NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer

Cancer of the bile duct or pancreas can block the channels that carry digestive juices from the gall bladder and pancreas to the small intestine. This can cause jaundice, nausea, bloating and abdominal pain. Often it is treated by inserting small tubes called stents, which help to keep the channels open and draining properly. But these stents can themselves become blocked. This procedure uses heat energy both to clear blockage in the channels before inserting stents and to clear blocked stents.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2017 and updated in March 2018.

Procedure name

- Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer

Specialist societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Northern Ireland (AUGIS)
- British Society of Gastroenterology (BSG)
- Royal College of Surgeons.

Description of the procedure

Indications and current treatment

Biliary obstruction caused by cancers such as cholangiocarcinoma or pancreatic adenocarcinoma causes symptoms including jaundice, nausea, bloating and abdominal pain. Surgical resection is often not possible.

Current management with unresectable cholangiocarcinoma or pancreatic cancer includes biliary stenting during endoscopic retrograde cholangiopancreatography, chemotherapy, biological therapies (for example, monoclonal antibodies), radiation therapy and photodynamic therapy (PDT), which involves using a light-

sensitive drug and a light source to destroy abnormal cells. Stents often need to be replaced because of blockage by tumour ingrowth.

What the procedure involves

Endoscopic radiofrequency ablation uses heat energy to ablate malignant tissue that is obstructing the bile or pancreatic ducts. This may be done before inserting stents or to clear obstructed stents.

The procedure is done with the patient under sedation. Endoscopic retrograde cholangiopancreatography with fluoroscopic guidance is used to establish the length, diameter and position of the stricture. Under endoscopic visualisation, a bipolar endoscopic radiofrequency ablation catheter is deployed over a guide wire across the stricture. Controlled pulses of radiofrequency energy are applied to obstructing tumour tissue to ablate it, and to allow stent insertion or to clear the lumen of a previously placed stent. Sequential applications are applied throughout the length of the stricture to achieve recanalisation. Repeat treatments may be used if obstruction recurs.

Efficacy summary

Improvement in malignant biliary obstruction

In a systematic review of 9 studies (263 patients), the mean increase in diameter at the site of biliary stricture after radiofrequency ablation (RFA) was 3.45 mm (95% confidence interval [CI] 3.36 mm to 3.54 mm).[2] In a non-randomised comparative study of 66 patients (also in the systematic review), there was a statistically significant improvement ($p<0.0001$) in mean stricture diameter both in patients who had RFA and stent insertion, and in those who had stent insertion alone.[4] In a case series of 69 patients (also in the systematic review), the mean stricture diameter statistically significantly increased from 2.0 mm before RFA to 4.9 mm after RFA ($p<0.0001$).[7]

In a non-randomised comparative study of 34 patients, there was a statistically significant reduction in the bilirubin level (from a mean of 3.3 mg/dl to 2.3 mg/dl, $p=0.046$) within 14 days of the first procedure in patients who had RFA. There was also a reduction in patients who had PDT (from a median of 4.1 mg/dl before the procedure to 3.5 mg/dl after 14 days) but it did not reach statistical significance. The difference between the groups was not statistically significant ($p=0.636$).[6]

Stent patency

In a randomised controlled trial (RCT) of 65 patients, the mean stent patency was statistically significantly longer in patients who had RFA and stent insertion

compared with those who had stent insertion alone (6.8 months compared with 3.4 months, p=0.02).[1] In the systematic review of 9 studies (263 patients), the median duration of stent patency after RFA was 7.6 months (95% CI 6.9 months to 8.4 months).[2] In a non-randomised comparative study of 69 patients (also in the systematic review), the median stent patency was 472 days for patients who had RFA and stent insertion compared with 324 days for those who had stent insertion alone (hazard ratio 1.19, 95% CI 0.54 to 2.66, p=0.669).[3] In the case series of 69 patients (also in the systematic review), stent patency was 96% (66/69) at 30 days follow-up.[7] In a case series of 58 patients (also in the systematic review), median stent patency was 170 days (95% CI 63 days to 277 days).[8] In a case series of 18 patients, median stent patency was 110 days (range 16 days to 374 days); at 90 days and 180 days after RFA, 80% (12/15) and 69% (9/13) of patients respectively were alive and had biliary patency.[9]

Survival

In the RCT of 65 patients, the overall mean survival time was statistically significantly longer in the RFA and stent group than in the stent-only group (13.2 months compared with 8.3 months, p<0.001).[1] In the systematic review of 9 studies (263 patients), the mean survival time after RFA was 9.6 months (95% CI 9.3 months to 9.9 months).[2] The pooled 30-day, 90-day and 2-year mortality were 2% (95% CI 0.5% to 5.9%; 5 studies), 21% (95% CI 5% to 37%; 3 studies) and 48% (95% CI 37% to 59%; 2 studies) respectively.[2] In the non-randomised comparative study of 69 patients (also in the systematic review), the median survival was 226 days for patients who had RFA and stent insertion compared with 124 days for those who had stent insertion alone (p=0.01).[3] In the non-randomised comparative study of 66 patients (also in the systematic review), the median survival was 5.9 months.[4] RFA was a predictor of survival in the multivariable Cox proportional hazard analysis (hazard ratio 0.29, 95% CI 0.11 to 0.76, p=0.012). In a non-randomised comparative study of 48 patients (also in the systematic review), the median survival was similar in patients who had RFA and those who had photodynamic therapy (9.6 months compared with 7.5 months, p=not significant).[5] In the case series of 69 patients (also in the systematic review), the mean survival was 14.6 months for patients with pancreatic cancer and 17.7 months for patients with cholangiocarcinoma.[7] In the case series of 58 patients (also in the systematic review), the extrapolated median survival after the first RFA session was 10.6 months; the overall median survival from initial diagnosis to death was 17.9 months.[8] In the case series of 18 patients, median survival was 227 days (range 16 to 374 days).[9]

Safety summary

Biliary bleeding

Biliary bleeding was reported in 3 patients in 1 study included in the systematic review of 263 patients; 2 patients died because of haemorrhagic shock and, in the other, the bleeding was successfully managed by inserting an uncovered self-expandable metal stent.[2]

Haemobilia was reported in 5% (3/58) of patients in the case series of 58 patients (also in the systematic review); 1 patient had an endoscopic retrograde cholangiopancreatography and the other 2 had conservative treatment.[8]

Biliary infection and inflammation

Severe cholecystitis, needing percutaneous drainage, was reported in 1 patient in the systematic review of 263 patients.[2] Mild cholecystitis, which was managed conservatively, was reported in 4% of patients in the same review.

Sepsis was reported in 1 patient who had RFA and 1 patient who had PDT, between the first and fifth intervention, in the non-randomised comparative study of 34 patients.[6] Cholangiosepsis was reported in 2 patients in the case series of 58 patients (also in the systematic review); both patients had conservative treatment.[8]

Gallbladder empyema was reported in 1 patient in the case series of 58 patients (also in the systematic review); the patient needed a cholecystectomy.[8]

Cholangitis was reported in 6% (2/32) of patients who had RFA and stent insertion and 3% (1/33) of patients who had stent insertion alone in an RCT of 65 patients.[1] Cholangitis, which was described as mild and could be managed conservatively, was reported in 8% of patients in the systematic review of 263 patients.[2] Cholangitis was reported in 14% (2/14) of patients who had RFA and 30% (6/20) of patients who had PDT in the non-randomised comparative study of 34 patients.[6] Mild cholangitis was reported in 22% (4/18) of patients within 24 hours of the procedure in a case series of 18 patients.[9]

Rigor, which was described as mild and could be managed conservatively, was reported in 6% of patients in the systematic review of 263 patients.[2]

Liver damage

Partial liver infarction after RFA was reported in 1 patient in the systematic review of 263 patients.[2] This was thought to be caused by thermal injury of a segmental liver artery and was managed conservatively.

