Endoscopic Therapy For Cholangio Carcinoma:

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Normal Hilum:
Hilar Lesion:
Distal Bile duct Tumor:
Introduction:

- Incidence 1-2% /100,000 (may be higher due to paucity of diagnostic techniques)
- 13% of primary liver cancers
- Outcomes different in intra vs extrahepatic cancers
- Surgery is only therapeutic option high mortality and 5 year survival low 30-40%.
- Better survival for ductal tumors
- Untreated 40% mortality in 4 months
Survival:

- Overall cholangiocarcinoma
- Intrahepatic cholangiocarcinoma
- Hilar cholangiocarcinoma

Cumulative survival vs. survival (month)
Primary malignant tumors of the bile ducts blocking bile flow and can be intrahepatic (IH) or extrahepatic (EH).

IH-CCA starts in the thin ducts that are spread throughout the liver.

EH-CCA starts in the thick portion of the bile duct that sits outside the liver comprised of:

- Perihilar CCAs involving the biliary confluence of the left and right hepatic ducts also called hilar CCA, or Klatskin tumor;
- Distal bile duct tumors arise between the junction of the cystic duct-bile duct and the ampulla of Vater.
Staging

The stage of disease at presentation and whether patients are treated by a palliative procedure or by complete tumor resection influence the long-term survival of these patients.

- **Type 1**
  limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts

- **Type 2**
  involves the confluence of the right and left hepatic ducts

- **Type 3a**
  type II + extends to the bifurcation of the right hepatic duct

- **Type 3b**
  type II + extends to the bifurcation of the left hepatic duct

- **Type 4**
  extending to the bifurcations of both right and left hepatic ducts OR multifocal involvement
Morphologic types and TNM:

- Intrahepatic mass forming
- Periductal
- Intraductal

<table>
<thead>
<tr>
<th>PRIMARY TUMOR (T)</th>
<th>TX</th>
<th>T0</th>
<th>Tis</th>
<th>T1</th>
<th>T2a</th>
<th>T2b</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary tumor cannot be assessed</td>
<td>No evidence of primary tumor</td>
<td>Carcinoma in situ</td>
<td>Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue</td>
<td>Tumor invades beyond the wall of the bile duct to surrounding adipose tissue</td>
<td>Tumor invades adjacent hepatic parenchyma</td>
<td>Tumor invades unilateral branches of the portal vein or hepatic artery</td>
<td>Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REGIONAL LYMPH NODES (N)</th>
<th>NX</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regional lymph nodes cannot be assessed</td>
<td>No regional lymph node metastasis</td>
<td>Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)</td>
<td>Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>DISTANT METASTASIS (M)</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis (no pathologic M0; use clinical M to complete stage group)</td>
<td>Distant metastasis</td>
<td></td>
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</table>
Epidemiology

- Second most common primary liver cancer worldwide.
- In the USA, the incidence is 1.0 per 100,000 people per year; about 3,000 cases of EH-CCA are diagnosed annually in the USA.
- Preponderance in males with the 50- to 70-age group more at risk.
- Incidence of EH-CCA is higher than that of IH-CCA in western countries and Japan while, the opposite occurs in eastern countries.
- Significant predisposing factors: primary sclerosing cholangitis (PSC), liver fluke infestations; hepatitis C virus infection (HCV), HIV, Caroli’s disease, biliary stasis, choledochal cysts, liver cirrhosis, chronic intrahepatic and bile duct lithiasis; chemical agents (such as asbestos, vinyl chloride, nitrosamines); and drugs (isoniazide and first generation oral contraceptives); Common to all these conditions are chronic inflammation and glandular regeneration, which may predispose to carcinogenesis.
Cholangiocarcinoma (CCA) is a rare and challenging tumor to diagnose and treat. Sampling techniques include cytology brushing, biopsy, and fine needle aspiration but are limited in their sensitivity, yield <15%. This often requires multiple imaging and procedural /biopsy techniques in order to make a diagnosis. It results in a costly and time-consuming process to a potentially time-sensitive disease process.
**Diagnosis**

- **Blood work:** Carcinoembriogenic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9), which may be elevated in patients with bile duct cancer.
- **Abdominal ultrasound**
- **CT scan/MRI**
- **Endoscopy (ERCP), Transcutaneous Cholangiography**
**TREATMENT OPTIONS**

