jelita grubego – przerzuty (CRC)	19 (11,6%)
Rak piersi – przerzuty (BC)	2 (1,2%)
Rak wątrobowokomórkowy (HCC)	2 (1,2%)
Niedrobnokomórkowy rak płuca (NSCLC)	1 (0,6%)
Rak neuroendokrynny	1 (0,6%)
Rak trzustki	1 (0,6%)
Metoda uzyskania wyniku histopatologicznego, liczba pacjentów (%)	
ECPW	90 (54,9%)
Operacja	50 (30,5%)
Biopsja celowana TK	17 (10,4%)
Biopsja celowana USG	2 (1,2%)
Kryteria HCC	2 (1,2%)
PTBD	1 (0,6%)
Paracenteza	1 (0,6%)
Endosonografia (EUS)	1 (0,6%)
Czas progresji do kolejnego stopnia zaawansowania choroby wg Bismutha- Corlette'a (dni), średnia (SD)	117,3 (83)
Liczba zabiegów ECPW przed rozpoznaniem, średnia (SD)	1,2 (1,0)
Łączna liczba zabiegów ERCP, średnia (SD)	4,0 (3,0)
Chemioterapia, liczba pacjentów (%)	86 (52,4%)
Ablacja prądem o częstotliwości radiowej (RFA), liczba pacjentów (%)	26 (15,9%)
Działania niepożądane inne niż nawrót niedrożności dróg żółciowych, liczba pacjentów (%)	
Zapalenie trzustki	40 (24,4%)
Krwawienie	15 (9,1%)
Perforacja	2 (1,2%)
Ropień wątroby	20 (12,2%)
Zapalenie pęcherzyka żółciowego	2 (1,2%)

Analizowaną kohortę podzielono na grupy: w zależności od rodzaju implantowanych protez, strategii protezowania oraz zastosowania RFA i chemioterapii:

- grupa leczona UCSEMS (n = 47) – obustronne protezowanie dwoma niepowlekanymi protezami metalowymi, po jednej do każdego przewodu wątrobowego.

- grupa leczona protezami plastikowymi (n = 61) – obustronne protezowanie dwiema protezami plastikowymi, po jednej do każdego przewodu wątrobowego.

- grupa leczona w sposób mieszany (n = 55) – obustronne protezowanie z użyciem jednej protezy pokrywanej metalowej (FCSEMS) oraz jednej protezy plastikowej. FCSEMS zazwyczaj umieszczano w przewodzie wątrobowym lewym, ze względu na mniejszą liczbę odgałęzień bocznych, a protezę plastikową w przewodzie prawym; pacjentów przypisywano do tej grupy wtedy, gdy strategia mieszana była technicznie wykonalna — to znaczy, gdy istniała wystarczająca przestrzeń do bezpiecznego i skutecznego umieszczenia FCSEMS oraz nie występowało ryzyko niedrożności przewodów sektorowych spowodowane przez protezę pokrywaną.

Ocena wyników leczenia w zależności od rodzaju protez i strategii protezowania

Najdłuższe przeżycie całkowite odnotowano w grupie leczonej UCSEMS (mediana 445 dni), w porównaniu z grupą leczoną protezami plastikowymi (110,5 dnia) oraz grupą leczoną w sposób mieszany (245 dni) ($p < 0,0001$) (Rycina 1). Czas drożności protez był również najdłuższy w grupie UCSEMS (122,5 dnia), a najkrótszy w grupie protez plastikowych (80 dni) ($p < 0,0001$). Średnia liczba reinterwencji była największa w grupie UCSEMS (5,4) w porównaniu z grupą protez plastikowych (2,5) oraz grupą mieszaną (4,5) ($p < 0,0001$). Średnia liczba epizodów zapalenia dróg żółciowych po ECPW wynosiła odpowiednio 2,1 (SD 2,0), 0,8 (SD 0,9) oraz 1,7 (SD 1,5) w grupie UCSEMS, grupie protez plastikowych oraz grupie mieszanego podejścia ($p < 0,0001$). Testy post-hoc wykazały istotnie większą liczbę epizodów zapalenia dróg żółciowych w grupie UCSEMS w porównaniu z grupą podejścia mieszanego ($p = 0,0085$). Częstość występowania ostrego zapalenia trzustki wyniosła 27,7% w grupie UCSEMS, 24,2% w grupie protez plastikowych oraz 21,8% w grupie mieszanego podejścia, bez istotnych statystycznie różnic pomiędzy grupami ($p = 0,79$). Powikłania krwotoczne wystąpiły u 10,6% pacjentów w grupie UCSEMS, 9,1% w grupie podejścia mieszanego oraz 6,6% w grupie protez plastikowych, również bez istotnych statystycznie różnic pomiędzy grupami ($p = 0,74$). Ropnie wątroby odnotowano u 14,9% pacjentów w grupie UCSEMS, 16,4% w grupie mieszanego podejścia oraz 6,6% w grupie protez plastikowych, bez istotnych statystycznie różnic pomiędzy grupami ($p = 0,22$).

W analizie dwóch grup, niezależnie od strategii protezowania (UCSEMS vs protezy plastikowe), leczenie metalowymi protezami niepowlekanymi wiązało się z istotnie dłuższym czasem przeżycia (445 vs 183 dni; $p < 0,0001$) oraz dłuższym czasem drożności

protez (122,5 vs 82,1 dnia; p = 0,0032). Średnia liczba zabiegów ECPW była wyższa w grupie leczonej UCSEMS (5,4 vs 3,4; p < 0,0001), po uwzględnieniu czasu przeżycia liczba zabiegów na rok również była niższa w grupie leczonej protezami plastikowymi (4,43 vs 8,26). W grupie UCSEMS odnotowano wyższy odsetek zapalenia dróg żółciowych po zabiegu (2,1% vs 1,2%; p = 0,0076), natomiast częstość ostrego zapalenia trzustki (27,7% vs 23,1%), krwawień (10,64% vs 5,17%) i ropni wątroby (14,89% vs 9,48%) nie różniła się istotnie między grupami.

Porównanie wyników leczenia metodą drenażu obustronnego i jednostronnego

Protezowanie obustronne nie wpływało istotnie na przeżycie w porównaniu z drenażem jednostronnym (p = 0,11). Średni czas drożności protez był nieco dłuższy w grupie drenażu jednostronnego (115,6 vs 99,4 dni), jednak różnica nie była istotna statystycznie (p = 0,27). Epizody zapalenia dróg żółciowych po ECPW występowały częściej w grupie drenażu obustronnego (1,5 vs 0,7; p = 0,24). Ostre zapalenie trzustki odnotowano u 50% pacjentów po drenażu jednostronnym oraz u 24,8% pacjentów po drenażu obustronnym (p = 0,53). Krwawienia wystąpiły odpowiednio u 20% i 8,93% pacjentów, a ropnie wątroby u 20% i 14,29% pacjentów w grupach jednostronnej i obustronnej (p > 0,05).

Ocena terapii uzupełniających

Zastosowanie ablacji prądem o częstotliwości radiowej (RFA) istotnie wydłużało przeżycie w porównaniu z grupą nieleczoną RFA (p < 0,0001). Średnia liczba zabiegów w grupie RFA wynosiła 7,6 i była istotnie wyższa niż w grupie bez RFA (3,3; p < 0,0001). Zastosowanie RFA nie wpływało jednak na odsetek niepowodzeń technicznych drenażu (p = 0,54). Średni czas do wystąpienia niedrożności protez wyniósł 79,6 dnia w grupie RFA oraz 96,3 dnia w grupie nieleczonej RFA (p = 0,5). Poza przemijającym bólem brzucha, u trzech pacjentów (11,5%) nie odnotowano powikłań specyficznych dla RFA.

Pacjenci leczeni chemioterapią żyli istotnie dłużej w porównaniu z osobami, które jej nie otrzymywały (p < 0,0001). Średnia liczba zabiegów ECPW w tej grupie wynosiła 4,8 i była istotnie wyższa niż w grupie bez chemioterapii (p < 0,0002). Chemioterapia nie miała istotnego wpływu na odsetek niepowodzeń technicznych zabiegów (p = 0,07). Średni czas drożności protez był istotnie dłuższy u pacjentów otrzymujących chemioterapię (103,6 dnia) w porównaniu z grupą bez leczenia (82,4 dnia; p = 0,0042).

Korelacje wybranych parametrów z czasem przeżycia przedstawiono w Tabeli 3.

Ocena skuteczności metod zastosowanych do leczenia niedrożności UCSEMS

U 49 pacjentów leczonych pierwotnie implantacją UCSEMS rozpoznano niedrożność protez. Odsetki sukcesu technicznego i klinicznego endoskopowego leczenia niedrożności protez wynosiły odpowiednio 91,2% i 61,4%. W zależności od zastosowanej metody drenażu rewizyjnego, odsetki sukcesu klinicznego przedstawiały się następująco: 50% dla udrożnienia balonem, 66% dla implantacji protezy plastikowej, 68% dla implantacji FCSEMS , 80% dla RFA z jednoczesnym założeniem protezy plastikowej oraz 80% dla

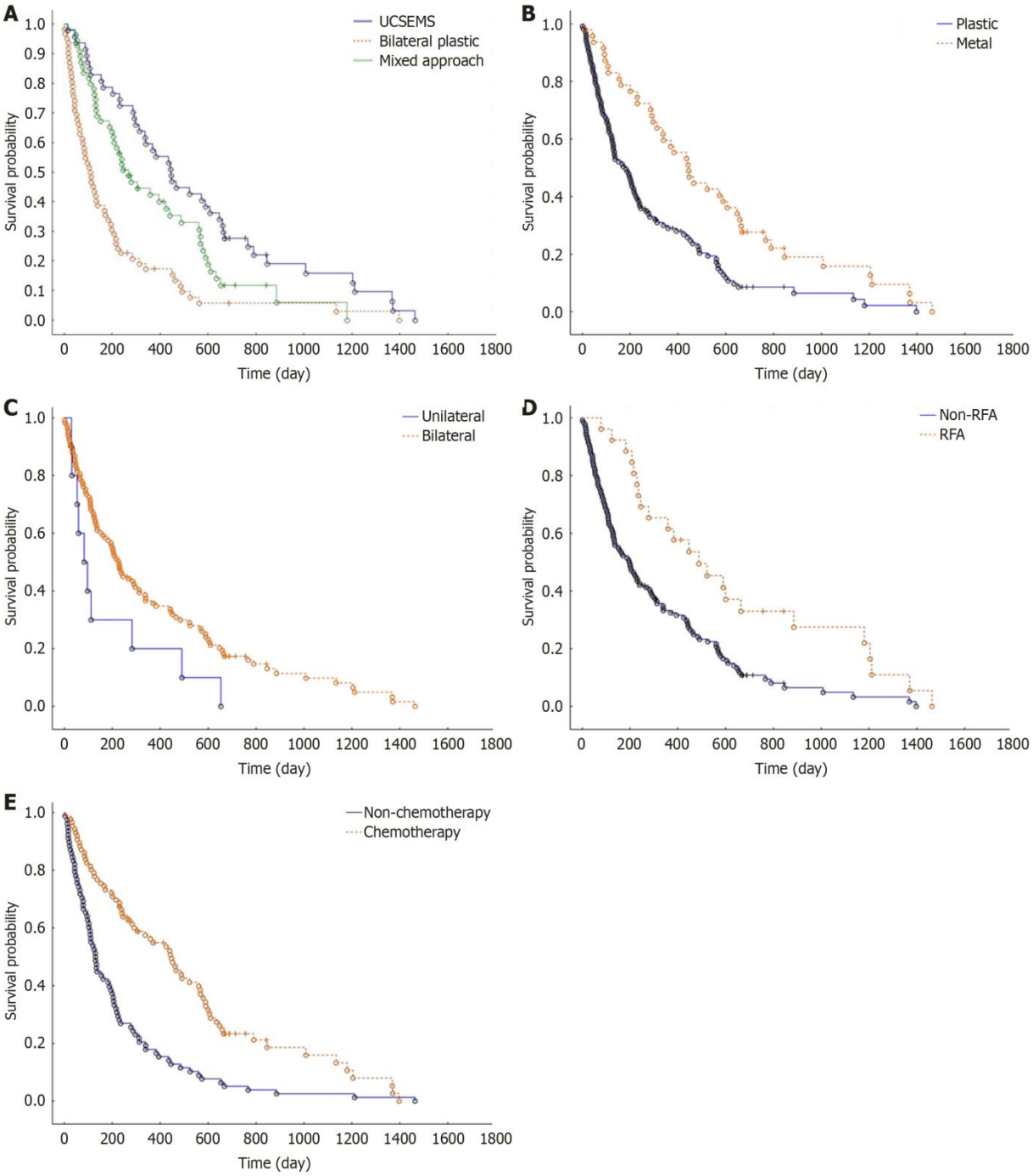
implantacji UCSEMS (p = 0,36). Średni czas do drugiej interwencji (drugiego ECPW po implantacji UCSEMS) wynosił odpowiednio 238, 201, 264, 78 i 205 dni (p = 0,5). Średni odstęp czasu między kolejnymi interwencjami wynosił odpowiednio 48, 75, 71, 66 i 95 dni (p = 0,03) (Tabela 4).