Hepatic coma, with a fatal outcome, was reported in 1 patient in the case series of 58 patients (also in the systematic review).[8]

Liver abscess was reported in 1 patient who had RFA and 1 patient who had PDT, between the first and fifth intervention, in a non-randomised comparative study of 34 patients.[6] An additional patient had a liver abscess diagnosed after RFA, which progressed to sepsis after a seventh RFA procedure.

Pain

Pain, which was described as mild and could be managed conservatively, was reported in 11% of patients in the systematic review of 263 patients.[2]

Pancreatitis

Post-endoscopic retrograde cholangiopancreatography pancreatitis, which was described as mild and could be managed conservatively, was reported in 2% of patients in the systematic review of 263 patients.[2] Post-endoscopic retrograde cholangiopancreatography pancreatitis was reported in 2 patients in the case series of 18 patients; 1 was only biochemical and the other had a mild, self-limiting course.[9]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers described the following anecdotal adverse event: abscess formation. They considered that the following were theoretical adverse events: stomach wall perforation, bile duct perforation, aneurysmal dilatation of the hepatic artery, necrotic infection and damage to neighbouring tissue.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer. The following databases were searched, covering the period from their start to 23 January 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see Literature search

strategy for details). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with biliary obstruction caused by cancer.
Intervention/test	Endoscopic bipolar radiofrequency ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 380 patients from 1 RCT, 1 systematic review, 4 non-randomised comparative studies (3 of which are also included in the systematic review), and 3 case series (2 of which are also included in the systematic review).[1–9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer

Study 1 Yang J (2018)

Details

Study type	**Randomised controlled trial**
Country	China
Recruitment period	2015 to 2016
Study population and number	**n=65 (32 radiofrequency ablation [RFA] and biliary stenting, 33 biliary stenting only)** Patients with unresectable extrahepatic cholangiocarcinoma.
Age and sex	• RFA and stenting: mean 62 years; 47% (15/32) male • Stenting only: mean 64.5 years; 55% (18/33) male
Patient selection criteria	Inclusion criteria: age 18 to 75 years; histologically or cytologically diagnosed cholangiocarcinoma; local infiltration of large vessels or distant metastasis in the tumour confirmed by CT, MRI or endoscopic ultrasound, and surgical unresectability; initial treatment; Karnofsky performance scores of 50 points or higher; written informed consent signed by the patient. Exclusion criteria: Bismuth type III and type IV hilar cholangiocarcinoma; combined with other malignancies; severe liver dysfunction or kidney dysfunction; women who were pregnant or lactating; other treatments that may affect the clinical follow-up, such as radioactive particles, particle stent implantation or chemotherapy; alcohol or substance abuse or poor compliance as determined by the physician.
Technique	Radiofrequency energy was applied using the Habib EndoHPB probe (EMcision, UK). RFA was done using a power of 7 to 10 W for 90 seconds with a rest period of 1 minute before moving the probe. If the structure was more than 2.5 cm, step-by-step RFA was done from the top to bottom. Plastic stents were used. All patients had stent replacement every 3 months or when they had recurrent jaundice or cholangitis symptoms.
Follow-up	**21 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: an additional 3 patients were enrolled in the study but were lost to follow-up (2 in the RFA group and 1 in the control group). All patients were followed up by telephone until the time of their death.

Study design issues: Prospective, single-centre, randomised controlled trial. Randomisation was done using a random number table, no other details were given. Investigators doing follow-up were unaware of group assignment until the end of the study. The primary outcome of the study was mean survival time, which was defined from the first RFA. Secondary outcomes were stent patency and the incidence of adverse events.

Study population issues: There were no statistically significant differences between the groups with regard to baseline characteristics.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **65 (32 versus 33)**

Overall mean survival time

- RFA and stent=13.2±0.6 months
- Stent alone=8.3±0.5 months, p<0.001

Survival rate (%)

Follow-up	RFA and stent n=32	Stent alone n=33	p value
6 months	96.9	81.8	0.08
9 months	87.5	24.2	<0.001
12 months	62.5	12.1	<0.001
15 months	28.1	3.0	<0.01

Mean stent patency

- RFA and stent=6.8 months
- Stent alone=3.4 months, p=0.02

Serum bilirubin

Follow-up	RFA and stent n=32	Stent alone n=33	p value
Total bilirubin, mean±standard deviation, µmol/l			
Baseline	266.8±88.5	245.9±76.2	0.23
2 weeks	106.8±51.5	196.8±88.5	0.02
1 month	85.8±15.1	102.8±45.6	0.35
3 months	39.2±6.3	46.9±8.9	0.68
Direct bilirubin, mean±standard deviation, µmol/l			
Baseline	188.5±48.6	169.5±58.4	0.43
2 weeks	69.8±28.5	106.2±83.5	0.03
1 month	56.9±8.9	68.5±7.8	0.69
3 months	19.3±5.9	22.6±7.8	0.58

Karnofsky performance scores

Follow-up	RFA and stent n=32	Stent alone n=33	p value
Baseline	82.9±9.3	79.9±7.8	0.28
1 month	86.1±6.8	72.4±8.2	0.02
3 months	71.4±7.1	60.3±5.4	0.04
6 months	61.4±7.1	48.2±6.2	0.03
9 months	58.2±11.5	22.5±8.9	<0.001

In the RFA group, 2 patients had 1 RFA, 13 patients had 2, 13 patients had 3 and 4 patients had 4 RFAs.

Safety

Incidence of postoperative adverse events

- RFA and stent=6.3% (2/32)
- Stent alone=9.1% (3/33), p=0.67

RFA and stent group

- Acute cholangitis=6.3% (2/32) (Both patients improved after nasobiliary drainage through the bile duct and intravenous antibiotic therapy)

Stent alone group

- Acute cholangitis=3.0% (1/33)
- Acute pancreatitis=3.0% (1/33)
- Haemorrhage of the incision margin of the papilla=3.0% (1/33)

All patients were successfully treated endoscopically.