### STENTING
- Non-operative palliative care achieved either endoscopically or percutaneously to relieve symptoms associated with jaundice and the prevention of biliary tract infection
- Drop in the bilirubin level has been reported as an important predictor of drainage effectiveness
- ERCP and non-operative drainage of bile percutaneously frequently introduce early complications such as cholangitis and sepsis

### CHEMOTHERAPY
- Responds poorly to chemotherapy with 5-FU alone or in combination with methotrexate, cisplatin, mitomycin C, leucovorin, and interferon alpha
- In a P3 (n=410) Cisplatin plus gemcitabine: median overall survival of 11.7 months versus 8.1 months in the gemcitabine alone (p < 0.001)

### LIVER TRANSPLANT/RADIATION
- Promising long-term survival data
- Palliative radiotherapy may prolong survival in EH-CCA but no definitive conclusion as to the efficacy of the approach

### PHOTODYNAMIC THERAPY (PDT)
- Uses a photosensitizing agent which accumulates in malignant tissue followed by photoactivation with a red laser light to destroy the malignant cells
- Photofrin: A well-established photosensitizing agent used in PDT to treat cancer and precancerous lesions
- Worldwide marketing authorization status in endobronchial cancer, Barrett’s esophagus, esophageal cancer and papillary bladder cancer
- A promising new approach in the treatment of...
Non-Resectability:

- Local tumor invasion bilateral hepatic duct involvement up to secondary biliary radicles
- Encasement or occlusion of the main portal vein
- Unilateral tumor extension to secondary biliary radicles with contralateral portal vein or hepatic artery encasement or occlusion.
- Hepatic lobar atrophy with contralateral portal vein or hepatic artery encasement or occlusion
- Hepatic lobar atrophy with contralateral tumor extension to secondary biliary radicles
- Distant metastasis (eg, lung, liver, peritoneal)
Non-Resectability:

- Metastatic disease lymph node metastases beyond the hepatoduodenal ligament (N2 lymph nodes) (peripancreatic, periduodenal, periportal, celiac, or superior mesenteric lymph nodes)

Vauthy and Baumgarten
Therapy:

- Surgery primary therapeutic modality
- Chemotherapy for unresectable (gemzar plus cisplatin) - median survival 11.7 months
- Survival better with ductal cancers vs intrahepatic (due to surgical techniques)
- Cholangiocarcinoma poorly radiosensitive
- Newer Options for Palliation: Ablation
Novel Diagnostic Tools:

- **FISH** (DNA probes detect chromosomal alterations)
- **Cholangioscopy** (single operator)
- **Endomicroscopy**
Case:

- 83 y/o Female, presents with
- Sudden onset, painless Jaundice
- No wt. loss
- Imaging CT - dilated intrahepatics
- H/O cholecystectomy
- Poor functional status
- ERCP brushings atypical cells non diagnostic
- CA19-9 - 1500
CT scan: Cholangiocarcinoma Hilar
Cholangioscope in Place:
Cholangioscopy:
Cholangioscopy:
Cholangiocarcinoma: Endomicroscopy for early diagnosis

Miami and Paris classification for evaluation of biliary strictures
Normal Bileduct Endomicroscopy
Patient ID: D001107264
Biopsy: no
2011-02-03 11:54:02.54 (UTC-5)
Su1662 Smart Atlas for Supporting the Interpretation of Probe-Based Confocal LASER Endomicroscopy (pCLE) of Biliary Strictures: First Classification Results of a Computer-Aided Diagnosis Software Based on Image Recognition

Marzieh Kohandani Tafreshi, Virendra Joshi, Alexander Meining, Charles J. Lightdale, Marc Giovannini, Julien Dauguet, Nicholas Ayache, Barbara André

Gastrointestinal Endoscopy
Volume 79, Issue 5, Pages AB357-AB358 (May 2014)
DOI: 10.1016/j.gie.2014.02.406
sensitivity: 88.9%
specificity: 70.8%
accuracy: 81.7%

sensitivity: 69.4%
specificity: 91.7%
accuracy: 78.3%
Dosimetry

7w, 2 min

2 applications

2.5 cms

Bipolar
Pilot Study to Assess Safety and Efficacy Of An Endoscopic Bipolar Radiofrequency Probe (EndoHPB) In the Management of Unresectable Bile Duct and Pancreatic Cancer

- **Primary Outcome:** Measures: Improvement in size (patency of bile duct) measured by cholangiography or cholangioscopy, immediately post ablation
- **Secondary:** T. bilirubin, quality of life, survival
Probe-Based Confocal laser Endomicroscopy in diagnosis of Cholangiocarcinoma

I Wysocki, P Frimberger, D Meining, M Meining, Institute of Medicine and Cancer Research, Chicago, IL

Introduction:
Confocal laser endomicroscopy (CLE) is a relatively new modality that offers en-vivo imaging of the gastrointestinal tract with microscopic detail in living cells.