Tabela 3. Korelacje wybranych parametrów z czasem przeżycia.

	R	*P*
Wiek	-0.13	0.1004
Czas do progresji do kolejnego stopnia według klasyfikacji Bismutha-Corlette'a	0.56	0.0035
Liczba zabiegów ECPW przed postawieniem rozpoznania	0.28	0.0003
Liczba zabiegów ECPW po założeniu protez UCSEMS	0.55	0.0004
Łączna liczba zabiegów ECPW	0.69	0.0001
Liczba epizodów zapalenia dróg żółciowych u pacjentów z protezami UCSEMS	0.39	0.0467
Liczba epizodów zapalenia dróg żółciowych u pacjentów z jednostronnymi protezami plastikowymi	-0.24	0.1666
Liczba epizodów zapalenia dróg żółciowych u pacjentów z obustronnymi protezami plastikowymi	0.19	0.1060
Liczba epizodów zapalenia dróg żółciowych u pacjentów z podejściem mieszanym	0.04	0.7837
Liczba nieudanych zabiegów ECPW	0.01	0.9236

Tabela 4. Efekty kliniczne różnych technik stosowanych w leczeniu niedrożności niepokrytych samorozprężalnych protez metalowych (UCSEMS).

	Udrożnienie balonem	Proteza plastikowa w UCSEMS	FCSEMS w UCSEMS	RFA i proteza plastikowa w UCSEMS	UCSEMS w UCSEMS	*P*
Średni czas do drugiej interwencji, dni (SD)	238,0 (289,8)	201,8 (143,7)	264,3 (157,7)	78,5 (88,4)	205,1 (219,3)	0,4999
Średni czas do następnego ECPW po zostawaniu danej metody, dni (SD)	48,2 (69,2)	74,9 (46,8)	70,9 (45,5)	65,8 (30,2)	95,5 (98,1)	0,0326
Sukces kliniczny	9/18 (50%)	35/53 (66%)	11/16 (68.7%)	8/10 (80%)	12/15 (80%)	0.0366



Rycina 1. Czas całkowitego przeżycia pacjentów w zależności od strategii protezowania, rodzaju zastosowanych protez oraz zastosowania chemioterapii i RFA.

Krzywe Kaplana-Meiera: oś pionowa przedstawia prawdopodobieństwo przeżycia, a oś pozioma — czas obserwacji w dniach.
A: Porównanie OS pacjentów w zależności od strategii protezowania;
B: Porównanie OS pacjentów w zależności od rodzaju protez;
C: Porównanie OS pacjentów w zależności od metody protezowania;
D: Porównanie OS pacjentów leczonych endoskopowo z chemioterapią oraz wyłącznie endoskopowo;
E: Porównanie OS pacjentów leczonych endoskopowo z RFA oraz bez RFA;

10. Wnioski

1. Wytyczne ASGE, ESGE i Asia-Pacific różnią się głównie siłą zaleceń i jakością dowodów. Wytyczne ASGE zawierają zalecenia warunkowe oparte na dowodach o niskiej jakości. Zarekomendowano w nich użycie zarówno protez plastikowych, jak i metalowych w leczeniu MHBO. ESGE sformułowało silne zalecenia oparte na dowodach umiarkowanej jakości i zaleca stosowanie niepowlekanych protez metalowych oraz drenaż ≥50% objętości wątroby. Zaktualizowany konsensus Asia-Pacific - oparty na dowodach umiarkowanej jakości i wysokim poziomie zgodności ekspertów - uzależnia dobór protez w zależności od możliwości leczenia systemowego.

2. Wyniki przeglądu systematycznego wskazują na przewagę niepowlekanych protez metalowych oraz strategii zapewniających drenaż ≥50% miąższu wątroby w leczeniu endoskopowym MHBO.

3. U chorych na MHBO leczenie z zastosowaniem niepowlekanych protez metalowych wiązało się z dłuższym przeżyciem oraz dłuższym czasem drożności protez w porównaniu z protezami plastikowymi i całkowicie powlekanymi protezami metalowymi.

4. Zastosowanie drenażu obustronnego w porównaniu z drenażem jednostronnym nie wiązało się z jednoznacznym wpływem na przeżycie całkowite.

5. Zarówno ablacja prądem o częstotliwości radiowej (RFA) jak i chemioterapia wpływały korzystnie na przeżycie oraz czas drożności protez.

6. U pacjentów z niedrożnością UCSEMS udrożnienie balonem, implantacja protezy plastikowej, implantacja pokrywanej samorozprężalnej protezy metalowej (FCSEMS), ablacja prądem o częstotliwości radiowej (RFA) z jednoczesnym założeniem protezy plastikowej oraz ponowna implantacja niepowlekanej samorozprężalnej protezy metalowej (UCSEMS) skutkowały podobnym, wysokim odsetkiem sukcesu technicznego (powyżej 90%). Najlepsze wyniki pod względem długości utrzymania drożności dróg żółciowych oraz sukcesu klinicznego uzyskano po ponownej implantacji UCSEMS oraz po zastosowaniu RFA w połączeniu z protezą plastikową.

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Review

Endoscopic Treatment of Malignant Hilar Biliary Obstruction

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Simple Summary: Biliary stenting is today the primary method of palliative and bridging treatment in patients with malignant hilar biliary obstructions. Systematization, collection and interpretation of the studies performed so far is necessary to form appropriate recommendations and guidelines for the management, selection of drainage methods, selection of appropriate types of stents, their quantity and possible additional methods of endoscopic treatment.

Abstract: Stent implantation is an effective approach for palliative treatment of Bismuth-Corlette type III–IV malignant hilar biliary obstructions (MHBOs). In this article, we reviewed the currently used access methods for biliary stent placement (percutaneous transhepatic biliary drainage, endoscopic biliary drainage, endosonography guided biliary drainage), the available stent types (plastic stent, self-expanding metallic stent, full cover self-expanding metallic stent, radioactive self-expanding metallic stent), major approaches (unilateral, bilateral) and deployment methods (stent-in-stent, stent-by-stent). Finally, this review gives an outlook on perspectives of development in stenting and other palliative methods in MHBO.

Keywords: cholangiocarcinoma; malignant hilar biliary obstruction; endoscopic biliary drainage; endoscopic retrograde cholangiopancreatography

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1. Introduction

Malignant hilar biliary obstructions may be caused by cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, pancreatic cancer or metastatic lymph node of liver hilum. The most common cause of malignant hilar biliary obstructions (MHBO) remains extrahepatic cholangiocarcinoma (CCA), which based on location, can be divided into perihilar CCA (accounts for ~50–70% of all CCA cases) and distal CCA. Bismuth-Corlette classification is used to classify the location of biliary strictures. The incidence in populations is variable; in Europe, it is between 0.5 and 3.4 per 100,000 people [1]. At the onset of disease symptoms, such as jaundice, pruritus, stool discoloration, dark urine, pain and cholangitis, most patients with Bismuth-Corlette III-IV stage are diagnosed at the inoperable stage. Median survival for inoperable cases ranges between 7 and 16 months [2]. Based on results of available studies, it is justified to conclude that biliary stenting not only relieves symptoms of obstruction but also prolongs survival time in MHBO [3–5].

2. Biliary Anatomy

Knowledge of biliary anatomy is essential for the technical success of the procedure and stent selection. The anatomy of the biliary tract is variable and sometimes complex, thus posing significant challenges for the optimal stent placement. In the most common anatomical variant [6,7], the right hepatic duct arises from the connection of the anterior and posterior sector bile ducts, which are responsible for the drainage of the 5th and 8th and 6th and 7th liver segments, respectively. Segments 2, 3 and 4 drain into the left bile duct, which in most cases is formed by connecting sector ducts 2 and 3 with the creation of the left lateral section duct, into which sector duct 4 enters. The longer length is generally

characteristic of the left hepatic duct. There are various classifications which describe the anatomical variants of the biliary tract, the most commonly used are Nakamura [8], Varotti [9] and Huang [10] (Figure 1).

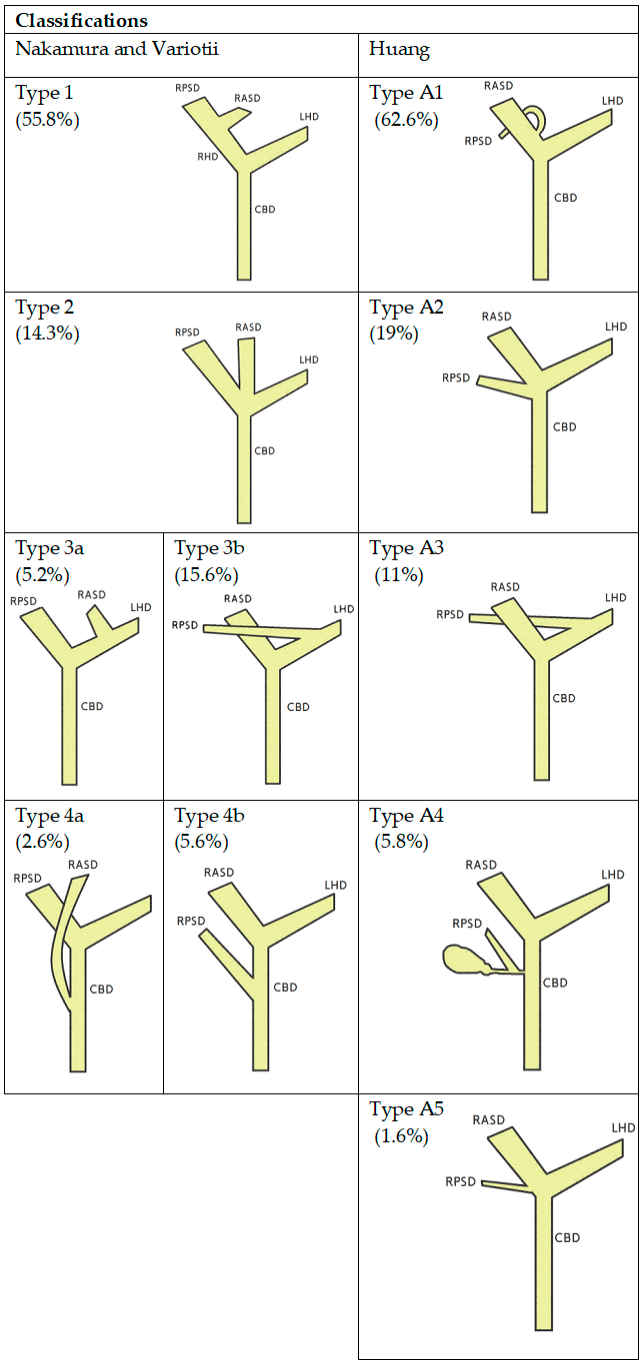

Figure 1. Schematic diagrams of the anatomical variants of the bile ducts according to Nakumra, Variotti, Huang and respective frequencies (in parenthesis). RPSD—right posterior sectoral duct, RASD—right anterior secoral duct, RHD-right hepatic duct, LHD—left hepatic duct, CBD—common biliary duct.