Abbreviations used: CI, confidence interval; RFA, radiofrequency ablation

Study 2 Zheng X (2016)

Details

Study type	**Systematic review and meta-analysis**
Country	Included studies were from Austria, Germany, Turkey, UK and USA.
Recruitment period	Search date: July 2015
Study population and number	**n=9 studies (263 patients)** Patients with unresectable malignant biliary strictures
Age and sex	Mean 68 years; 53% (138/263) male
Patient selection criteria	Inclusion criteria: observational human studies including patients with unresectable malignant biliary strictures, such as cholangiocarcinoma and pancreatic cancer, who had a life expectancy of over 3 months; patients were treated with endoscopic biliary radiofrequency ablation (RFA); patient outcomes including technical success, median overall survival, 2-year survival rate and complications were analysed; studies included the comparison of RFA with non-RFA; patients had provided their informed consent before their inclusion in the study. Exclusion criteria: case reports, review articles, meta-analyses, letters, comments and conference abstracts; studies on cell lines or animals; studies investigating other than the safety and efficacy of endoscopic biliary RFA in the treatment of malignant biliary obstruction, such as guidelines; studies on interventions that were not related to therapeutic biliary endoscopy.
Technique	All the endoscopic RFA procedures were done under conscious sedation or general anaesthesia. Cholangiogram was routinely done to identify the location, length and diameter of bile duct stricture. Energy was delivered at 7 to 10 W for 1 to 2 minutes with a rest period of 1 to 2 minutes before moving the catheter. Depending on the length of the stricture, sequential applications were made without significant overlap of the treated areas. Biliary stents (plastic or self-expandable metal stents, uncovered of fully covered) were deployed after RFA.
Follow-up	**Up to 2 years**
Conflict of interest/source of funding	None for the systematic review

Analysis

Study design issues: Data extraction was done by 2 authors independently and any disagreement was resolved by consensus. The quality of the included studies was assessed using GRADE. The pooled proportions of 30-day, 90-day, and 2-year survival rates and complication rates were the main outcomes. All the studies except 1 were retrospective. All 9 studies were rated as low or moderate quality. The sample size was small in most of the included studies.

Study population issues: The indications for RFA were cholangiocarcinoma or bile duct cancer (n=173, 66%), pancreatic cancer (n=77, 29%), metastatic cancer (n=4, 2%), gallbladder cancer (n=4, 2%), hepatocellular carcinoma (n=3, 1%), gastric cancer (n=1, 0.4%) and intraductal papillary mucinous neoplasm (n=1, 0.4%), Among those with cholangiocarcinoma and bile duct cancer, 38% (65/173) had a Klatskin tumour. The mean length of malignant biliary obstruction was 19.4 mm.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **263 (9 studies)** Technical success rate of endoscopic biliary radiofrequency ablation (RFA)=96.8% (95% CI 95.5 to 98.1%) ***Improvement in malignant biliary obstruction*** • Mean diameter at site of biliary stricture before RFA=1.19 mm (95% CI 1.04 to 1.34 mm) • Mean diameter at site of biliary stricture after RFA=4.64 mm (95% CI 4.54 to 4.74 mm) • Increase in diameter=3.45 mm (95% CI 3.36 to 3.54 mm) Median duration of stent patency=7.64 months (95% CI 6.87 to 8.41) ***Overall survival*** • Pooled 30-day mortality=2% (95% CI 0.5 to 5.9%; 5 studies, I^2=0%) • Pooled 90-day mortality=21% (95% CI 5 to 37%; 3 studies, I^2=70%) • Pooled 2-year mortality=48% (95% CI 37 to 59%; 2 studies, I^2=0%) Overall survival time=9.6 months (95% CI 9.3 to 9.9 months)	**Complications** Significant adverse events were reported in 3 studies. Pooled rate of adverse events=17% (95% CI 10 to 25%) • Partial liver infarction after RFA, n=1 (probably caused by thermal injury of a segmental liver artery, managed conservatively; patient had Bismuth type IV cholangiocarcinoma) • Biliary bleeding, n=3 (occurred 4 to 6 weeks after RFA; 2 patients died because of haemorrhagic shock and the other was successfully managed by the insertion of an uncovered self-expandable metal stent.) • Severe cholecystitis after the procedure, needing percutaneous drainage, n=1 ***Mild complications (managed conservatively)*** • Pain=11% (95% CI 0.9 to 31%) • Cholangitis=8% (95% CI 1 to 14%) • Cholecystitis=4% (95% CI 1 to 7%) • Rigor=6% (95% CI 1 to 14%) • Bleeding=2% (95% CI 0 to 5%) • Post-endoscopic retrograde cholangiopancreatography pancreatitis=2% (95% 0 to 5%)
Abbreviations used: CI, confidence interval; RFA, radiofrequency ablation	

Study 3 Kallis Y (2015) – also included in the systematic review by Zheng X et al. (study 1)

Details

Study type	**Non-randomised comparative study**
Country	UK
Recruitment period	2009 to 2011
Study population and number	**n=69 (23 radiofrequency ablation [RFA] and self-expanding metal stent [SEMS] insertion versus 46 SEMS insertion alone)** Patients with surgically unresectable pancreatic carcinoma and malignant biliary obstruction.
Age and sex	Mean 69 years; 52% (36/69) male
Patient selection criteria	Inclusion criteria for RFA treatment: patients with surgically unresectable pancreatic cancer with associated biliary obstruction amenable to endoscopic drainage, assessed by cross-sectional imaging. Only patients deemed to be of sufficient health for palliative chemotherapy at the time of disease presentation were included in the analysis. The control group comprised patients with surgically unresectable pancreatic cancer, chosen from the same patient population, treated with an uncovered SEMS alone between September 2005 and August 2010. The inclusion criteria for the control group was the same as those for the RFA-treated cohort. Patients in the control group were not treated with RFA because they had either presented before the introduction of such treatment or because they had presented during periods when the RFA catheter was not available.
Technique	Radiofrequency energy was applied to the malignant biliary stricture using the Habib EndoHPB RFA catheter (EMcision, UK). Energy was delivered at 10 W over a 2 minute period for each application. Sequential ablative energy was applied to the stricture under fluoroscopic guidance to induce coagulative tissue necrosis over its entire length. This was immediately followed by the insertion of an uncovered biliary SEMS to preserve bile duct patency and integrity.
Follow-up	**Until death (median survival in RFA group was 226 days)**
Conflict of interest/source of funding	One of the authors is a stockholder and director of EMcision, UK.

Analysis

Follow-up issues: All patients were followed up until death.

Study design issues: Retrospective, single-centre case-control study. The RFA treatment and control patients were matched by age (within a 10-year range), sex, comorbidity, ASA category, and the presence or absence of metastases at the time of treatment. Two control patients were selected for each RFA-treated patient. The primary end point of the study was patient survival. Secondary end points were stent patency and procedure-related safety and tolerability.

Study population issues: There were no statistically significant differences between the 2 groups at baseline with regard to age, sex, presence of metastases, ASA grade, and period between diagnosis and treatment. Tumour burden was similar between the groups, with 39% of patients in each group having metastatic spread at the time of treatment. A statistically significantly higher number of patients in the RFA group compared with the control group had had an endoscopic retrograde cholangiopancreatography (ERCP) with temporary plastic stenting of the biliary tree before enrolment into the study (82.6% versus 39.1% respectively, p=0.0008).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 69 (23 versus 46)

Median survival
• RFA=226 days (IQR 140 to 526 days)
• Control=123.5 days (IQR 44 to 328 days, p=0.01)

Most patients in both groups died of progressive malignant disease or carcinomatosis (22/23 RFA, 43/46 controls).

Kaplan-Meier survival analysis
<table>
<tr><th>Survival</th><th>90 days</th><th>180 days</th><th>270 days</th><th>360 days</th></tr>
<tr><td>Hazard ratio</td><td>0.10</td><td>0.31</td><td>0.69</td><td>0.54</td></tr>
<tr><td>95% CI</td><td>0.09 to 0.65</td><td>0.19 to 0.75</td><td>0.38 to 1.29</td><td>0.32 to 0.99</td></tr>
<tr><td>p value</td><td>0.004</td><td>0.005</td><td>0.25</td><td>0.06</td></tr>
</table>
In multivariate analysis, RFA was independently predictive of survival at 90 days (OR 21.07, 95% CI 1.45 to 306.6, p=0.026) and 180 days (OR 4.48, 95% CI 1.04 to 19.3, p=0.044).