Background:
Despite technologic advances in endoscopy and new cytoclogic techniques, cholangiocarcinoma (CCA) is a challenging diagnosis for the endoscopist and oncologists. Current sampling techniques include cytology brushing, biopsy, and fine needle aspiration but are limited in their sensitivity. Confocal laser endomicroscopy (CLE) is a relatively new modality that offers en-vivo imaging of the gastrointestinal tract with microscopic detail in living cells.

Methods:
This was an observational study of 10 non-consecutive patients with indeterminate biliary strictures who were evaluated with ERCP, cholangioscopy, and CLE to determine the sensitivity and specificity of tissue biopsy compared to virtual biopsy using this new technology, pCLE. All cases were confirmed to be CCA by histopathology. Fluorescein 10% was used as a contrast agent.

Results:
Ten ERCP cases were reviewed and demonstrated biliary strictures that were suspicious for malignancy based on history and clinical presentation. Nearly all initial brushings and traditional biopsies were inconclusive. Subsequent ERCP and cholangioscopy with pCLE imaging was performed. The biliary architecture was concerning for malignancy according to the Miami Criteria. Images were reviewed by 2 independent physicians. Every case demonstrated thick bands >20 mm and dark clumps of glands. Bright vessels (>20 mm) with tortuosity were visualized in seven cases. Other findings included reticular networks of dark bands and small, fine branching bands <20um; however these patterns were infrequent. Imaging results from one of the 10 patients is shown below. The diagnosis of cholangiocarcinoma was made by pCLE and confirmed with histopathology. This patient demonstrated features consistent with malignancy as described by the Miami Criteria.

Conclusion:
CLE is a novel tool to investigate indeterminate biliary strictures and potentially diagnose cholangiocarcinoma in conjunction with other diagnostic modalities during the initial ERCP and cholangioscopy.

2. Our early experience found sensitivity 90%, specificity of 100%, NPV 90%

3. CLE gives the opportunity to obtain en-vivo targeted biopsies during cholangioscopy as well as reduce repeat procedures and cost.

References

Image 1: ERCP/cholangiogram demonstrating common bile duct stricture

Image 2a: Features of benign bile duct histology are shown in image 2a with branching bands and 20um white bands. Features suggestive of malignant histology are shown in image 2b with dark bands 20um thick. Band widths 20um. Evidence of fluorescein leak before and 20 after injection, and 20 dark clumps.

Image 2b: Features of malignant bile duct histology are shown in image 2b with thick branching bands >20um and dark clumps of glands. Bright vessels >20um with tortuosity were visualized in seven cases. Other findings included reticular networks of dark bands and small, fine branching bands <20um; however these patterns were infrequent. Imaging results from one of the 10 patients is shown below. The diagnosis of cholangiocarcinoma was made by pCLE and confirmed with histopathology. This patient demonstrated features consistent with malignancy as described by the Miami Criteria.

Image 3: Invasive poorly differentiated adenocarcinoma of the biliary duct
Probe Based Confocal Laser Endomicroscopy (pCLE) in the Evaluation of Bile Duct Strictures

John Wysocki, MD, Virendra Joshi, MD; Tulane University Health Sciences Center, Ochsner Health System, New Orleans, Louisiana

Background

Despite technological advances in endoscopy and new cytologic techniques, evaluating bile duct strictures is a challenging task for the endoscopist. Current sampling techniques include cytology, brushing, biopsy, and fine needle aspiration but are limited in their sensitivity. Confocal laser endomicroscopy (CLE) is a relatively new modality that offers in vivo imaging of the gastrointestinal tract with microscopic detail in living cells.

Methods

This was an observational, retrospective study of 16 patients with indeterminate biliary strictures who were evaluated with ERCP, cholangiography, and CLE to determine the sensitivity and specificity of tissue biopsy compared to virtual biopsy using this new technology, CLE. All cases were confirmed to be either neoplasia or benign strictures by histopathology with a 1 year follow-up. Fluorescein 10% was used as a contrast agent. The imaging characteristics of these patients were reviewed based on Miami and Paris Criteria.