Averaging the volume of liver drainage through the bile ducts, the right hepatic duct is responsible for draining 50–60%, the left hepatic duct 30–40% and 10% of the liver volume from the caudate lobe, whose duct usually drains into the right hepatic duct.

The minimum liver drainage volume recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and Asia-Pacific consensus [11] is ≥50%. Drainage of >50%

of liver volume usually requires bilateral stenting. Vienne et al. [12] showed that drainage above 50% reduces the risk of cholangitis (OR 3.04, $p = 0.01$) and prolongs survival (119 vs. 59 days, $p = 0.005$).

There are no clear recommendations for disqualification of MHBO patients from biliary drainage, each case should be analyzed individually. It seems that the basic aspects indicating the lack of the expected effect of drainage may be the absence of obvious biliary dilatation, significant involvement of the liver parenchyma and poor general condition of the patient.

3. Methods, Findings and Search Strategy

A search for randomized controlled trials [RCTs], case series, retrospective studies and meta-analyses has been performed. The PubMed(R) database (National Library of Medicine, Bethesda, MD, USA) was searched by keyword "malignant hilar biliary obstruction", and the timeframe used in the search was from database inception until May, 2023. Included studies and case series covered patients diagnosed with malignant hilar biliary obstruction and treated with endoscopic or percutaneous biliary stenting. The initial search returned 671 articles, of which 48 studies met the inclusion criteria for this review. PRISMA plot for this review is available as Figure 2.

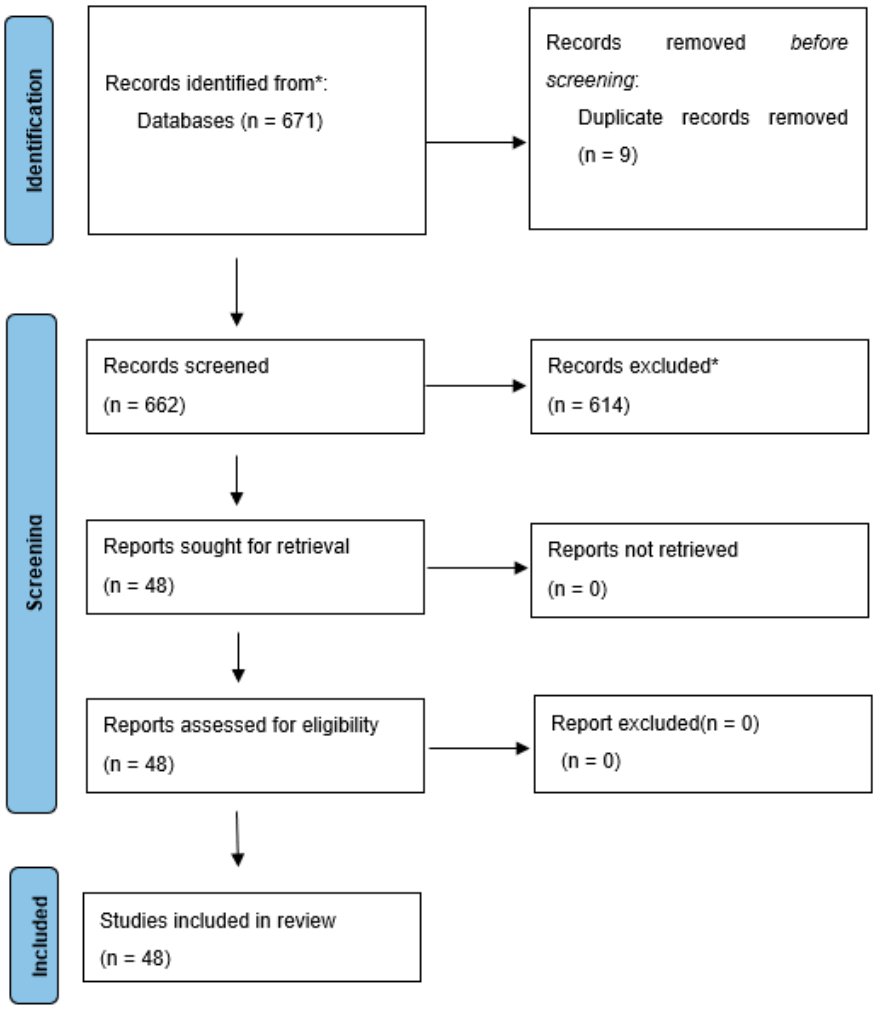

Figure 2. Malignant hilar biliary obstruction (PRISMA)**.** From: Page et al. [13]. * Reasons for excluding records or full-text articles were as follows: publications non concerning endoscopic or percutaneous methods of biliary drainage or studies on distal or benign biliary obstruction, absence of abstract, review papers topic, articles in a language other than English, single case reports.

4. Access Methods

Both methods endoscopic biliary drainage (EBD) and percutaneous transhepatic biliary drainage (PTBD) have certain advantages as well as limitations. The choice of drainage method should depend on the localization of the obstruction, the clinical condition of the patient, the severity of the primary disease (ascites, gastrointestinal stenosis), and the level of experience in biliary drainage at each center.

American Society for Gastrointestinal Endoscopy (ASGE) 2021 [14] recommends endoscopic biliary drainage (EBD) as the first choice for potentially resectable MHBO, while for unresectable or palliative drainage, it recommends PTBD/EBD depending on patient preferences, disease characteristics and local expertise.

ESGE 2018 [15] recommends EBD if the preoperative drainage of MHBO is necessary (plastic stents or naso-biliary drains are preferred), while for unresectable or palliative drainage, ESGE recommends PTBD or a combination of PTBD and EBD.

Many studies to date have unequivocally found PTBD superior to EBD in terms of therapeutic success (Paik et al. [16], Moole et al. [17], Van Eecke et al. [18]), longer stent patency (Lee et al. [19]), incidence of overall complications, 30-day mortality, sepsis and duodenal perforation. In a recently published 10-year analysis, Páez-Carpio et al. [20] confirmed the safety and effectiveness of PTBD in MHBO with a technical success rate of 87.7%. Also, the largest meta-analysis comparing PTBD with EBD by Duan et al. [21] found a significantly lower incidence of cholangitis and pancreatitis in PTBD, with ORs of 0.48 (95% CI, 0.31 to 0.74) and 0.16 (95% CI, 0.05 to 0.52) for cholangitis and pancreatitis, respectively. Only for bleeding and stent dislocation the risk was higher for PTBD than EBD, with ORs of 1.81 (95% CI, 1.35 to 2.44) and 3.41 (95% CI, 1.10 to 10.60), respectively.

In clinical practice, EBD is a more frequently performed procedure than PTBD, despite slightly better success rates in favor of PTBD; however, endoscopic drainage seems to be definitely more patient-friendly, which is crucial in palliative drainage with the goal to improve quality of life. Moreover, EBD seems to be definitely the first choice method due to the higher risk of metastatic spread during PTBD (Wang et al. [22]). Despite the recent decline in the frequency of PTBD performed in favor of EBD, the success rate of technically difficult PTBD procedures is promising, forcing further development of this method. A recent example would be a case of the PTBD approach with fusion imaging of real-time ultrasonography and computed-tomography (Hosokawa et al. [23]) in a patient with MHBO (Bismuth IV), in whom right posterior sectional bile duct stenting was not feasible during EBD.

In summary, PTBD is mentioned as a first-line drainage method in guidelines, but in the majority of MHBO cases, ERCP is advised as the primary intervention. In the case of possible resectability, the presence of ascites, coagulation disorders, insufficient biliary dilatation and multiple liver metastases, ERCP should clearly be the first-choice method. However, in cases of an obstruction of the gastrointestinal tract or previous surgery that makes the biliary tract (Roux-en-Y) difficult to reach, PTBD should remain as the method of first choice. Failure of ERCP is also an indication for PTBD.

An alternative method of biliary access in MHBO is the endosonography-guided biliary drainage (EUS-BD). Sundaram et al. [24] and Winkler et al. [25] proved the usefulness of this method in MHBO, with satisfactory technical success and reasonable clinical success. The method involves the creation of a fistula with implantation of a stent between the stomach (EUS-guided hepaticogastrostomy) or duodenum (EUS-guided choldeochoduodenostomy). In the case of distal biliary obstruction, it is becoming the method of second choice, and numerous meta-analyses have confirmed its considerable efficacy (Jin et al. [26]). However, larger trials are still required for MHBO to include this method in the management pathway. It seems that it may become the primary method of access after ERCP failure, especially with the further development of tools and the continued growth of operators experience.

5. Stent Selection

There are two basic types of biliary stents: metal and plastic. Multiple sizes and shapes are available to accommodate physician preferences, different disease stage and patient anatomy. Among the plastic stents, there are straight stents, double pig tails with bent ends, perforated stents and self-removable stents. Self-expandable metal stents are divided into full covered self-expandable metal stents (FCSEMS) and uncovered self-expandable metal stents (UCSEMS). All stents are available in different diameters (3–12 mm) and lengths (40–120 mm).

Plastic stents, compared to metal stents, are characterized by smaller diameter and shorter patency time. A multicenter study by Xia et al. [27] revealed that the median symptom-free stent patency in the plastic stent placement group was 4.4 months, while in the SEMS group, the median symptom-free stent patency was 8.7 months. SEMS also achieved a better clinical success rate than plastic stents (90.8% vs. 68.6%, respectively, $p < 0.001$). The incidence of postoperative cholangitis was higher in the plastic stents group than in the SEMS group (27.9% vs. 13.0%, respectively, $p < 0.001$). An additional advantage of UCSEMS over the plastic stent is that UCSEMS does not block a side branch of the biliary tree (such as the cystic duct) (Table 1).

Table 1. Studies on uncovered metal stents and plastic stents in malignant hilar biliary obstruction.

	Type, Number of Patients	Clinical Success Rate (%)	Median Time to RBO (Day)	Mean Number of Reintervention	The Incidence of Post-ERCP Cholangitis
Wagner et al. (1993) [28]	USEMS, 11;	100%	-	2.4 +/− 2.6	9.1%
	plastic, 9	88.9%	-	1.1 +/− 0.8	33.3%
Liberato et al. (2012) [29]	USEMS, 246;	97.9%	189	-	5.7%
	plastic, 204	84.8%	140	-	33.3%
Sangchan et al. (2013) [30]	USEMS, 54;	70.4%	103	1.16	14.8%
	plastic, 54	46.3%	35	1.23	24%
Gao et al. (2017) [31]	USEMS, 28;	92.9%	119	-	10.7%
	plastic, 31	93.5%	93	-	12.9%
Xia et al. (2020) [27]	USEMS, 184;	90.8%	264.8	1.5 +/− 0.7	13.0%
	plastic, 172	68.6%	133.9	2.2 +/− 1,4	27.9%
Kim et al. (2021) [32]	USEMS, 35;	71.4%	112	-	significantly higher in the plastic group
	plastic, 64	65.6%	56	-	

USEMS—uncovered metal stent; RBO—recurrent biliary obstruction.