Median stent patency
• RFA=472 days
• Control=324 days (Hazard ratio 1.19, 95% CI 0.54 to 2.66, p=0.669)
Only 9/23 patients in the RFA group and 14/46 patients in the control group reached the end point of stent occlusion.

The authors note that the true stent patency rates may be difficult to ascertain because many patients will have died with a patent stent before exposure to the risk of occlusion.</td><td>The paper states that ‘RFA was well tolerated with minimal side effects.’</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; IQR, interquartile range; OR, odds ratio; RFA, radiofrequency ablation</td></tr>
</table>

Study 4 Sharaiha RZ (2014) – also included in the systematic review by Zheng X et al. (study 1)

Details

Study type	**Non-randomised comparative study**
Country	US
Recruitment period	2010 to 2013
Study population and number	**n=66 (26 radiofrequency ablation [RFA] and self-expanding metal stent [SEMS] insertion versus 40 SEMS insertion alone)** Patients with a biliary obstruction from pancreatic cancer or cholangiocarcinoma.
Age and sex	• RFA: mean 66 years; 69% (18/26) male • Control: mean 67 years; 33% (13/40) male
Patient selection criteria	Not reported
Technique	Radiofrequency energy was applied to the malignant biliary stricture using the Habib EndoHPB RFA catheter (EMcision, UK). Energy was delivered at 7 to 10 W for 90 to 120 seconds for each application. Sequential ablative energy was applied to the stricture under fluoroscopic guidance to induce coagulative tissue necrosis over its entire length. This was immediately followed by the insertion of an uncovered or fully covered SEMS or plastic stent, depending on the location of the malignant obstruction.
Follow-up	**Median 29 months**
Conflict of interest/source of funding	None

Analysis

Study design issues: Data were captured in a prospectively established database. Patient who had RFA were compared with 2 controls who had endoscopic retrograde cholangiopancreatography (ERCP) with stent placement only, matched by age (±2 years), diagnosis, performance status and treatment with chemotherapy. For assessment of survival, patients who died within 30 days of the date of endoscopy (n=6) were excluded from survival analyses.

Study population issues: There was a statistically significantly higher proportion of men in the RFA group compared with the control group (69% versus 33%, p=0.01). There were no statistically significant differences between the groups with regard to age, mean stricture length or diagnosis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **66 (26 versus 40)**

Mean stricture diameter (mm±SD)

	RFA	No RFA	p value
Before procedure	1.6±0.75	1.38±0.18	Not significant
After procedure	4.5±1.99	4.36±1.7	0.86

There was a statistically significant improvement in stricture diameter in both groups after the procedure (p<0.0001).

Survival

Median survival=5.9 months (IQR=4.6 to 14.1); in the log-rank analysis, there was no difference in survival between the groups (p=0.87). In univariate Cox proportional analysis, age and chemotherapy treatment were predictors of survival. In multivariable Cox proportional hazard, RFA was also a predictor of survival.

	Univariate HR (95% CI)	p value	Multivariable HR (95% CI)	p value
RFA	0.77 (0.41 to 1.45)	0.424	0.29 (0.11 to 0.76)	0.012
Age	1.04 (1.01 to 1.07)	0.002	1.04 (1.01 to 1.07)	0.011
Chemotherapy	0.37 (0.097 to 0.71)	0.002	0.26 (0.10 to 0.70)	0.007
Stricture improvement	0.81 (0.64 to 1.02)	0.067	0.84 (0.65 to 1.09)	0.208

Safety

There were no differences in adverse events between the 2 groups.

In total, there were 3 mild adverse events (abdominal pain) and 2 moderate adverse events (1 pancreatitis and 1 cholecystitis).

Abbreviations used: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; RFA, radiofrequency ablation; SD, standard deviation

Study 5 Strand DS (2014) – also included in the systematic review by Zheng X et al. (study 1)

Details

Study type	**Non-randomised comparative study**
Country	US
Recruitment period	2008 to 2012
Study population and number	**n=48** (16 radiofrequency ablation [RFA] versus 32 photodynamic therapy [PDT]) Patients with unresectable cholangiocarcinoma.
Age and sex	Mean 64 years (RFA), 70 years (PDT); 60% (29/48) male
Patient selection criteria	Consecutive patients older than 18 years with unresectable cholangiocarcinoma. Non-resectability was established through either direct patient consultation with a hepatobiliary surgeon or the consensus opinion of a multidisciplinary tumour board. Criteria used to determine non-resectability included: the patient was medically unfit for surgery, the presence of distant metastatic disease, extensive local involvement, or an inadequate future liver remnant after resection.
Technique	The Habib EndoHPB probe (EMcision UK) was used for RFA. Energy was delivered at 7 W (intrahepatic strictures) or 10 W (extrahepatic strictures) for 2 applications of 90 seconds with a 60 second resting interval. Additional applications were done with minimal overlap as needed to ensure treatment of the entire length of the stricture. Uncovered or covered self-expanding metal stents (SEMS) were placed after the procedure, in preference to plastic stents. RFA was usually done once, but could be repeated during a subsequent procedure at the discretion of the treating endoscopist. For PDT, the photosensitiser was infused intravenously 2 days before the procedure. Plastic stents were preferentially placed to decompress opacified and PDT-treated bile ducts. PDT was done at least once, but could be repeated during a subsequent procedure at the discretion of the treating endoscopist.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues: Retrospective, single-centre cohort study. The primary outcome was a comparison of overall survival in patients who had RFA compared with PDT. Data for adverse events were analysed throughout the entire clinical course of the patient and not just in the period after endoscopic therapy with RFA or PDT.

Study population issues: Baseline characteristics of patients in the 2 treatment groups were similar with respect to age, sex, stage, and palliative chemoradiation therapy. Tumour location was predominantly perihilar in both groups (81% [13/16] in the RFA group versus 100% [32/32] in the PDT group, p=0.032).

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 48 (16 versus 32)

Median survival after initial treatment
• RFA=9.6 months (95% CI 5.1 to 11.7)
• PDT=7.5 months (95% CI 4.3 to 16), p=not significant

Of the 16 patients who had RFA treatment, 4 were still alive at the time of data analysis. All 32 patients in the PDT group had died by the time of data analysis.

In a multivariate analysis, the only variable that was statistically significantly associated with survival was the presence of distant metastases, which had a negative effect (hazard ratio 3.55, 95% CI 1.29 to 9.77, p=0.014).

Secondary outcome measures
In both groups, there was a similar number of observed monthly ERCP procedures (0.59 versus 0.71, p=0.60) and ablative treatment sessions (0.18 versus 0.25, p=0.175).</td><td>Adverse events (number of occurrences per month)
<table><tr><th>Adverse event</th><th>RFA, n=16
Mean (SD)</th><th>PDT, n=32
Mean (SD)</th><th>p value</th></tr><tr><td>Stent occlusion</td><td>0.06 (0.10)</td><td>0.02 (0.10)</td><td>0.008</td></tr><tr><td>Stent migration</td><td>0.02 (0.05)</td><td>0.05 (0.13)</td><td>0.754</td></tr><tr><td>Cholangitis</td><td>0.13 (0.17)</td><td>0.05 (0.10)</td><td>0.008</td></tr><tr><td>Hepatic abscess</td><td>0.02 (0.04)</td><td>0.01 (0.03)</td><td>0.155</td></tr><tr><td>Percutaneous transhepatic cholangiography drainage</td><td>0.01 (0.03)</td><td>0.04 (0.09)</td><td>0.189</td></tr><tr><td>Mild pain</td><td>0.08 (0.11)</td><td>0.07 (0.14)</td><td>0.848</td></tr><tr><td>Moderate or severe pain</td><td>0.02 (0.04)</td><td>0.07 (0.13)</td><td>0.497</td></tr></table>
Mild pain was defined as any pain needing short-term treatment with oral opiate analgesics.
Moderate or severe pain was defined as pain that included any symptoms needing hospital admission or intravenous opiate analgesics.

The authors noted that stent occlusion and cholangitis typically occurred in conjunction with one another, and were readily treated with ERCP and stent revision.</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; PDT, photodynamic therapy; RFA, radiofrequency ablation</td></tr>
</table>

Study 6 Schmidt A (2016)

Details

Study type	**Non-randomised comparative study**
Country	Germany (2 centres)
Recruitment period	2011 to 2013
Study population and number	**n=34** (14 radiofrequency ablation [RFA] versus 20 photodynamic therapy [PDT]) Patients with hilar cholangiocarcinoma.
Age and sex	Mean 73 years (RFA), 70 years (PDT); 41% (14/34) male
Patient selection criteria	For every patient, palliative therapy was concluded by the tumour board because of unresectable bile duct cancer Bismuth IIIa to IV or unresectability because of liver metastases. Exclusion criteria: pregnancy, instability for endoscopy, uncorrected coagulopathy, and previous bleeding out of the bile duct.
Technique	The Habib EndoHPB probe (EMcision UK) was used for RFA. Plastic stents were routinely placed after the procedure. The mean number of procedures per patient was 2.2 (range 1 to 7). For PDT, patients were given Photofrin at a dose of 2 mg/kg body weight intravenously 48 hours before the procedure. Patients remained in a darkened room for 3 to 4 days after the injection. The mean number of procedures per patient was 1.8 (range 1 to 5).
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues: The study only included a small number of patients. The RFA study data were collected prospectively from December 2012 to May 2013; the rest of the data were collected retrospectively. A retrospectively analysed group of patients treated by PDT served as a historical control group. Quality of life was assessed before and after each RFA application, using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire. Patients could choose either PDT or RFA.

Study population issues: There were no statistically significant differences in baseline characteristics between the groups. In the RFA group, 36% (5/14) of patients had proven distant metastases; 3 patients had previous systemic chemotherapy and 4 patients had concomitant chemotherapy. One of the 14 patients had previously been treated by PDT 8 months before the first RFA treatment. The mean interval from initial diagnosis to the first RFA was 10±9 months. In the PDT group, 40% (8/20) of patients had proven distant metastases; 4 patients had concomitant chemotherapy and 1 patient had previously been treated by PDT. The mean interval from initial diagnosis to the first PDT was 4±3 months.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **34 (14 versus 20)**

Drainage success

In the RFA group, there was a statistically significant reduction (p=0.046) in the bilirubin level within 14 days of the first procedure, from a mean of 3.3±3.9 mg/dl to 2.3±2.6 mg/dl after RFA.

In the PDT group, the median bilirubin level was 4.1±6.9 mg/dl before the procedure and 3.5±5.3 mg/dl after 14 days (p=not significant).

The difference between the groups was not statistically significant (p=0.636).

For subsequent interventions, there was a slight reduction in the mean bilirubin levels in the RFA group and an increase in the PDT group, but neither reached statistical significance.

Premature stent replacements (<3 months after first intervention)

- RFA=29% (4/14)
- PDT=65% (13/20), p<0.01

Quality of life scores (EORTC QLQ-C30; scale 0 to 100)

	Test 1 (before RFA)	Test 2 (follow-up)	Test 3 (before 2nd RFA)	Test 4 (follow-up)	Test 5 (before 3rd RFA)	Test 6 (follow-up)
Functional scales (higher scores better)						
Physical	24±6	24±6	25±7	28±11	24±8	29±16
Role	24±10	26±8	20±0	28±10	25±7	33±11
Emotional	25±5	25±7	23±7	24±12	25±4	31±12
Cognitive	18±8	18±9	18±8	22±13	15±7	25±21
Social	28±3	24±9	27±13	22±8	20±7	30±14
Global QoL	43±13	35±16	28±10	28±8	33±4	28±25
Symptom scales (lower scores better)						
Fatigue	27±4	28±7	28±7	28±7	28±2	32±12
Nausea and vomiting	13±4	13±4	13±6	12±3	15±0	25±14
Pain	22±7	23±5	28±3	27±6	15±7	33±4
Dyspnoea	18±10	20±9	20±10	20±17	10±0	25±21
Diarrhoea	12±4	12±4	13±6	10±0	15±7	20±14
Sleep disturbance	32±8	33±8	20±10	17±12	25±21	30±14
Loss of appetite	23±10	23±10	27±15	20±10	15±7	25±21
Obstipation	10±0	17±8	13±6	10±0	20±14	25±21
Financial burden	17±8	18±8	20±14	17±12	20±14	25±21

Safety

There were no adverse events during the RFA procedures.

Procedure-related adverse events (between first and fifth intervention in each group)

Adverse event	RFA	PDT
Cholangitis	2 (14%)	6 (30%)
Liver abscess	1 (7%)	1 (5%)
Sepsis	1 (7%)	1 (5%)
Bleeding	0	0
Perforation	0	0
Phototoxic reaction	-	2 (10%)

An additional patient had a liver abscess diagnosed after RFA, which progressed to sepsis after a seventh RFA procedure.

Endoscopic interventions because of occluded stents were necessary in 38% (5/13) of patients with recurrent RFA in the interval.

Abbreviations used: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PDT, photodynamic therapy; QoL, quality of life; RFA, radiofrequency ablation

Study 7 Sharaiha RZ (2015) – also included in the systematic review by Zheng X et al. (study 1)

Details

Study type	**Case series (registry)**
Country	US
Recruitment period	2010 to 2013
Study population and number	**n=69** Patients with unresectable neoplastic lesions and malignant biliary obstruction.
Age and sex	Mean 66 years (range 36 to 94); 31% (22/69) male
Patient selection criteria	All patients who had radiofrequency ablation (RFA) for malignant biliary obstruction were included in the registry. All patients had unresectable malignancies (stage 3 or 4).
Technique	The Habib EndoHPB probe (EMcision UK) was used for RFA. Uncovered or fully covered self-expanding metal stents (SEMS) or plastic stents were placed after the procedure, depending on the location of the malignant obstruction. The mean number of procedures per patient was 1.3 (range 1 to 4). RFA sessions were repeated once every 3 months if clinically indicated, for up to 4 sessions a year.
Follow-up	**Not reported**
Conflict of interest/source of funding	One author has received grant support from a number of companies, including EMcision UK, and is a consultant for Boston Scientific and Xlumena Inc. Another author is a consultant for Boston Scientific. The remaining 14 authors reported no conflicts of interest.

Analysis

Study design issues: Prospective and retrospective multicentre registry (NCT01439698). Overall survival, from date of diagnosis to date of death was calculated as well as survival stratified by diagnosis. The primary study end point was stent patency at 30 days after stent implantation, as well as stricture improvement. Patient survival was calculated from the date of diagnosis until the final date of follow-up or date of death. Survival of this cohort was also compared with the Surveillance, Epidemiology and End Results (SEER) database stratified by stage. Technical success was defined as a delivering RFA successfully without immediate adverse events. Clinical success was considered to be relief of obstructive symptoms or improvement of liver function tests over the following 2 week period.

Study population issues: Underlying malignancy included cholangiocarcinoma (n=45), pancreatic cancer (n=19), gallbladder cancer (n=1), gastric cancer (n=1), and liver metastases from colon cancer (n=3). Cholangiocarcinoma patients had strictures at multiple sites. Before having RFA, nearly 78% of patients had had chemotherapy for biliary or pancreatic malignancy. The mean stricture length was 14.5±8.5 mm (range 3.5 to 60 mm).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **69 (98 RFA procedures)** Technical success=100% (98/98) 49 (71%) patients had metal stents and 20 (29%) had plastic stents. **Stent patency at 30 days=95.7% (66/69)** **Mean stricture diameter** • Before RFA=2.02±1.2 mm • After RFA=4.9±2.1 mm, p<0.0001 Pancreatic cancer was associated with stricture improvement (RR 1.83, 95% CI 1.02 to 5.64), even after adjusting for age, gender, number of RFA sessions, and receipt of chemotherapy or radiation. There was no difference between stricture improvement in metal versus plastic stents (p=0.35). **Mean survival** • Patients with pancreatic cancer=14.6±11.4 months • Patients with cholangiocarcinoma=17.7±15.4 months **Overall survival and SEER data** For pancreatic cancer, the mean survival in the SEER database was 5.9 months, compared with 14.6 months in the RFA-treated cohort (log rank p<0.0001). For cholangiocarcinoma, the mean survival in the SEER database was 6.2 months compared with 17.7 months in the RFA-treated cohort (log rank p<0.0001).	**Adverse events** • Pancreatitis=1.4% (1/69) • Cholecystitis=2.8% (2/69) • Haemobilia=1.4% (1/69) • Mild abdominal pain that did not need further intervention=4.3% (3/69) There was no device- or procedure-related mortality. Patients with plastic stents were more likely to have complications (p=0.007) than those with metal stents.
Abbreviations used: CI, confidence interval; RFA, radiofrequency ablation; RR, relative risk; SEER, Surveillance, Epidemiology and End Results	

Study 8 Dolak W (2014) – also included in the systematic review by Zheng X et al. (study 1)

Details

Study type	**Case series**
Country	Austria (11 centres)
Recruitment period	2010 to 2012
Study population and number	**n=58** Patients with malignant biliary obstruction.
Age and sex	Median 75 years (range 28 to 88); 53% (31/58) male
Patient selection criteria	Not reported.
Technique	The Habib EndoHPB probe (EMcision UK) was used for RFA. Energy was delivered at 7 to 10 W, typically for up to 120 seconds. Depending on the stricture size, energy was delivered repetitively at different sites within the same procedure. In most patients (60%; 35/58), self-expanding metal stents (SEMS) were placed after the RFA procedure. Plastic stents were placed in 19 patients and no stenting was done in 4 patients. Most patients had only 1 RFA session. There were a total of 84 biliary RFA procedures, of which 6 were done percutaneously; 15 were done within previously implanted SEMS.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues: Retrospective study of prospectively collected clinical data. Examination reports and patient charts were analysed to assess procedure-related complications, hospital stay, adverse events within 30 days of the procedure, stent patency after the last elective RFA procedure in each patient, biliary re-interventions, and 30-day, 90-day and overall mortality.

Study population issues: Underlying malignancy included Klatskin tumour (n=45), distal cholangiocarcinoma (n=5), pancreatic adenocarcinoma (n=4), central hepatocellular carcinoma (n=1), mixed hepatocellular carcinoma and cholangiocarcinoma (n=1), gallbladder carcinoma (n=1), metastatic colorectal cancer (n=1). Of the 58 patients, 24 had previous or concomitant chemotherapy, 4 had previous liver surgery with curative intent, 2 had previous PDT, 2 had prior radiotherapy and 1 patient had previously had 3 sessions of transarterial chemoembolisation.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **58 (84 RFA procedures)** Repeat RFA sessions (up to 5) were done electively in 12 patients during prophylactic stent exchange. Repeat RFA was done non-electively in 2 patients because of stent occlusion. **Median stent patency=170 days (95% CI 63 to 277)** Between metal and plastic stents, an almost statistically significantly different stent patency was observed at a log-rank analysis (218 versus 115 days, p=0.051). During follow-up, 8 patients needed additional percutaneous biliary drainage and 13 needed non-elective ERCP because of stent occlusion or for treatment of adverse events. **Mortality (defining the first RFA procedure as the starting point)** • 30-day=1.7% • 90-day=19.0% 6 patients died because of cachexia (after 36 to 85 days), 2 patients died from cholangiosepsis after 55 and 71 days, and 1 patient each died from hepatic coma after 12 days, acute myocardial infarction after 65 days, and oesophageal variceal bleeding after 77 days. **Extrapolated median survival after first RFA=10.6 months (95% CI 6.9 to 14.4)** **Overall median survival (from initial diagnosis until death)=17.9 months (95% CI 10.3 to 25.6).**	**Interventional complications** • Partial liver infarction, n=1 (probably caused by thermal injury of a segmental liver artery. This was managed conservatively and the patient was discharged after 8 days.) **Adverse events within 30 days** • Cholangitis, n=5 (treated conservatively) • Haemobilia, n=3 (1 patient had ERCP; the other 2 were treated conservatively) • Cholangiosepsis, n=2 (treated conservatively) • Gallbladder empyema, n=1 (led to cholecystectomy) • Hepatic coma, n=1 (fatal outcome) • Newly diagnosed left bundle branch block, n=1
Abbreviations used: CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; RFA, radiofrequency ablation	

Study 9 Laleman W (2017)

Details

Study type	**Case series**
Country	Belgium
Recruitment period	2014 to 2015
Study population and number	**n=18** Patients with unresectable pancreatic or biliary cancer complicated with obstructive jaundice.
Age and sex	Mean 72 years; 83% (15/18) male
Patient selection criteria	Patients with a confirmed diagnosis of unresectable pancreatic or biliary cancer complicated with obstructive jaundice. Exclusion criteria included: age <18 years, refusal of consent, biliary obstruction not caused by a tumour, availability of <50% of liver parenchyma drainable on pre-intervention imaging, coagulopathy, or the presence of concomitant severe comorbidities.
Technique	Radiofrequency ablation (RFA) was done with an ELRA probe and VIVA combo generator (Taewoong Medical, Korea). This has a feedback-sensing system that interrupts the procedure if there rapidly rising impedance. A specified energy application of 7 to 10 W for 2 minutes was set to induce a homogenous thermoablative effect along the full length between the distal and proximal electrode margins. In 3 procedures, the generator aborted the pre-set 2 minutes of energy delivery prematurely because the threshold impedance was attained. For patients with distal malignancy, a fully covered self-expandable metal stent (SEMS) was inserted after RFA. For hilar malignancy, depending on the local anatomy and lumen diameter, either an uncovered SEMS or plastic stents were inserted.
Follow-up	**Mean 213 days (range 16 to 374)**
Conflict of interest/source of funding	The RFA catheters and generators were provided to the study group by Taewoong Medical, South Korea. The authors report no conflicts of interest.

Analysis

Follow-up issues: No patients were lost to follow-up.

Study design issues: Prospective, single centre open-label pilot study. The aim of the study was to demonstrate safety, feasibility and biliary patency (defined as the absence of recurrent jaundice or cholangitis).

Study population issues: 7 patients had pancreatic cancer, 2 had distal cholangiocarcinoma and 9 had hilar cholangiocarcinoma; 11 patients had been given chemotherapy before the RFA procedure.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **18** The procedure was feasible in all 18 patients. **Patient alive with biliary patency, n (%)** • at 90 days=80% (12/15) • at 180 days=69% (9/13) **Median stent patency (range), days** • Overall=110 (16 to 374) • Distal stenting=187 (16 to 374) • Hilar stenting=139 (50 to 340) **Median patient survival=227 days (range 16 to 374)**	There were no direct RFA-related complications within the first 72 hours after the procedure. • Mild cholangitis within 24 hours of the procedure, n=4 (3 patients had hilar strictures) • Post-ERCP pancreatitis, n=2 (1 was only biochemical and 1 had a mild self-limiting course) All complications were managed conservatively and patients recovered uneventfully.
Abbreviations used: ERCP, endoscopic retrograde cholangiopancreatography; RFA, radiofrequency ablation	

Validity and generalisability of the studies

- Only 1 RCT was identified, which was based in China.
- Of the 9 studies included in the systematic review, all were rated as low or moderate quality.
- Most of the studies were retrospective with small sample sizes.
- Most of the evidence is from patients with cholangiocarcinoma or pancreatic cancer. One study only included patients with hilar cholangiocarcinoma and 1 study presented results separately for hilar and distal cholangiocarcinoma[6,9].
- The studies included some patients who were treated in the UK.
- There is more than 1 device available for this procedure.
- Most patients had metal or plastic stents inserted immediately after the radiofrequency and these may have different safety and efficacy profiles.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma. NICE interventional procedure guidance 464 (2013) [Current guidance]. Available from: http://www.nice.org.uk/guidance/IPG464
- Irreversible electroporation for treating pancreatic cancer. NICE interventional procedure guidance 579 (2017). Available from http://www.nice.org.uk/guidance/IPG579

- Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma. NICE interventional procedure guidance 459 (2013). Available from http://www.nice.org.uk/guidance/IPG459
- Photodynamic therapy for bile duct cancer. NICE interventional procedure guidance 134 (2005). Available from http://www.nice.org.uk/guidance/IPG134

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Adviser Questionnaires for endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Some studies that used a percutaneous approach to deliver radiofrequency ablation were identified in the literature search for this procedure. These studies have not been included in this overview.

- Ongoing trials:

- Endoscopic Radiofrequency Ablation for Malignant Biliary Strictures Due to Unresectable Cholangiocarcinoma or Ampullary Carcinoma: a Randomised, Controlled, Multicentre Clinical Trial (NCT01844245); China; estimated enrolment: 240; study start date: May 2013; estimated study completion date: June 2018.
- Radio Frequency Ablation in the Management of Pancreatico-biliary Disorders: A Multicenter Registry (NCT01439698); US; estimated enrolment: 200; study start date: September 2011; estimated study completion date: December 2018.
- A Randomized Controlled Trial of Endoscopic Biliary Radiofrequency Ablation of Malignant Distal Common Bile Duct Strictures (NCT01721174); Hong Kong; estimated enrolment: 116; study start date: November 2012; estimated primary completion date: November 2016.
- Efficacy and Safety of Endobiliary Radiofrequency Ablation by Using a Novel RF Catheter (ELRA®) on Maintaining the Patency of Endobiliary Metal Drainage in Patients With Malignant Biliary Strictures: A Double-arm Comparable Study (NCT02646514); Korea; estimated enrolment: 48; study start date: September 2015; estimated study completion date: February 2017.
- Randomized Controlled Trial Comparing Radiofrequency Ablation and Stenting vs. Stenting Alone for Biliary Obstruction Due to Unresectable Cholangiocarcinoma and Pancreatic Cancer (NCT02166190); US; estimated enrolment: 44; study start date: June 2014; estimated study completion date: June 2017. *The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than 2 years.*

References

1. Yang J, Wang J, Zhou H et al. (2018) Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. Endoscopy DOI: https://doi.org/10.1055/s-0043-124870
2. Zheng X, Bo ZY, Wan W et al. (2016) Endoscopic radiofrequency ablation may be preferable in the management of malignant biliary obstruction: A systematic review and meta-analysis. Journal of Digestive Diseases 17: 716–24
3. Kallis Y, Phillips N, Steel A et al. (2015) Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit. Digestive Diseases & Sciences 60: 3449–55
4. Sharaiha RZ, Natov N, Glockenberg KS et al. (2014) Comparison of metal stenting with radiofrequency ablation versus stenting alone for treating malignant biliary strictures: is there an added benefit? Digestive Diseases & Sciences 59: 3099–3102
5. Strand DS, Cosgrove ND, Patrie JT et al. (2014) ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. Gastrointestinal endoscopy 80: 794–804
6. Schmidt A, Bloechinger M, Weber A et al. (2016) Short-term effects and adverse events of endoscopically applied radiofrequency ablation appear to be comparable with photodynamic therapy in hilar cholangiocarcinoma. United European Gastroenterology Journal 4: 570–79
7. Sharaiha RZ, Sethi A, Weaver KR et al. (2015) Impact of Radiofrequency Ablation on Malignant Biliary Strictures: Results of a Collaborative Registry. Digestive Diseases & Sciences 60: 2164–69
8. Dolak W, Schreiber F, Schwaighofer H et al. (2014) Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. Surgical Endoscopy 28: 854–60
9. Laleman W, Merwe S, Verbeke L, et al. (2017) A new intraductal radiofrequency ablation device for inoperable biliopancreatic tumors complicated by obstructive jaundice: the IGNITE-1 study. Endoscopy 49: 977–82

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	23/01/2018	Issue 1 of 12, January 2018
HTA database (Cochrane Library)	23/01/2018	Issue 12 of 12, December 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	23/01/2018	-
MEDLINE (Ovid)	23/01/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid)	23/01/2018	January 22, 2018
EMBASE (Ovid)	23/01/2018	January 22, 2018
PubMed	23/01/2018	1974 to 2018 Week 04

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	*endoscopy/mt
2	*Endoscopes/
3	(endoscop* or scope* or probe*).tw.
4	endobiliary.tw.
5	or/1-4
6	*catheter ablation/mt
7	((catheter* or radiofrequen* or radio frequen* or radio-frequen*) adj4 ablat*).tw.
8	RFA.tw.
9	Cholangiopancreatography, Endoscopic Retrograde/mt [Methods]
10	Cholangiopancreatograph*.tw.
11	ERCP.tw.
12	or/6-11
13	5 and 12
14	Pancreatic Neoplasms/
15	(pancreat* adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas*)).tw.
16	exp Bile Duct Neoplasms/

17 (bile duct adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas* or stricture* or obstruct*)).tw.
18 Biliary Tract Diseases/
19 (Biliary adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas* or stricture* or obstruct*)).tw.
20 Cholangiocarcinoma/
21 Cholangiocarcinom*.tw.
22 CCA.tw.
23 exp Cholestasis/
24 cholestas*.tw.
25 or/14-24
26 13 and 25
27 (EndoHBP or ELRA).tw.
28 26 or 27
29 Animals/ not Humans/
30 28 not 29
31 (201306* or 201307* or 201308* or 201309* or 20131* or 2014* or 2015* or 2016* or 2017*).ed.
32 30 and 31
33 limit 32 to english language

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Alis H, Sengoz C, Gonenc M et al. (2013) Endobiliary radiofrequency ablation for malignant biliary obstruction. Hepatobiliary & Pancreatic Diseases International 12: 423– 27	Case series n=10	In 2 patients, mild pancreatitis occurred because of the endobiliary procedure. In 1 patient, endobiliary decompression could not be achieved, and percutaneous transhepatic biliary drainage was carried out. The median duration of stent patency in 9 patients with successful biliary decompression was 9 months (range 6-15).	Larger studies are included. Study is included in the systematic review by Zheng et al. (2016).
Alvarez-Sanchez MV, Napoleon B (2016) Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety. World Journal of Gastroenterology 22: 8257–70	Review	A literature review makes it clear that RFA in biliopancreatic tumours is feasible with high rates of technical success and acceptable safety profile. Although available data suggest a benefit of survival with RFA, there is not enough evidence to draw a firm conclusion about its efficacy. For this reason, prospective randomised trials comparing RFA with standard palliative treatments with quality-of-life and survival endpoints are required.	A systematic review is already included.
Figueroa-Barojas P, Bakhru MR Habib NA et al. (2013) Safety and Efficacy of Radiofrequency Ablation in the Management of Unresectable Bile Duct and Pancreatic Cancer: A Novel Palliation Technique. Journal of Oncology Article ID 910897 http://dx.doi.org/10.1155/2013/910897	Case series n=20	There was a significant increase of 3.5mm ($p \leq 0.0001$) in the bile duct diameter after RFA. Five patients presented with pain after the procedure, but only 1 developed mild post-ERCP pancreatitis and cholecystitis.	Larger or more recent studies are included. Study is included in the systematic review by Zheng et al. (2016).

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Laquiere A, Boustiere C, Leblanc S et al. (2016) Safety and feasibility of endoscopic biliary radiofrequency ablation treatment of extrahepatic cholangiocarcinoma. Surgical Endoscopy 30: 1242–48	Case series n=12	Mean survival=12.3 months. Endoscopic radiofrequency treatment of inoperable cholangiocarcinoma appears without major risks and is feasible. No major adverse events or biliary fistula were identified.	Larger studies are included.
Law R, Pai M, Baron TH et al. (2013) The effects of endobiliary radiofrequency ablation in two patients with pancreatic cancer: Gross and microscopic findings. Gastrointestinal Intervention 2: 124-126	Case reports n=2	A histopathologic review showed a circumferential zone of necrosis of 1.0 to 1.5 mm in depth. When compared to published animal data, the zone of necrosis was demonstrably reduced. These discrepant findings are likely multifactorial (e.g., heat-sink phenomenon, differences in study protocol, and comparison of dissimilar tissues). Based on our preliminary histopathologic findings, further studies may be necessary to definitively determine the depth of penetration within the human bile duct during endobiliary RFA.	Larger studies are included.
Mensah ET, Martin J and Topazian M (2016) Radiofrequency ablation for biliary malignancies. Current Opinion in Gastroenterology 32: 238–43	Review	Intraductal biliary RFA is a promising modality for management of malignant biliary obstruction. Prospective randomized studies are required to determine whether RFA truly confers a survival benefit or decreases the number of biliary interventions.	A systematic review is already included.
Musquer N, Menager Tabourel E, Luet D et al. (2016) Recanalization of obstructed metallic uncovered biliary stent using endobiliary radiofrequency ablation. Gastrointestinal Endoscopy 83: 256–7	Case report	Successful stent recanalization using endobiliary RFA.	Larger studies are included.

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Ogura T, Onda S, Sano T et al. (2017) Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope (with videos). Digestive Endoscopy 29: 712–17	Case series n=12	RFA was technically successful in all patients, and clinical success was confirmed in all patients by peroral cholangioscope imaging. Adverse events were seen in only 1 patient. Median stent patency was 154 days.	Larger studies are included.
Patel J, Rizk N, Kahaleh M (2015) Role of photodynamic therapy and intraductal radiofrequency ablation in cholangiocarcinoma. Best Practice & Research in Clinical Gastroenterology 29: 309–18	Review	Photodynamic therapy and Radiofrequency ablation are 2 innovative approaches done endoscopically to locally destruct the malignant tissue.	A systematic review is already included.
Rustagi T, Jamidar PA (2014) Intraductal radiofrequency ablation for management of malignant biliary obstruction. Digestive Diseases & Sciences 59: 2635–41	Review	Several reports have demonstrated the technical feasibility and safety of intraductal radiofrequency ablation (RFA), by both endoscopic and percutaneous approaches, in palliation of malignant strictures of the bile duct.	A more recent systematic review is already included.
Sarkisian AM, Andalib I, Kumta NA et al. (2016) Radiofrequency ablation for pancreatobiliary disease. Curr Opin Gastroenterol 32: 353–57	Review	Intraductal biliary RFA and pancreatic endoscopic ultrasound-guided RFA are important modalities in malignant biliary obstruction and unresectable pancreatic cancer. Intraductal biliary RFA should be used as an adjunct to biliary stenting. Further trials are needed to determine if RFA leads to a benefit in pancreatic cancer treatment. Two prospective trials are currently underway to determine if intraductal biliary RFA indeed confers a survival advantage in malignant obstruction.	A systematic review is already included.

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Smith I, Kahaleh M (2015) Biliary Tumor Ablation with Photodynamic Therapy and Radiofrequency Ablation. Gastrointestinal Endoscopy Clinics of North America 25: 793–804	Review	RFA is emerging as a potentially effective treatment of malignant biliary occlusion and has been used before insertion of biliary stents and as a treatment of metal stent occlusion.	A systematic review is already included.
Steel AW, Postgate AJ, Khorsandi S et al. (2011). Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. Gastrointestinal Endoscopy 73: 149–53	Case series n=22	Median stricture diameter increased to 4 mm (range 3 to 6) compared with 0 mm (range 0 to 1) before RFA. 1 patient had asymptomatic biochemical pancreatitis and 2 patients had cholecystitis after the procedure.	Larger or more recent studies are included. Study is included in the systematic review by Zheng et al. (2016).
Tal AO, Vermehren J, Friedrich-Rust M et al. (2014) Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. World Journal of Gastrointestinal Endoscopy 6: 13–19	Case series n=12	Biliary bleeding was observed 4 to 6 weeks after the intervention in 3 patients and 2 of these patients died: in 1 patient, spontaneous haemobilia occurred, whereas bleeding started during stent extraction in the other. In the third patient, bleeding was stopped by insertion of a non-covered self-expanding metal stent. Another 3 patients developed cholangitis during follow-up. Seven patients died during follow-up and median survival was 6.4 months (95% CI 0.05 to 12.7) from the time of the first RFA.	Larger studies are included. Study is included in the systematic review by Zheng et al. (2016).
Wang F, Li Q, Zhang X (2016) Endoscopic radiofrequency ablation for malignant biliary strictures. Experimental and Therapeutic Medicine 11: 2484–88	Case series n=12	There was a significant increase of 7.3 mm in the bile duct diameter after RFA ($p \leq 0.001$). Of the 11 patients with stents inserted after RFA, the median stent patency was 125 days [95% confidence interval (CI), 95 to 155 days]. Extrapolated median survival after the first RFA was 232 days (95% CI, 94 to 370 days).	Larger studies are included.