Results

Sixteen patients were evaluated by ERCP and CLE who demonstrated biliary strictures that were suspicious for malignancy based on history and clinical presentation. Nearly all initial brushings and traditional biopsies were inconclusive. The biliary architecture was concerning for neoplasia according to the Miami Criteria in 11 of the 16 patients, and benign or inflammatory in the remaining 5 patients. Images were reviewed by 2 independent physicians with good interobserver agreement. Every case of neoplasm demonstrated at thick bands >60 μ and dark clumps of epithelial structures. Bright vessels (><20 μ) with tortuosity were also visualized in a few cases. Other findings included bright space in between the bands with no flow. We added the inflammatory criteria: Multiple thin white bands (vascular congestion), dark granular patterns with scales, increased spaces between scales (20 μm), and thickened reticular structures also to our analysis.

Conclusion

1. pCLE is a novel tool to investigate indeterminate biliary strictures and potentially diagnose cholangiocarcinoma in conjunction with other diagnostic modalities during the initial ERCP and cholangiography.
2. Retrospective review of the images found a sensitivity 100%, specificity of 20%, PPV 100%, PPV 73.3%, and an accuracy of 75% in diagnosing neoplasia based upon the Miami criteria.
3. Based upon the modified Paris criteria for inflammatory strictures, sensitivity 91.7%, specificity of 100%, NPV 80%, PPV 100%, and an accuracy of 93.75% in diagnosing neoplasia.
4. We were also able to define endoscopic characteristics of strictures with high PPV reducing the false positives.
5. pCLE may give the opportunity to obtain in vivo targeted biopsies during cholangiography as well as reduce repeat procedures and cost.
Cholangiocarcinoma in PSC:

Risk for CCA 5-36%

Most important risk factor in western hemispheres
Psc Stricture Cholangioscopy: A dilemma
Senstivities of CEA/CA 19-9 and biopsies range from 30-75%
Specificities are in range of 80%
Thus, the goal for the diagnostic process is to differentiate benign and malignant PSC strictures with the least number of procedures, with least amount of invasiveness and the least amount of time to treatment (or no treatment).
pCLE could potentially play a role in this diagnostic process of PSC strictures by providing an *in vivo*, real time diagnosis during ERCP procedure.
PSC Endomicroscopy Registry:

- Registry Trial to Determine pCLE Image Interpretation Criteria and Preliminary Accuracy for Primary Sclerosing Cholangitis Biliary Strictures Study Design
- Prospective, longitudinal, observational, multicenter registry

UC denver, Cornell, U. Pittsburgh, Columbia University, Ochsner
Objectives
Primary sclerosing cholangitis
1. Prospectively validate interpretation criteria for the characterization of PSC strictures
2. Prospectively evaluate the accuracy of pCLE for the characterization of PSC strictures (differentiation between malignant vs. non malignant strictures), using the newly developed interpretation criteria
3. Evaluate the feasibility and safety of pCLE for the characterization of PSC strictures
Hypothesis:
ERCP with probe-based confocal endomicroscopy results in differentiable microscopic images for healthy versus diseased PSC.

Sample size:
Until inclusion of 20 malignant strictures
Photodynamic therapy session:
Earlier Results

Combined with stenting, PDT has given encouraging results in patients with Bismuth type III and IV CCA with a local tumor response of 30-75% and reversibility of hilar bile ducts occlusion.

<table>
<thead>
<tr>
<th>Berr et al.</th>
<th>Weidmann et al.</th>
<th>Dumoulin et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHO 2 mg/kg and biliary endoprosthesis (n=23)</td>
<td>PDT as a neoadjuvant treatment for hilar-CCA (n=73)</td>
<td>Historical control design (n=24)</td>
</tr>
<tr>
<td>• 6-month survival rate of 74%.</td>
<td>• Serum bilirubin levels significantly decreased one week after PDT (p &lt; 0.05).</td>
<td>• 30-day and 60-day mortality rates were 0%</td>
</tr>
<tr>
<td>• Response rate was 74%, 54%, 29%, and 67% after the initial (1\textsuperscript{st} and 2\textsuperscript{nd}), 3\textsuperscript{rd}, 4\textsuperscript{th}, and 5\textsuperscript{th} PDT session, respectively.</td>
<td>• The one-year recurrence free survival rate was 83%.</td>
<td>• Serum bilirubin levels significantly decreased in all patients.</td>
</tr>
<tr>
<td>• Survival at 1 year (39%), 2 years (17%), 3 years (95), and 4 years (4%).</td>
<td>• Occasional pruritus, moderate pain, epigastric distress, severe sepsis occurred in one patient.</td>
<td>• The quality of life remained unchanged.</td>
</tr>
<tr>
<td>• Occasional pruritus, moderate pain, epigastric distress, severe sepsis occurred in one patient.</td>
<td>• Serum bilirubin levels significantly decreased in all patients.</td>
<td>• The median survival time was 9.9 months after PDT, which was not significantly different from 5.6.</td>
</tr>
</tbody>
</table>
### Earlier Results (cont’d)