According to the classical approach, the average interval for scheduled plastic stent replacement should be no longer than 3 months. Despite the significantly lower cost of plastic stents, the overall cost-effectiveness may be adversely affected by frequent replacement.

ASGE [14] guidelines recommend that the choice of the stents should be based on the patient's estimated survival time, desire to avoid reintervention and the possible lack of a definitive strategy. In the case of short life expectancy and a preference to avoid reintervention, UCSEMS are recommend, while when further management has not been fully established, the ASGE recommends implantation of a plastic stent with a possible replacement.

ESGE's [15] recommendations are similar to those of the ASGE, in the absence of an established diagnosis, plastic stents are recommended, while for palliative drainage, the ESGE specifies the choice of UCSEMS. The ESGE's guidelines mention the first retrospective study on FCSEMS efficacy in MHBO. Inoue et al. [33] showed a high technical success rate and a long time to recurrent biliary obstruction (210 days), however, liver abscesses were reported in 7% of patients as a complication of stent crossing a duct bifurcation. The guidelines do not specify or recommend the use of FCSEMS.

For preoperative drainage, the ASGE and ESGE guidelines appear to be adequate. A recently published study comparing FCSEMS with plastic stent (Mori et al. [34]) showed no

difference for RBO until surgery, while it confirmed fewer postoperative complications with plastic stents. Regarding the method of stent placement for preoperative drainage, above the papilla or inside the bile duct, Ishiwatari et al. [35] in a recent retrospective multicenter study showed comparable results in these two methods. In contrast, She et al. [36] and Hameed at al. [37] compared the effect of the choice of preoperative drainage method (ERCP, PTBD, combination of ERCP and PTBD) on postoperative outcomes, finding no significant differences.

It seems that in non-operative cases, the role of FCSEMS in MHBO is underestimated. With recent developments in chemotherapy and prolonging survival of patients with MHBO (for example with CCA) stenting with UCSEMS is becoming a suboptimal strategy due to tumor overgrowth by the wire mesh of UCSEMS and the inability to replace the stent (Table 2.).

Table 2. Studies on full cover metal stents in malignant hilar biliary obstruction.

	Method, Number of Patients	Technical Success Rate (%)	Clinical Success Rate (%)	Percentage of RBO (%)	Median Time to RBO (Day)	Success Rate of Reintervention (%)	The Incidence of Post-ERCP Cholangitis
Inoue et al. (2016) [33]	SBS, 17	94%	100%	31%	210	100%	5.8%
Yoshida et al. (2016) [38]	SBS, 32	96.9%	93.5%	61%	95	83.3%	0%
Kitamura et al. (2017) [39]	SBS, 17	100%	82%	71%	79	46%	5.8%
Takahashi et al. (2022) [40]	SBS, 54	100%	92.5%	35.2%	181	100%	1.8%
Matsubara et al. (2022) [41]	SBS, 11	100%	100%	36.4%	187	100%	0%

SBS—stent-by-stent; RBO—recurrent biliary obstruction.

To date, there have been only five studies published evaluating the use of FCSEMS in MHBO (Inoue et al. [33], Yoshida et al. [38], Kitamura et al. [39], Takahashi et al. [40], Matsubara et al. [41]). Each one has shown high technical and clinical success rates and the high success rate of endoscopic re-intervention. Inoue et al. [26] report the highest time to stent patency of all the papers (210 days in the initial group after bilateral placement and 112 days and 152 days in the re-intervention group after bilateral and unilateral placements, respectively). Intrahepatic bile duct occlusions and stent migration appear to be the greatest limitation of the method. Virtually all available studies were performed with too small number of patients to definitively determine the efficacy of the method (17, 32, 17, 54, 11 patients, respectively). Large prospective studies are needed to evaluate the method.

6. Stent Placement Strategy (Unilateral, Bilateral, Trisegmental)

The multicenter study comparing unilateral vs. bilateral stenting in MHBO by Xia et al. [27] showed better jaundice control, longer stent patency (8.1 months [95% CI, 6.8–9.4] vs. 5.4 months [95% CI, 4.7–6.2]; P Z 0.018) and longer overall survival (5.2 months [95% CI, 4.6–5.8] vs. 4.0 months [95% CI, 3.3–4.7]; P Z 0.040) in favor of bilateral stenting. Also, one of the larger meta-analyses by Chen et al. [42] confirms better clinical success rates (odds ratio: 3.56; 95% CI: 1.62–7.82, $p = 0.002$) and a reduced incidence of stent dysfunction (odds ratio: 0.51; 95% CI: 0.30–1.00, $p = 0.05$) in patients undergoing bilateral stenting (Table 3). Despite more favorable results for bilateral stenting, the issue is still unresolved. The studies conducted to date (e.g., Xia et al. [27]), despite the large number of patients and the use of propensity score matching (PSM), are retrospective papers evaluating different diseases at different stages of development.

It is technically more difficult to implant two stents than to perform unilateral stenting (Yang et al. [43]). Bilateral stenting prevents accidental blockage of bile outflow from

the non-stented hepatic ducts. If technically possible, bilateral metal stent placement is preferred.

Table 3. Studies on unilateral and bilateral stenting in malignant hilar biliary obstruction.

	Type, Number of Patients	Clinical Success Rate (%)	Median Time to RBO (Days)	Rates or Mean Number of Reintervention	The Incidence of Post-ERCP Cholangitis
Naitoh et al. (2009) [44]	bi, 29;	96%,	488	-	3%
	uni, 17	100%	210	-	0%
Lee et al. (2017) [45]	bi, 67;	95.3%,	252	42.2%	10.4%
	uni, 66	84.9%	193	57.6%	10.6%
Teng et al. (2019) [46]	bi, 52;	98%,	198	-	-
	uni, 58	96%	182	-	-
Staub et al. (2020) [47]	bi, 137;	82.5%,	168	-	6.3%
	uni, 50	86%	158	-	0%
Xia et al. (2020) [27]	bi, 178;	84.8%,	246.5	1.7 +/− 1.2	17.4%
	uni, 178	75.3%	164.4	1.8 +/− 1.1	23%

Stent-by-stent (SBS) involves the simultaneous placement of two stents next to each other, depending on technical feasibility either into sectoral conduits or intrahepatic conduits. This method allows for multiple choices of stents, for example, two UNSEMS, two FCSEMS, two plastic stents or a combination between plastic and FCSEMS/UCSEMS.

Stent-in-stent (SIS) involves the placement of two UCSEMS with one stent crossing the other more than halfway through the stent and passing through a wire mesh. Both methods have their pros and cons; in general, SIS seems to be a method resembling natural drainage, but it is associated with the impossibility of eventual replacement or removal of the stents. Available studies and meta-analyses show different results with regard to the clinical success, complications, stent dysfunction and technical success.

Meta-analysis by Cao et al. [48] showed a marginally better success rate in the SIS method compared to SBS, with no significant differences for clinical success, complications and stent dysfunction. Also, Hong et al. [49], Kim et al. [50] and Ishigaki et al. [51] found similar results in both methods. In contrast, de Souza et al. [52] in their meta-analysis found longer stent patency for SIS compared to SBS and no differences in technical success, clinical success, rates of both early and late adverse events, reintervention and procedure-related mortality.

In cases of advanced Bismuth III-IV hilar obstruction, obtaining satisfactory drainage may require trisegmental drainage. A multicenter retrospective study comparing bilateral and trisegment drainage has recently emerged. Matsumoto et al. [53] found no statistically significant difference for stent patency but observed a significant difference in clinical success rates for reinterventions with trisegmental drainage (73% [11/15] vs. 96% [47/49], $p = 0.009$). It seems that with the development of the slim delivery system and novel endoscopic technique (Maruki et al. [54]), the placement of trisegmental drainage will increase.

7. Additional Palliative Therapies

Radiation-emitting metallic stents (REMS) are a combination of uncovered metal stents with brachytherapy realized by multiple I^{125} seeds. The main assumption of using REMS is not only to decongest the biliary tract but also a reduction in the tumor mass. To date, there have been several studies or case series published evaluating the efficacy and safety of REMS placement in MHBO. The results so far are very encouraging. REMS seem to prolong survival as well as effective biliary drainage in these patients (Lu et al. [55]). Also, one of the largest meta-analyses performed by Huang et al. [56] comparing the regular and radiation-emitting SEMS showed that REMS insertion is associated with longer overall survival and stent patency in patients with inoperable MHBO. Despite the proven efficacy of REMS, their position in MHBO treatment and widespread use remains questionable, thus additional multicenter clinical trials are expected in order to determine the appropriate

indications. Additionally, the still limited access to nuclear medicine facilities remains a limitation of the method. (Table 4).

Table 4. Studies on radiation-emitting metallic stent in malignant hilar biliary obstruction.

	Type, Number of Patients	The Median Overall Survival (Days)	The Median Stent Patency (Days)	The Clinical Success Rate (%)	The Incidence of Overall Complications (%)
Lu et al. (2017) [55]	REMS, 33	338,	385	87.9%	27.3%
	UCSEMS, 26	141	142	84.6%	26.9%
Zhou et al. (2020) [57]	REMS, 40	177,	387	95%	50%
	UCSEMS, 36	123	121	97.2%	38.9%
Chen et al. (2021) [58]	REMS, 36	250,	225	100%	19.4%
	UCSEMS, 48	188	165	93.3%	22.9%
Zhang et al. (2023) [59]	REMS, 34	405,	-	94.1%	11.8%
	UCSEMS, 30	264	-	93.3%	10%

REMS—radiation-emitting metallic stent; UCSEMS—uncovered metal stent.

Radiofrequency ablation (RFA) is a method involving cancer cell reduction through high temperature achieved by high-frequency radio-waves. High temperature (>60 °C) generated by radio-waves causes denaturation of proteins which leads to coagulation and necrosis. In general, RFA is a method with proven efficacy in the palliative treatment of MHBO. To date, there have been several studies published evaluating its effectiveness. Of special note is a meta-analysis performed by Sofi et al. [60], comparing RFA with metallic or plastic stent placement (n = 239) or biliary stent placement only (n = 266). This meta-analysis showed prolonged survival (285 vs. 248 days) and improved stent patency in the group of patients treated with RFA. However, RFA was associated with a higher rate of adverse events, such as abdominal pain (31% vs. 20%, p = 0.003) (Table 5.).

Table 5. Studies on radiofrequency ablation in malignant hilar biliary obstruction.

	Type, Number of Patients	The Median Overall Survival (Days)	The Median Stent Patency (Days)	The Clinical Success Rate (%)	The Incidence of Post-ERCP Cholangitis (%)
Sofi et al. (2017) [60] (meta-analysis)	RFA, 239	285	Mean time 50.6 longer in the RFA group	100%	-
	stent, 266	248		93.3%	-
Han et al. (2020) [61]	RFA, 16	147	90	100%	6.3%
Inoue et al. (2020) [62]	RFA, 41	244	230	95.1%	2.5%
Kang et al. (2022) [63]	RFA, 15	230	178	100%	-
	stent, 15	144	122	93.3%	-
Oh et al. (2022) [64]	RFA, 28	311	140	100%	-
	stent, 51	311	192	100%	-

RFA—Radiofrequency ablation.

An interesting aspect is the use of RFA in patients with originally implanted SEMS who have had tumor ingrowth through the stent wire mesh. Kadayifci et al. [65] compared 25 patients with an occluded SEMS treated with RFA and 25 patients after plastic stent placement only. The study found a significantly longer time of stent patency in the RFA group compared to the plastic stent placement only (119.5 vs. 65.3 days, p = 0.03).

In conclusion, RFA is a method with proven efficacy, but it seems inadequate as a single method of biliary decongestion in MHBO, while it may be recommended in patients with recurrent stenosis after primary SEMS implantation.

8. Conclusions

The multitude of available methods confirms the recent development (the introduction of the new delivery system and RFA) in the field of endoscopic treatment of MHBO. Due

to the increasing number of patients with MHBO, further development of endoscopic techniques is required. Future perspectives in endoscopic biliary treatment involve several areas that aim to prevent stent occlusion, facilitate stent implantation, enhance ablation techniques and ultimately improve patient outcomes.

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Abbreviations

MHBO—malignant hilar biliary obstruction; PTBD—percutaneous transhepatic biliary drainage; EBD—endoscopic biliary drainage; EUS-BD—endosonography-guided biliary drainage; SEMS—self-expanding metallic stent; FCSEMS—full cover self-expanding metallic stent; REMS—radiation-emitting metallic stent; HCCA—hilar cholangiocarcinoma; RBO—recurrent biliary obstruction; SIS—stent-in-stent; SBS—stent-by-stent.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic treatment of malignant hilar biliary obstruction: A retrospective cohort study

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Abstract

BACKGROUND

Endoscopic biliary drainage for malignant hilar biliary obstruction (MHBO) remains a highly complex endoscopic retrograde cholangiopancreatography (ERCP) procedure. Each case requires an individualized approach, with outcomes influenced by the expertise of the medical center and access to advanced endoscopic tools.

AIM

To compare different stent types and drainage strategies, including the use of adjunctive therapies, in patients with MHBO treated endoscopically.

METHODS

We retrospectively analyzed 164 patients with MHBO (Bismuth types 3–4) who underwent exclusive endoscopic drainage. Patients were grouped by stent type—uncovered self-expandable metal stents (UCSEMS), bilateral plastic stents, or a mixed approach (fully covered self-expandable metal stents + plastic)—as well as by drainage strategy (unilateral/bilateral) and use of radiofrequency ablation (RFA) or chemotherapy.

RESULTS

Patients receiving UCSEMS had significantly longer overall survival compared to those with plastic stents or the mixed approach ($P < 0.0001$). Mean stent occlusion times were 80 days (bilateral plastic), 84.4 days (mixed approach), and 122.5 days (UCSEMS; $P < 0.0001$). The mean number of ERCP reinterventions was highest in the UCSEMS group (5.4) compared to bilateral plastic (2.5) and mixed approach group (4.5; $P < 0.0001$). Patients who received RFA or chemotherapy had significantly longer survival ($P < 0.0001$).

CONCLUSION
Bilateral UCSEMS stenting appears most effective for palliative treatment of MHBO. Adjunctive use of RFA and chemotherapy may further enhance survival, supporting a personalized, multidisciplinary approach.

Key Words: Biliary; Drainage; Hilar; Obstruction; Stent; Malignant

Core Tip: This retrospective cohort study analyzed 164 patients with malignant hilar biliary obstruction (MHBO) treated through endoscopic intervention using different stent types and drainage strategies. Uncovered self-expandable metal stents were associated with the longest survival and stent patency. Adjunctive therapies such as radiofrequency ablation and chemotherapy improved outcomes. The results support the patient-specific, multidisciplinary approach to MHBO management.

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INTRODUCTION

Malignant hilar biliary obstructions (MHBOs) may result from cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, pancreatic cancer, or metastatic lymph nodes at the liver hilum. Due to the challenging location, the variability of biliary anatomy, and the hilum's role as the confluence of the bile ducts, achieving effective drainage requires careful planning and specific considerations. For biliary drainage to be successful, more than 50% of the liver volume must be drained, which often necessitates bilateral drainage[1,2]. A comparison of technical success rates between MHBO (80%-90%)[3] and distal biliary obstruction (95%-98%)[4] highlights the complexity of stenting in MHBO. However, technical difficulty does not always correlate with clinical outcomes in practice. The reported technical success rate of up to 90% in MHBO appears to be overestimated due to the broad definitions used in many studies, which consider any biliary duct cannulation as a success, without specifying critical details. This may overlook essential aspects of effective stenting in MHBO.

Despite guidelines clearly indicating the superiority of bilateral drainage using uncovered self-expandable metal stents (UCSEMS), their placement remains technically demanding for endoscopists[5,6]. Reinterventions may be more difficult compared to the scheduled, regular replacement of plastic stents or fully covered self-expandable metal stents (FCSEMS). Furthermore, with advances in chemotherapy[7] and the development of adjunctive therapies such as radiofrequency ablation (RFA), patients treated with UCSEMS often live beyond the typical occlusion period of these stents.

Currently, two classical approaches to MHBO stenting are used, depending on technical feasibility: Unilateral drainage with plastic stents or UCSEMS, and bilateral drainage using the same stent types[8]. A third approach—bilateral drainage with double FCSEMS—has shown promising results in a few studies but has not yet been widely adopted by specialists [9-13]. To date, no single cohort study has directly compared plastic stents, FCSEMS, and UCSEMS in MHBO patients. This study aimed to evaluate different stent types and adjunctive therapies, focusing on their impact on overall survival (OS), stent patency, frequency of reinterventions, and incidence of complications.

MATERIALS AND METHODS

This retrospective analysis covers 164 consecutive patients who were treated between 2016 and 2024 at the Department of Gastroenterology and Internal Medicine, Medical University of Warsaw. The inclusion criteria for the study were a diagnosis of MHBO Bismuth 3 to 4 in a cholangiogram confirmed by two endoscopists, a diagnosis of malignancy confirmed by histopathological examination, or, in the case of hepatocellular carcinoma, typical radiological criteria as per European Association for the Study of the Liver Barcelona 2001 guidelines, endoscopic treatment performed exclusively in our endoscopy unit, and the availability of complete medical records and patient follow-up. Baseline characteristics of the study population, including demographics, cancer etiology, diagnostic approach, number of endoscopic retrograde cholangiopancreatography (ERCP) procedures, and adverse events, are summarized in Table 1.

Patients were excluded from the study if they had incomplete data or were lost to follow-up after endoscopic treatment, lacked histopathological confirmation of malignancy, were treated with surgical resection, or died within one month following stent placement.

The primary endpoint of the study was OS, measured from the date of the first ERCP procedure to the date of death. Secondary endpoints included the incidence of cholangitis post-ERCP, failure rates, other post-procedural complications, total number of procedures, and mean stent patency duration. Cholangitis was defined as an increase in temperature

Table 1 Baseline characteristics of study group

Characteristics		Mean ± SD or *n* (%)
Sex (women/men)		86 (52.4)/78 (47.6)
Age (year)		67 ± 65.6
	≤ 60	45 (27.4)
	> 60	119 (72.6)
Etiology	Cholangiocarcinoma	102 (62.2)
	Gallbladder carcinoma	36 (21.9)
	Colorectal cancer - metastases	19 (11.6)
	Breast cancer - metastases	2 (1.2)
	HCC	2 (1.2)
	Non-small-cell lung cancer	1 (0.6)
	Neuroendocrine carcinoma	1 (0.6)
	Pancreatic cancer	1 (0.6)
Method of obtaining a histopathological result	ERCP	90 (54.9)
	Surgery	50 (30.5)
	CT-guided biopsy	17 (10.4)
	USG-guided biopsy	2 (1.2)
	HCC criteria	2 (1.2)
	Percutaneous transhepatic biliary drainage	1 (0.6)
	Paracentesis	1 (0.6)
	Endoscopic ultrasound	1 (0.6)
Time of progression to the next Bismuth degree (day)		117.3 ± 83
Number of ERCP procedures before diagnosis		1.2 ± 1.0
Total number of ERCP procedures		4.0 ± 3.0
Chemotherapy		86 (52.4)
Radiofrequency ablation		26 (15.9)
Patient presenting adverse events other then recurrent biliary obstruction	Pancreatitis	40 (24.4)
	Bleeding	15 (9.1)
	Perforation	2 (1.2)
	Liver abscesses	20 (12.2)
	Cholecystitis	2 (1.2)

ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; USG: Ultrasonography; HCC: Hepatocellular carcinoma.

> 38 °C, white blood cell count < 4000/μL or > 10000/μL, an increase in C-reactive protein ≥ 1 mg/dL, absence of other potential sources of infection, and duration of symptoms > 24 hours within three days post-procedure. Failure rate was calculated based on unsuccessful stent placement into the targeted bile duct segment or failure to achieve bile drainage through the stent. Technical success was defined as the successful placement of at least one stent into either the right or left hepatic duct. Whenever possible, bilateral drainage was attempted as the preferred goal during each procedure. Post-ERCP bleeding was defined as a hemoglobin concentration drop of > 2 g/dL within 24 hours post-procedure, confirmed endoscopically. Post-ERCP pancreatitis (PEP) was diagnosed when at least two of three criteria were present within 24 hours post-ERCP: Imaging evidence consistent with pancreatitis, amylase or lipase elevation ≥ 3 times the upper normal limit, and the onset of new abdominal pain localized to the epigastrium. Liver abscess was diagnosed based on characteristic findings on computed tomography or cholangiography during ERCP. Cholecystitis was defined by the Tokyo Guidelines 2018 as typical imaging findings, fever > 38 °C, and systemic inflammatory symptoms occurring within 24 hours post-procedure. The total number of procedures was defined as the average number of ERCPs performed (both elective and urgent), depending on the study group. Mean occlusion time was defined as the number of days between

stent exchanges or stent cleaning procedures, excluding planned stent replacements.

All ERCP procedures were performed under full anesthesia with endotracheal intubation. The endoscopists performing the procedures were highly experienced, having conducted more than 3000 ERCPs and performing over 300 ERCPs annually. No formal protocol dictated the drainage approach, but bilateral stenting was consistently preferred and performed whenever technically feasible. Unilateral drainage was used only when placement of two stents was not possible due to anatomical or technical constraints. The preferred stenting strategy was bilateral UCSEMS placement whenever technically feasible, followed by FCSEMS and plastic stents. Bilateral plastic stenting was reserved for cases where anatomical constraints or limited ductal space prevented the safe placement of metal stents. Additionally, a temporal trend was observed in our center, with an increasing preference for UCSEMS-based bilateral drainage strategies after 2018, reflecting evolving procedural expertise and availability of equipment. To prevent PEP, 100 mg of rectal diclofenac was administered prior to the procedure. For planned procedures without cholangitis, patients received perioperative antibiotic prophylaxis with ampicillin-sulbactam. In cases of cholangitis, patients received antibiotics based on bile or blood culture results or broad-spectrum empirical therapy initiated earlier. Duodenoscopes used for ERCP were from Olympus Medical Systems Corp., Tokyo, Japan. The stents used included plastic stents (7-10 Fr in diameter and 10-15 cm in length, primarily straight Boston Scientific), uncovered SEMS (6-10 mm in diameter and 8-12 cm in length; Boston Scientific, Cook Medical, MicroTech), and fully covered SEMS (6-10 mm in diameter and 8-12 cm in length; Boston Scientific). All stents were inserted using a transpapillary approach. RFA was performed using the Habib™ EndoHPB catheter (EMcision Ltd, London, United Kingdom) with standard ERCP duodenoscopes, delivering 10 Watts for 90 seconds per cycle.

The study was conducted in accordance with institutional and national ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Statistical analysis

All statistical analyses were performed using STATISTICA (version 12.0, StatSoft Inc.) and Microsoft Excel. Quantitative variables were described using the mean, standard deviation, median, range, and 95% confidence intervals. Categorical variables were presented as counts and percentages. Normality was assessed with the Shapiro-Wilk test, and variance homogeneity with Levene's or Brown-Forsythe's test. Group comparisons used the *t*-test or Mann-Whitney *U* test (for two groups), and ANOVA or Kruskal-Wallis test (for multiple groups), with Tukey's or Dunn's *post hoc* tests, respectively. Paired data were analyzed using paired *t*-tests or Wilcoxon's test; repeated measures used repeated-measures ANOVA or Friedman's test. The χ^2 test (with Yates' correction or Fisher's exact test when needed) was used for categorical comparisons. Correlations were evaluated using Pearson's or Spearman's coefficients. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical outcomes according to stenting strategy and stent type

Patients were categorized into three groups based on the stent implantation strategy: UCSEMS ($n = 47$), bilateral plastic ($n = 61$), and mixed approach ($n = 55$). In the UCSEMS group, two UCSEMS were placed—one into each hepatic duct. In the bilateral plastic group, two plastic stents were placed in the same manner. The mixed group included patients in whom a combination of a FCSEMS and a plastic stent was used. In this approach, the FCSEMS was typically placed in the left hepatic duct, due to its fewer side branches, and the plastic stent in the right duct. Patients were assigned to this group when a mixed stenting strategy was technically feasible—that is, when there was sufficient space for safe and effective FCSEMS placement, and no sectoral ducts were at risk of being obstructed by the stent.

OS: The log-rank test demonstrated significantly higher survival in the UCSEMS group compared to plastic stents ($P < 0.0001$). The log-rank test also showed significantly higher survival in the UCSEMS group compared to the mixed approach group ($P = 0.0242$). Additionally, the log-rank test indicated significantly higher survival in the mixed approach group compared to the plastic group ($P = 0.0008$). The median survival time was 445 days, 110.5 days and 245 days for the UCSEMS, plastic and mixed approach groups, respectively ($P < 0.0001$; Figure 1A).

Total number of interventions: The mean number of interventions was 5.4 ± 3.7, 2.5 ± 2.1 and 4.5 ± 2.9 in the UCSEMS, bilateral plastic and mixed approach group respectively ($P < 0,0001$; Table 2).

Occlusion time: The UCSEMS group exhibited the longest mean occlusion time at 122.5 days. In the mixed approach group (84.4 days), the occlusion time was significantly longer compared to the bilateral plastic group ($P = 0.0333$). In contrast, in the bilateral plastic group (80.0 days), the occlusion time was significantly shorter compared to the UCSEMS group ($P < 0.0001$) and the mixed approach group ($P = 0.0248$; Table 2).

Adverse events: The mean number of cholangitis episodes was 2.1 ± 2.0, 0.8 ± 0.9 and 1.7 ± 1.5 in the UCSEMS, bilateral plastic and mixed approach group ($P < 0.0001$) respectively. *Post-hoc* tests showed significantly more episodes of cholangitis in the UCSEMS group relative to the mixed approach group ($P = 0.0085$). The incidence of acute pancreatitis was observed in 27.7% of patients in the UCSEMS group, 24.2% in the plastic bilateral group, and 21.8% in the mixed approach group, with no statistically significant difference between the groups ($P = 0.7902$). Bleeding complications occurred in 10.6% of patients in the UCSEMS group, 9.1% in the mixed approach group and 6.6% in the plastic group, with no statistically significant difference between the groups ($P = 0.745$). Liver abscesses occurred in 14.9% of patients in

Table 2 Clinical outcomes according to treatment strategy, mean ± SD

	Number of ERCP	Number of failures	Episodes of cholangitis	Occlusion time in days
Stent implantation strategy				
UCSEMS	5.4 ± 3.7	0.7 ± 1.0	2.1 ± 2.0	122.5 ± 124.8
Plastic	2.5 ± 2.1	0.6 ± 1.1	0.8 ± 0.9	80.0 ± 99.9
Mixed approach	4.5 ± 2.9	0.5 ± 0.8	1.7 ± 1.5	84.4 ± 91.3
P value	< 0.0001	0.7354	0.0001	0.0066
Drainage approach				
Unilateral	1.9 ± 0.9	1.5 ± 1.0	0.7 ± 0.8	115.6 ± 195.1
Bilateral	4.0 ± 3.4	0.4 ± 0.9	1.5 ± 1.7	99.4 ± 111.4
P value	0.0276	0.0001	0.2412	0.2748
Stent type				
Plastic	3.4 ± 2.7	0.5 ± 1.0	1.2 ± 1.3	82.1 ± 95.5
Metal	5.4 ± 3.7	0.7 ± 1.0	2.1 ± 2.0	122.5 ± 124.8
P value	0.0001	0.5364	0.0076	0.0032
Adjunctive therapy				
RFA	7.6 ± 4.2	0.5 ± 1.0	3.0 ± 2.4	79.6 ± 43.7
Non-RFA	3.3 ± 2.4	0.6 ± 1.0	1.2 ± 1.2	96.3 ± 113.9
P value	< 0.0001	0.4589	0.0002	0.5418
Chemotherapy	3.1 ± 2.5	0.4 ± 0.6	1.7 ± 1.7	103.6 ± 101.9
Non-chemotherapy	4.8 ± 3.5	0.7 ± 1.2	1.2 ± 1.4	82.7 ± 109.9
P value	0.0002	0.6782	0.0509	0.0042

ERCP: Endoscopic retrograde cholangiopancreatography; UCSEMS: Uncovered self-expandable metal stents; RFA: Radiofrequency ablation.

the UCSEMS group, 16.4% in the mixed approach group and 6.6% in the bilateral plastic group, with no statistically significant difference between the groups ($P = 0.222$).

UCSEMS vs plastic stents

For this analysis, study participants were categorized into two groups based on the type of stent used: Plastic ($n = 116$) and UCSEMS ($n = 47$).

OS: The log-rank test demonstrated significantly higher OS in the UCSEMS stent group compared to the plastic stent group ($P < 0.0001$). The median survival time was 183 and 445 days for the plastic and UCSEMS groups, respectively ($P < 0.0001$; Figure 1B).

Total number of interventions: Statistical analysis revealed a significantly higher number of ERCP procedures in the metal stent group compared to the plastic stent group, with mean values of 5.4 and 3.4, respectively ($P < 0,0001$; Table 2). When adjusted for survival time, the mean number of ERCP procedures per patient-year was lowest in the UCSEMS group (4.43), compared to the mixed approach (6.71) and plastic stent group (8.26).

Occlusion time: The UCSEMS group showed a statistically significantly longer stent occlusion time of 122.5 days compared to the plastic stent group, which had an occlusion time of 82.1 days ($P = 0.0032$).

Adverse events: The UCSEMS group showed a significantly higher rate of postprocedural cholangitis (2.1%) compared to the plastic stent group (1.2%; $P = 0.0076$). Acute pancreatitis occurred in 23.1% of patients in the plastic stent group and in 27.7% of patients in the UCSEMS group ($P = 0.5366$). Bleeding occurred in 10.64% of cases in the UCSEMS group and 5.17% in the plastic stent group ($P = 0.299$). Liver abscesses were observed in 14.89% of patients in the UCSEMS group and 9.48% in the plastic stent group ($P = 0.408$).

Bilateral vs unilateral stent placement

For this subanalysis patients were divided into two groups based on the drainage approach: Unilateral ($n = 10$) and bilateral ($n = 112$).

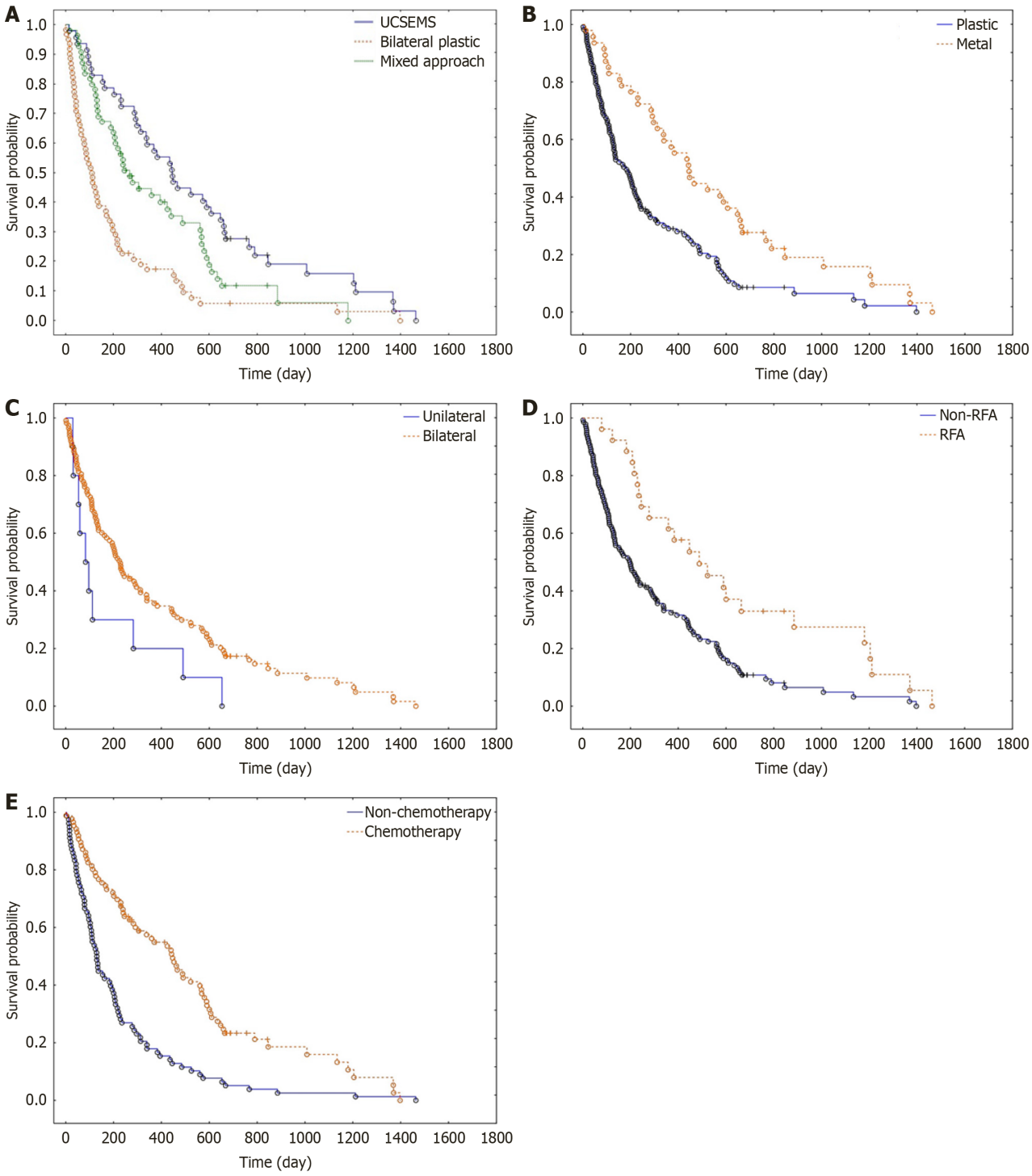

Figure 1 Kaplan-Meier curves. A: Kaplan-Meier curve comparing overall survival (OS) among the 4 groups; B-D: Kaplan-Meier curve comparing OS among the 2 groups plastic and metal stents (B), unilateral and bilateral (C) and patients undergoing radiofrequency ablation (RFA) and non-RFA (D); E: Kaplan-Meier curves of patients treated with endoscopy and chemotherapy and endoscopy only. UCSEMS: Uncovered self-expandable metal stents; RFA: Radiofrequency ablation.

OS: The log-rank test did not show statistically significant differences in OS time between bilateral and unilateral stenting; however, survival was longer in the bilateral group (P = 0.1129; Figure 1C).

Total number of interventions: Statistical analysis revealed a significantly higher number of ERCP procedures in the bilateral group compared to the unilateral group, with mean values of 4.0 and 1.9, respectively (P = 0.0276). Additionally, the unilateral group had a statistically significantly higher rate of unsuccessful procedures, with mean values of 1.5 and 0.4 for the unilateral and bilateral groups, respectively (P < 0.0001; Table 2).

Occlusion time: The mean stent occlusion time was longer in the unilateral group (115.6 days *vs* 99.4 days), but the difference was not statistically significant (P = 0.2748).

Adverse events: Cholangitis episodes were more frequent in the bilateral group than in the unilateral group (1.5 *vs* 0.7; $P = 0.2412$). Acute pancreatitis occurred in 50% of unilateral and 24.8% of bilateral group patients ($P = 0.53$). Bleeding rates were 20% (unilateral) and 8.93% (bilateral; $P = 0.18$). Liver abscesses were observed in 20% (unilateral) and 14.29% (bilateral; $P = 0.64$).

Adjunctive therapy

RFA: The log-rank test demonstrated a statistically significant higher survival in the group of patients who were treated with RFA ($P < 0.0001$). The mean number of procedures in the group of patients who underwent RFA was 7.6, which was significantly higher compared to the non-RFA group, with a mean of 3.3 ($P < 0.0001$). However, RFA did not have an impact on the rate of unsuccessful procedures ($P = 0.4589$). The mean time to stent occlusion was 79.6 days in the RFA group compared to 96.3 days in the non-RFA group ($P = 0.54$). Except for transient abdominal pain in three patients (11.5%), no RFA-specific complications were observed (Figure 1D).

Chemotherapy: The log-rank test demonstrated significantly higher survival in patients who underwent chemotherapy ($P < 0.0001$). The mean number of ERCP procedures in patients receiving chemotherapy was 4.8, which was significantly higher compared to those who did not receive chemotherapy ($P < 0.0002$). Chemotherapy had no significant impact on the rate of unsuccessful procedures ($P = 0.06782$). The mean stent occlusion time was significantly longer in the group of patients receiving chemotherapy (103.6 days) compared to those not receiving chemotherapy (82.4 days; $P = 0.0042$; Figure 1E).

DISCUSSION

Endoscopic stenting remains a fundamental component of palliative therapy for patients with MHBO, particularly for those ineligible for curative surgery. Unlike distal biliary obstruction, MHBO poses distinct anatomical and technical challenges due to its proximity to the hepatic duct bifurcation. This requires meticulous planning to achieve effective biliary drainage while minimizing complications. Current guidelines recommend that these complex procedures be performed in specialized centers with significant procedural volumes and access to multidisciplinary hepatobiliary teams to ensure optimal patient outcomes. Nevertheless, despite advancements in stent technology and endoscopic techniques, considerable debate persists regarding the optimal stenting approach, including the type of stent (metal *vs* plastic) and the drainage strategy (unilateral *vs* bilateral).

Metal stents are consistently favored over plastic stents for MHBO due to their superior performance in terms of stent patency, reduced intervention rates, and lower risk of post-procedural cholangitis[14]. This aligns with prior research indicating that metal stents provide more effective and durable biliary decompression. In our study, the use of UCSEMS was associated with the longest median stent patency (122.5 days) and the best OS. However, these advantages were accompanied by the highest rates of adverse events, including cholangitis (2.2 episodes per patient) and procedural failure (0.7 per patient).

Interestingly, the UCSEMS group, which had the longest survival, also exhibited the highest rate of cholangitis episodes (Table 3). While this correlation is likely confounded by prolonged exposure time due to longer survival, it raises questions about possible immune-modulatory effects that warrant further investigation. One hypothesis is that recurrent inflammation may trigger localized immune responses, though there is no direct evidence of an antitumor effect. The association likely reflects confounding factors and should be interpreted with caution. While this hypothesis requires further validation, it aligns with emerging data suggesting that tumor-immune interactions play a critical role in cancer progression and treatment response[15].

We investigated mixed stenting strategies, including FCSEMS combined with plastic stents or sequential switching. Although these approaches lowered cholangitis rates, they were linked to poorer survival compared to consistent UCSEMS use. This paradox may reflect underlying disease severity or anatomical complexity in patients selected for mixed stenting, which could have negatively influenced survival outcomes. This underscores the need for individualized decisions. Mixed strategies may be considered in select high-risk patients but should not replace standard protocols.

The optimal drainage strategy for MHBO—unilateral or bilateral—remains a topic of ongoing debate[5,16-20]. Prior randomized trials have reported inconsistent findings, with some studies favoring unilateral stenting due to its technical simplicity and lower complication rates, while others advocate bilateral stenting for its superior biliary decompression. It is well established that effective drainage of more than 50% of the liver volume is associated with better clinical outcomes, including reduced cholangitis rates, improved liver function, and prolonged stent patency. In our study, bilateral stenting did not yield a statistically significant improvement in OS compared to unilateral stenting. However, bilateral stenting was associated with fewer procedural failures and improved biliary decompression, supporting its use when technically feasible. These findings suggest that bilateral drainage, when technically feasible, may offer advantages in terms of reducing reintervention rates and maintaining better liver function, even if its impact on survival is less pronounced.

In addition to stenting, we evaluated adjunctive therapies such as RFA and chemotherapy, both of which significantly prolonged survival in MHBO patients. Chemotherapy is already standard, and our findings support incorporating RFA into routine care, as it improves biliary decompression and stent patency. These therapies may complement each other and should be considered as part of a comprehensive treatment strategy. It is important to acknowledge that patients who received RFA or chemotherapy may have had better baseline liver function or lower tumor burden, which could have introduced selection bias and influenced the observed survival benefit.

Table 3 Correlation of selected clinical parameters with overall survival time

	r value	*P* value
Age	-0.13	0.1004
Time to progression to the next Bismuth stage	0.56	0.0035
Number of ERCP procedures before diagnosis	0.28	0.0003
Number of ERCP procedures after placement of UCSEMS stents	0.55	0.0004
Total number of ERCP procedures	0.69	0.0001
Number of cholangitis episodes in patients with UCSEMS	0.39	0.0467
Number of cholangitis episodes in patients with unilateral plastic	-0.24	0.1666
Number of cholangitis episodes in patients with bilateral plastic	0.19	0.1060
Number of cholangitis episodes in patients with mixed approach group	0.04	0.7837
Number of failed ERCP	0.01	0.9236

ERCP: Endoscopic retrograde cholangiopancreatography; UCSEMS: Uncovered self-expandable metal stents.

Unlike most previous studies, we included all ERCP procedures in our analysis, not just the first intervention. We focused on OS as the primary endpoint, aligning with the desirability of outcome ranking framework. We did not emphasize technical success, recognizing that it does not always translate into clinical benefit. Limitations include the observational design, extended recruitment period, and potential confounding factors such as operator technique and stent variability.

CONCLUSION

Our findings confirm the superior efficacy of metal stents, especially UCSEMS, in managing MHBO, despite their higher rates of complications. Bilateral drainage enhances biliary decompression and procedural success, although its impact on OS remains uncertain. RFA and chemotherapy should be considered standard components of care, given their complementary benefits in prolonging survival and maintaining stent patency. Future research should focus on optimizing stent designs and investigating the synergistic effects of endoscopic, ablative, and systemic therapies. Well-designed prospective trials are essential to define the most effective drainage strategies and to better clarify the role of RFA. A personalized, multimodal treatment strategy appears most promising for improving outcomes in this complex patient population.

FOOTNOTES

Author contributions: Pietrzak J conceived the study and designed the methodology; Pietrzak J, Ligocka J, Pertkiewicz J, Kozieł S, and Babski P performed the endoscopic procedures; Pietrzak J collected and analyzed the data and drafted the manuscript; Przybyłkowski A conducted the critical review and revised the manuscript; all authors participated in the final review, approved the manuscript, and ensured the accuracy and integrity of the work.

Institutional review board statement: The study was submitted to the Bioethics Committee of the Medical University of Warsaw, which confirmed that formal approval was not required due to the retrospective design and full anonymization of patient data. The study was conducted in accordance with institutional and national ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Informed consent statement: Informed consent was waived due to the retrospective nature of the study and the use of fully anonymized data, as approved by the institutional bioethics committee.

Conflict-of-interest statement: The authors declare no conflicts of interest related to this study. No financial or non-financial support from any commercial entity was received.

Data sharing statement: The anonymized datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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ORIGINAL PAPER

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Managing Occluded Uncovered Self-expanding Metal Stents in Patients with Malignant Hilar Biliary Obstruction: A Retrospective Cohort Study

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ABSTRACT

Background & Aims: The implantation of uncovered self-expanding metal stents (UCSEMS) is an established method for the palliative treatment of malignant hilar biliary obstruction (MHBO). However, with advances in chemotherapy extending patient survival, individuals treated primarily with UCSEMS increasingly encounter overgrowth of the tumour in the stent lumen and occlusion. In this study, we aimed to compare various methods of managing occluded UCSEMS.

Methods: We analyzed a cohort of 49 patients with malignant hilar biliary obstruction who were treated with UCSEMS implantation as first-line endoscopic treatment. We evaluated their follow-up data, recorded complications, and assessed the methods used to manage occluded stents: balloon cleaning, plastic stent in stent implantation, UCSEMS stent in stent implantation, fully covered self-expandable metal stent (FCSEMS) stent in stent implantation and radiofrequency ablation (RFA).

Results: Technical and clinical success rates of the reinterventions were 91.2% and 61.4%, respectively. Depending on the type of revisionary drainage method used, clinical success rates were as follows: 50% for balloon cleaning only, 66% for plastic stent placement, 68% for FCSEMS stent placement, 80% for RFA with simultaneous plastic stent placement, and 80% for UCSEMS stent placement (p=0.366). The mean time to the second reintervention (second ERCP after UCSEMS placement) was 238, 201, 264, 78, and 205 days, respectively (p=0.4999). The mean interval time for all reinterventions was 48, 75, 71, 66, and 95 days, respectively (p=0.0326).

Conclusions: All techniques demonstrated high technical feasibility. While UCSEMS re-stenting and RFA with plastic stents showed promising trends in clinical success and stent patency, definitive conclusions about superiority cannot be drawn. Further multicentre prospective studies are needed to validate these findings.

Key words: biliary obstruction – malignant hilar biliary obstruction – stent – biliary stenting – self-expanding metal stents – SEMS – occluded uncovered SEMS.

Abbreviations: ERCP: endoscopic retrograde colangiopancreatography; FCSEMS: fully covered self-expandable metal stent; MHBO: malignant hilar biliary obstruction; PTBD: percutaneous transhepatic biliary drainage; RBO: recurrent biliary obstruction; RFA: radiofrequency ablations; UCSEMS: uncovered self-expandable metal stents.

INTRODUCTION

Numerous studies have confirmed the superiority of metal stents over plastic stents in the biliary stenting of patients with malignant hilar biliary obstruction (MHBO) [1-3]. Uncovered self-expandable metal stents (UCSEMS) demonstrate longer patency, extended over survival, and a higher rate of cholangitis compared to plastic stents. Despite the superior outcomes, controversies remain, primarily due to the permanence of UCSEMS implantation. This is associated with challenges in determining the appropriate management strategy during subsequent endoscopic retrograde colangiopancreatography (ERCP) procedures, whether due to cholangitis or recurrent jaundice caused by the overgrowth and ingrowth of the tumour in the implanted stents. Moreover, with advancements in chemotherapy [4] and local treatment modalities such as radiofrequency ablation (RFA) [5] and radiotherapy [6], patients with UCSEMS often require an increasing number of reinterventions. However,

there is still a limited body of research comparing the patency duration (time to subsequent ERCP) of UCSEMS following different reintervention techniques. Current guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) [7], the European Society of Gastrointestinal Endoscopy (ESGE) [8] and Asia-Pacific consensus [9] recommend the implantation of UCSEMS in cases of malignant biliary obstruction. However, there are no established guidelines on the optimal method for managing occluded UCSEMS. To address this gap, we compared various methods of managing obstructed stents in terms of technical success, clinical success, and time to recurrent biliary obstruction (RBO).

METHODS

We carried out a retrospective analysis of 49 patients who underwent biliary stenting with uncovered self-expandable metal stents (UCSEMS) between 2016 and 2024 at the Endoscopy Unit of the Central Clinical Hospital of the Medical University of Warsaw, Poland. Stent occlusion was defined as the recurrence of jaundice confirmed by elevated bilirubin or gamaglutamyl transpeptidase and alkaline phosphatase levels, along with imaging evidence (ultrasound or computed tomography) of intrahepatic bile duct dilatation or cholangitis diagnosed in accordance with the Tokyo Guidelines 2018 [10]. Clinical success was defined as a decrease in bilirubin levels below 2.5 mg/dL or a reduction of more than 50% compared to the most recent pre-procedure value. Technical success was defined as the successful cannulation of the bile ducts. Recurrent biliary obstruction was defined as the time between consecutive ERCP procedures. The study included only patients treated with endoscopic interventions, excluding those requiring percutaneous transhepatic biliary drainage (PTBD). We also included patients who required only bile duct balloon cleaning to remove biliary sludge or stones. In cases where cholangiography confirmed stent overgrowth, additional interventions such as repeat stenting or radiofrequency ablation (RFA) followed by plastic stent placement were performed.

All ERCP procedures were performed under intravenous sedation and endotracheal intubation. The endoscopists performing the procedures were highly experienced, having conducted more than 3,000 ERCPs and performing over 300 ERCPs annually. To prevent post-ERCP pancreatitis, 100 mg of rectal diclofenac was administered prior to the procedure. Duodenoscopes used for ERCP were from Olympus Medical Systems Corp., Tokyo, Japan. The stents used included plastic stents (7–10 Fr in diameter and 10–15 cm in length, primarily straight Boston Scientific), UCSEMS (6–10 mm in diameter and 8–12 cm in length; TaeWoong, Zilver 635, Evo, LCD, MicroTech), and fully covered self extended metal stents (FCSEMS) (6–10 mm in diameter and 8–12 cm in length; Hanarostent, WallFlex).

Given the retrospective design and single-centre setting, our analysis is inherently limited in its generalizability. Furthermore, the small sample sizes in certain intervention subgroups limit the power to detect statistically significant differences. As such, the findings should be viewed as hypothesis-generating and interpreted cautiously.

All statistical analyses were performed using the StatSoft Inc. (2014) STATISTICA software (version 12.0; www.statsoft.com) and Microsoft Excel. Quantitative variables were described using the arithmetic mean, standard deviation, median, minimum and maximum values (range). Qualitative variables were presented as frequencies and percentages. The normality of the distribution of quantitative variables was assessed using the Shapiro-Wilk test, while the homogeneity of variances was evaluated with Levene's or Brown-Forsythe's test. Differences between two independent groups were tested using Student's t-test (or Welch's test in the case of unequal variances) or the Mann-Whitney U test (when conditions for the t-test were not met or for ordinal variables). Differences among more than two groups were analyzed using ANOVA (F-test) or the Kruskal-Wallis test (when ANOVA assumptions were not met). Post hoc analyses were conducted with Tukey's test (following ANOVA) or Dunn's test (following Kruskal-Wallis). For paired data, differences between two groups were assessed using Student's t-test or Wilcoxon's signed-rank test (when conditions for the t-test were not met or for ordinal variables). Differences among more than two paired groups were evaluated using repeated-measures ANOVA or Friedman's test (when assumptions for repeated-measures ANOVA were not met or for ordinal variables). The Chi-square test of independence was used for qualitative variables, with Yates' correction applied for expected cell counts below 10, Cochran's conditions checked, or Fisher's exact test when appropriate. Correlations between variables, including their strength and direction, were analyzed using Pearson's and/or Spearman's correlation coefficients. A significance level of $p<0.05$ was considered statistically significant for all analyses.

RESULTS

The baseline characteristic of patients are detalied in Table I. The management of occluded UCSEMS and the efficacy of different type of procedures are depicted in Table II.

Table I. Baseline characteristics of patients treated with uncovered self extended metal stents (n=49)

Age, median (range), y	
mean (SD), range	64.1 (10)
range	26 - 87
Gender, n (%)	
men	20 (40.8)
women	29 (59.2)
Etiology, n (%)	
Colangiocarcinoma	33 (67.3)
Gall blader cancer	11 (22.4)
Malignant lymph nodes due to colorectal cancer	5 (10.2)
Bismuth classification, n (%)	
III	5 (10.2)
IV	44 (89.8)
Mean time to progression to the next stage, days (SD)	224.8 (113.8)
Method of obtaining a histopathological result, n (%)	
ERCP	27 (55.1)

Table I (continued)	
Surgery	15 (30.6)
CT-guided biopsy	5 (10.2)
PTBD	1 (2.0)
Ultrasound-guided biopsy	1 (2.0)
The average number of ERCP procedures following UCSEMS implantation (SD)	3.1 (3.7)
Median time to occlusion of initial UCSEMS, days (SD)	169.8 (160.0)
Overgrowth of initial UCSEMS, n (%).	31 (63.6)
Initial UCSEMS placement	
Side-by-side	38
Stent-in-stent	11

CT: computed tomography; ERCP: endoscopic retrograde colangiopancreatography; PTBD: percutaneous transhepatic biliary drainage; UCSEMS: uncovered self-expandable metal stents; SD: standard deviation; y: year.

The overall clinical success rate for all procedures was 61.4% (70/114). Depending on the method of stent management, it was demonstrated that technique with balloon cleaning alone had the lowest clinical success rate, reaching only 50%. Slightly better results were observed with plastic stents and FCSEMS, achieving success rates of 66% and 68.75%, respectively. Among the evaluated reintervention methods, RFA followed by plastic stent implantation and UCSEMS re-stenting were associated with numerically higher clinical success rates (80%). However, while a statistically significant difference was observed across groups (p=0.0366), the limited subgroup sizes preclude firm conclusions about the comparative effectiveness of these techniques.

All methods demonstrated a high technical success rate of 91.2% (104/114). Reasons for technical failures included: inability to remove a previously placed plastic stent within the UCSEMS lumen, preventing bile duct cannulation in one patient; breakage of a plastic stent during removal in one patient; catheter blockage due to damage to the wire mesh of UCSEMS in seven patients; and duodenal stenosis preventing proper positioning of the endoscope in two patients.

Complications other than RBO included acute pancreatitis in five patients, liver abscesses in four patients, gastrointestinal perforation in one patient, and acute cholecystitis in one patient, which required cholecystoduodenostomy.

The mean time to the first reintervention, defined as the time to the first procedure following initial UCSEMS placement, was 169.8 days. The mean time to the second reintervention varied depending on the method used, as follows: 238 days for balloon cleaning alone, 201 days for plastic stenting, 264 days for FCSEMS placement, 78 days for RFA followed by plastic stenting, and 205 days for repeat UCSEMS implantation (p=0.4999). The mean RBO time for all ERCP procedures was as follows: 48 days for balloon cleaning alone, 75 days for plastic stenting, 71 days for FCSEMS placement, 66 days for RFA followed by plastic stenting, and 96 days for UCSEMS re-stenting (p=0.0326).

DISCUSSION

Stenting in MHBO remains one of the most challenging types of ERCP procedures. When combined with the reinterventional nature of procedures following UCSEMS placement, these interventions become even more demanding. Despite significant technical challenges, the technical success rate we achieved was high. However, this does not translate into an average therapeutic success rate, which remains relatively low.

Regarding our clinical success rates, the outcomes observed in our cohort are generally consistent with trends reported in previous studies [11, 12]. Although UCSEMS re-stenting and RFA appeared to yield numerically higher success rates in our sample, these findings did not consistently reach statistical significance. Notably, in terms of RBO, balloon cleaning during the first reintervention showed a relatively favourable outcome. This may suggest that early stent occlusion is often due to sludge accumulation rather than tumour overgrowth, and that simpler methods such as balloon cleaning or FCSEMS placement can be effective at this stage.

Balloon cleaning was used as a method of stent clearance only in cases where no strictures were visible on the cholangiogram. This suggests that during the first reintervention, stent occlusion is more likely due to mucus sludge rather than tumour overgrowth of the stent's wire mesh. In the long term, plastic stents appear to be the least effective method both clinically and in terms of stent patency. They require more frequent ERCP procedures and seem to serve either as a bridge before UCSEMS or RFA placement or as an option when the stricture is so tight that other stent types cannot be introduced. FCSEMS appear to be a good option, particularly for initial reinterventions. They demonstrate a higher clinical success rate compared to plastic stents and a slightly longer RBO. However, their placement seems to carry an increased risk of liver abscesses (3 out of 4 liver abscess cases occurred after FCSEMS placement). Regarding RFA as a clearance method, it is worth mentioning that RFA is an independent factor

Table II. Clinical effects of various techniques used to treat UCSEMS occlusion

	Balloon cleaning only of UCSEMS	Plastic stent in UCSEMS	FCSEMS in UCSEMS	RFA and plastic stent in UCSEMS	UCSEMS in UCSEMS	p
Mean time to second reinterventio, days (SD)	238.0 (289.8)	201.8 (143.7)	264.3 (157.7)	78.5 (88.4)	205.1 (219.3)	0.4999
Mean interval time across all ERCP procedure, days (SD)	48.2 (69.2)	74.9 (46.8)	70.9 (45.5)	65.8 (30.2)	95.5 (98.1)	0.0326
Clinical success (%)	9/18 (50)	35/53 (66)	11/16 (68.75)	8/10 (80)	12/15 (80)	0.366

FCSEMS: full covered self extended metal stents; RFA: radiofrequency ablation. For the rest of abbreviations see Table I.

associated with improved overall survival in patients with MHBO [13, 14]. Additionally, it shows good clinical efficacy. Finally, UCSEMS reintervention has the best RBO duration and clinical success rate. This approach is further supported by advancements in thin-profile stent delivery systems, which make their placement significantly easier [15]. In the broader perspective, however, during the second and subsequent reinterventions, the use of UCSEMS and RFA should take on greater importance. This approach seems crucial given the average of three ERCP procedures performed after the initial SEMS placement in our cohort. Unlike previously published studies [16], we were able to gather a relatively large group of patients and include all reinterventions, not just the first ones.

Our intention is not to assert the superiority of any particular method, but rather to share observed trends that could inform future research and clinical decision-making. Importantly, we acknowledge that the descriptive nature of our data, combined with a lack of statistical significance in most comparisons, precludes definitive conclusions.

To strengthen the evidence base, future research should involve multicentre collaborations that allow for larger sample sizes and stratified analyses. This would enable more robust comparisons and inform future guideline development for managing occluded UCSEMS.

CONCLUSIONS

All evaluated reintervention techniques demonstrated high technical success rates in patients with occluded UCSEMS. Among them, UCSEMS re-stenting and RFA combined with plastic stenting were associated with numerically higher clinical success and longer RBO durations. However, given the retrospective design, single-centre nature, and limited cohort size, these trends should be interpreted with caution. Our findings underscore the need for larger multicentre studies to determine the most effective strategy for managing UCSEMS occlusion in MHBO.

Conflicts of interest: None to declare.

Authors' contributions: J.P. conceived the study and designed the methodology, J.P. collected and analyzed the data, and drafted the manuscript. A.P. conducted a critical review and manuscript revision. All authors participated in the final review, approved the manuscript, and ensured the accuracy and integrity of the work.

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