Combined with stenting, PDT has given encouraging results in patients with Bismuth type III and IV CCA with a local tumor response of 30-75% and reversibility of hilar bile ducts occlusion.

<table>
<thead>
<tr>
<th>Ortner et al.</th>
<th>Zoepf et al.</th>
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<tbody>
<tr>
<td>(N=39: PDT + stenting (n=20) vs. stenting alone (n=19) patients)</td>
<td>(N=32: PDT + stenting (n=16) vs. stenting alone (n=16) patients)</td>
</tr>
</tbody>
</table>

- **Ortner et al.**
  - Median Survival: 493 days in PDT group vs 98 days stent alone group, \( p < 0.0001 \).
  - Mean serum bilirubin levels did not change after stenting in either group but significantly decreased after PDT \( p < 0.01 \).
  - Improved KPS index from baseline in both groups \( p < 0.01 \). After PDT, physical functioning \( p < 0.01 \) and global quality of life \( p < 0.001 \) both further improved compared to the control group.
  - Photosensitivity reactions were reported by 10% of the PDT patients. Two inflammatory fibrotic stenoses occurred.

- **Zoepf et al.**
  - Median serum bilirubin levels declined from 2.75 mg/dL (range, 0.9-38) to 1.3 mg/dL (range, 0.8-21.4) in the PDT group and declined from 3.6 mg/dL (range, 0.6-54.3) to 2.4 mg/dL (range, 0.6-13.3) in the stent alone group.
  - The Kaplan-Meier survival analysis showed a significantly longer median survival time in the PDT group as compared to the control group (21 months [range, 3-31 months; 95% CI 13-19] versus 7 months [range, 1-24 months; 95% CI 1-13], \( p=0.01 \)).
Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study.

Cholangitis was low in PDT group.
Stent(s) Before and After PDT
Photodynamic Therapy : PDT

- Photodynamic reaction (PDR)

PHOTOFRIN® (porfimer sodium) absorbs red light

A porphyrin-excited state occurs

Propagation of radical reactions:
- ischemic necrosis

Cell Destruction
PDT with PHOTOFRIN: A Two Stage Process

Photosensitizing agent (IV administration)

Nonthermal Laser Light
Stage 1: PHOTOFRIN Administration

- Each vial is reconstituted with 31.8 mL of either 5% Dextrose or 0.9% Sodium Chloride
- Gloves recommended when mixing – skin exposure may result in photosensitivity to that area
- Photofrinn is not to be mixed with other drugs in the same solution
Stage 1: PHOTOFRIN Administration

- Mixed product should be protected from bright light and used immediately
- Overdosage
- Administered as a single slow intravenous injection over 3-5 minutes
- Recommended large vein – viscous product
- Infiltration – protect site from normal light for 2-3 months
Stage 2

630nm Light Application

- 40-50 hrs after injection patient returns for light application
- Light is applied through normal endoscopy, bronchoscopy or during surgery
- Light is nonthermal
- Red light penetrates tissue up to 1cm
- Diffusers and balloons come in different lengths
- Light dosimetry is predetermined by indication

Diomed Laser

Fiber Optic Diffuser

RED LIGHT

Bile transmits the light

Dosimetry: complex formula

180 j/cms2/ power density

Stent size and stricture length
Contraindications

Photodynamic therapy with PHOTOFRIN® (porfimer sodium) for Injection is a photoactivated drug contraindicated in patients with:

- Porphyria¹

- Existing tracheoesophageal or bronchoesophageal fistula¹

- Tumors eroding into a major blood vessel¹

- Severe acute respiratory distress caused by an obstructing endobronchial lesion requiring emergency treatment because 40 to 50 hours are required between injection of PHOTOFRIN® and laser light treatment¹

- Esophageal or gastric varices or esophageal ulcers >1 cm in diameter¹
I. Initial Consultation
   Review patient education

II. Injection Day (Day 1)
   Confirm patient has proper clothing
   Patient view video
   Review patient brochure
   Ensure patient leaves clinic wearing protective clothing

III. 1st Procedure Day (Day 2)
   Reconfirm above photosensitivity information

IV. 2nd Procedure Day (Day 3)
   Reconfirm above photosensitivity information
   Reconfirm photobleaching
   Reconfirm skin test
   Reconfirm gradual exposure to sunlight
Multicenter, open-label, randomized, controlled phase 3 clinical study of the efficacy & safety of PDT using porfimer sodium for injection as treatment for unresectable advanced perihilar CCA
### Study Rationale

<table>
<thead>
<tr>
<th>Metastatic or unresectable disease = Poor prognosis</th>
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<tbody>
<tr>
<td>• Median survival 5-8 months, 1-year survival is 50%, with 20% surviving at 2 years &amp; 10% at 3 years.</td>
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<tr>
<td>• Stents placement to relieve pruritus and treat cholestasis, prevent cholangitis.</td>
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<tr>
<td>• Successful drainage is often not achieved in Bismuth Type III and IV perihilar cancers or maintained due to infection, blood clot or tumor in growth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PDT in unresectable advanced perihilar CCA</th>
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<tr>
<td>• Can be repeated every 3 months</td>
</tr>
<tr>
<td>• Earlier treatment intervention may prevent biliary obstruction and loss of hepatic function</td>
</tr>
<tr>
<td>• Survival benefit of biliary decompression (UNMET NEED)</td>
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<th>PRIMARY OBJECTIVE</th>
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<td>• Overall Survival</td>
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</table>
Study Design

Phase III, Prospective, Multicenter, Open-label, Randomized, Controlled

Subject Population:
Unresectable CCA Bismuth type III or IV

Sample Size
- 200 subjects
- 100 subjects in each arm

Study Milestones
- Study duration = 4 years
- Enrollment = 30 months
Current Indications

Photodynamic therapy with PHOTOFRIN® (porfimer sodium) for Injection is a photoactivated drug indicated for:

**Esophageal Cancer**
- PHOTOFRIN® is indicated for the palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

**Endobronchial Cancer**
- PHOTOFRIN® is indicated for the treatment of microinvasive endobronchial non-small-cell lung cancer (NSCLC) in patients for whom surgery and radiotherapy are not indicated.
- PHOTOFRIN® is indicated for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC.

**High-Grade Dysplasia in Barrett’s Esophagus**
- PHOTOFRIN® is indicated for the ablation of high-grade dysplasia in Barrett’s esophagus patients who do not undergo esophagectomy.
Objectives of CCA Study

- **Primary Objective**
  - Assess effect of:
    - Adjuvant PHOPDT plus standard medical care (SMC) vs. SMC on overall survival of subjects with unresectable perihilar Bismuth type III or IV, tumor TNM stage III or IVa CCA

- **Secondary Objectives**
  - Assess effect of:
    - Adjuvant PHOPDT plus SMC compared to SMC on
      - Time-to-bilirubin response, tumor response, time-to-tumor progression, performance status; and health-related quality of life (HRQoL)

- **Tertiary Objective**
  - Explore the role of interleukin-6 (IL-6) as potential marker in CCA
Initiation Date: June 2014
Global: US (25 sites), Germany, Belgium, Switzerland, Canada

Interim Analysis Planned
Efficacy Endpoints

- **Primary Efficacy Endpoint**
  - Overall survival
  - Duration of survival from the date of randomization until the date of death

- **Secondary Efficacy Endpoints**
  - Time-to-bilirubin response measured from date of randomization until the date of first documented bilirubin response less than 2 times the upper limit of normal (ULN)
  - Tumor response as measured by the RECIST 1.1 criteria
  - Time-to-tumor progression using RECIST 1.1 criteria
  - Performance status as measured by the Karnofsky Performance Scale (KPS)
  - HRQoL as measured by the EORCT QLQ-C30
Future- Improved survival:

- Early detection (Advanced Imaging)
- Innovative strategies (RFA and PDT) to improve survival
- Combination of Endoscopic therapies with targeted therapies
- Better Photosensitizers with enhanced tumoricidal properties
Multidisciplinary TEAM approach: