Management of biliary malignancies
Radiation oncology perspective including contouring

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ROADMAP

Anatomy and classification
With general introduction

Radiological diagnosis

Rationale for use of RT

Evidence supported with guidelines
Trials

Contouring
Guidelines.
Biliary Anatomy
Biliary malignancies

- Intrahepatic Cholangiocarcinomas
- Extrahepatic Cholangiocarcinomas
- Perihilar Bile-Duct carcinomas
- Gall Bladder carcinomas
Gall bladder carcinoma (GBC): Rising incidences in the Malwa belt region of northern India a hospital based cancer registry

Sapna Marcus¹, Jasmeet Kaur², H P Yadav³

Department of Radiation Oncology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, INDIA.
Email: sapnamarcus@gmail.com
Classification of biliary tract tumors

- 5%-10% of cholangiocarcinoma are located in the intra-hepatic bile ducts.
- 60%-70% of cholangiocarcinoma are located at the bifurcation of the biliary system (Klatskin tumors).
- 20%-30% of cholangiocarcinoma are located at the extra-hepatic bile ducts.
Anatomically, biliary tree is divided into 3 parts, upper 3rd-55%, middle 3rd 15% and lower 3rd 10%. Of these tumours, 10% are diffuse.

Bismuth-Corlette classification of perihilar cholangiocarcinomas

![Diagram of Bismuth-Corlette classification]

1  2  3A  3B  4
Radiological Appearance of IHCC

(A) Arterial phase CT scan shows a large mass (arrows) with irregular peripheral enhancement.

(B) Three-minute delay phase CT scan shows progression of enhancement within the mass (arrows).

(C) Contrast-enhanced sonogram at 19 s delay shows hypervascularity of the mass (arrows).

(D) Contrast-enhanced sonogram at 34 s delay shows early complete washout of enhancement of the mass (arrows).
Ultrasonographic Appearance of GBC
Usual presentation

- Fever - 20%
- Diarrhoea, anorexia,
- Changes in urine & stool colour and weight loss.
- Liver may be enlarged and smooth - 25-40%
- Distended and non tender gallbladder 10%
- Epigastric tenderness.
Which patient group are we going to offer radiotherapy to?
Rationale for using RT in biliary carcinomas

- Neoadjuvant radio-therapy reduced risk of implantation metastases after endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography

- Palliative for symptom relief (metastatic ds OR CPS C)
High Risk Group for Adjuvant RT

- Poor histologic differentiation.
- Lymph Node metastasis
- Positive RM status
- Higher primary tumor stage
Where does radiation fit in??

- Adjuvant setting
- Neoadjuvant setting
- Definitive setting
- Palliative setting
### NCCN Guidelines Version 2.2019

#### Intrahepatic Cholangiocarcinoma

**PRESENTATION**

<table>
<thead>
<tr>
<th>Isolated intrahepatic mass &lt;sup&gt;a&lt;/sup&gt; (imaging characteristics consistent with malignancy but not consistent with hepatocellular carcinoma) (See NCCN Guidelines for Occult Primary Cancers)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&amp;P</strong></td>
</tr>
<tr>
<td><strong>Multiphasic abdominal/pelvic CT/MRI with IV contrast&lt;sup&gt;b&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>Chest CT +/- contrast&lt;sup&gt;c&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>Consider CEA&lt;sup&gt;d&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>Consider CA 19-9&lt;sup&gt;e&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td><strong>LFTs</strong></td>
</tr>
<tr>
<td><strong>Surgical consultation</strong></td>
</tr>
<tr>
<td><strong>Esophagogastroduodenoscopy (EGD) and colonoscopy</strong></td>
</tr>
<tr>
<td><strong>Consider viral hepatitis serologies</strong></td>
</tr>
<tr>
<td><strong>Consider biopsy</strong></td>
</tr>
<tr>
<td><strong>Consider AFP</strong></td>
</tr>
</tbody>
</table>

**WORKUP**

<table>
<thead>
<tr>
<th>Resectable&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider staging laparoscopy</strong></td>
</tr>
<tr>
<td><strong>Resection</strong></td>
</tr>
<tr>
<td><strong>Consider lymphadenectomy for accurate staging</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unresectable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBRT with concurrent fluoropyrimidine&lt;sup&gt;f&lt;/sup&gt;</strong></td>
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**PRIMARY TREATMENT**

<table>
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<tr>
<th>Options&lt;sup&gt;g&lt;/sup&gt;</th>
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<tr>
<td><strong>Gemcitabine/cisplatin combination therapy</strong> &lt;sup&gt;g&lt;/sup&gt; (category 1)</td>
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<tr>
<td><strong>Clinical trial</strong></td>
</tr>
<tr>
<td><strong>Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen&lt;sup&gt;g&lt;/sup&gt;</strong></td>
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<tr>
<td><strong>Consider locoregional therapy</strong></td>
</tr>
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<td><strong>Radiation therapy</strong></td>
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<tr>
<td><strong>Arterially directed therapies</strong></td>
</tr>
<tr>
<td><strong>Best supportive care</strong></td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong> (only for MSI-H/dMMR tumors)</td>
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<tr>
<td><strong>MSI/MMR testing</strong></td>
</tr>
<tr>
<td><strong>Consider molecular testing</strong></td>
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<sup>a</sup>See Principles of Surgery (INTRA-A).<br>
<sup>b</sup>See Principles of Imaging (HCC-A).<br>
<sup>c</sup>CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.<br>
<sup>d</sup>Consult with multidisciplinary team.<br>
<sup>e</sup>Laparoscopy may be done in conjunction with surgery if no distant metastases are found.<br>
<sup>f</sup>Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.<br>
<sup>g</sup>See Principles of Radiation Therapy (GALL-C).<br>

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**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2019
Intrahepatic Cholangiocarcinoma

TREATMENT

No residual local disease (R0 resection)
- Options:
  - Observe
  - Clinical trial

Fluoropyrimidine-based or gemcitabine-based chemotherapy

Fluoropyrimidine-based chemoradiation

Fluoropyrimidine-based or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation

Residual local disease (R2 resection)
- See treatment for unresectable disease (INTRA-1)

SURVEILLANCE

Consider multiphasic abdominal/pelvic CT/MRI with IV contrast and chest CT +/- contrast every 6 mo for 2 y if clinically indicated, then annually up to 5 years

Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/capeptabine, and 5-fluorouracil/cisplatin, and the single agents gemcitabine, capetabine, and 5-fluorouracil in the unresectable or metastatic setting. The phase III BILCAP study shows improved overall survival for adjuvant capetabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al. Adjuvant capetabine for biliary tract cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4066.


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### NCCN Guidelines Version 2.2019
Extrahepatic Cholangiocarcinoma

#### Presentation
- Pain
- Jaundice
- Abnormal LFTs
- Obstruction or abnormality on imaging

**H&P**
- Multiphasic abdominal/pelvic CT/MRI (assess for vascular invasion) with IV contrast
- Chest CT (HR-contrast)
- Cholangiography
- Consider CEA
- Consider CA 19-9

**LFTs**
- Consider endoscopic ultrasound (EUS) after surgical consultation
- Consider serum IgG4 to rule out autoimmune cholangitis

#### Workup
- **Unresectable**
  - Biliary drainage, if indicated
  - Biopsy (only after determining transplant status)
  - MSI/MMR testing
  - Consider molecular testing
  - Consider referral to transplant center

- **Resectable**
  - Surgical exploration
  - Consider laparoscopic staging
  - Consider preoperative biliary drainage
  - Multidisciplinary review

#### Primary Treatment
- **Unresectable, see above**

- **Resectable**
  - Resection
  - **Unresectable**
    - EBRT with concurrent fluoropyrimidine
  - Best supportive care

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1. A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/albumin-bound paclitaxel, capcitabine/cisplatin, capcitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting.

2. There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH, Palliative and postoperative chemotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954.)

3. A phase III trial supporting carboplatin/paclitaxel is ongoing. (Parikh RB, Glynn RJ, Gandara DR, et al. A phase III trial comparing gemcitabine plus carboplatin with gemcitabine alone in previously untreated patients with advanced biliary tract cancer. Proc ASCO 2011;20:1504.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/albumin-bound paclitaxel, capcitabine/cisplatin, capcitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting.

See Principles of Imaging (EXTRA-A).

4. Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC) are used more for therapeutic intervention.

5. CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.

6. Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.

7. Unresectable perihilar hilar cholangiocarcinomas that measure ≤3 cm in radial diameter, with the absence of intrapancreatic or extrahepatic metastases and without nodal disease, may be considered for liver transplantation at a transplant center that has an UNOS-approved protocol for transplantation of cholangiocarcinoma.

See Principles of Surgery (EXTRA-B).

8. Consider biliary drainage for patients with jaundice prior to instituting chemotherapy.

9. Consider baseline CA 19-9 after biliary decompression.

10. Surgery may be performed when index of suspicion is high, biopsy is not required.
NCCN Guidelines Version 2.2019
Extrahepatic Cholangiocarcinoma

TREATMENT

- Observe
- Fluoropyrimidine chemoradiation
- Fluoropyrimidine-based or gemcitabine-based chemotherapy
- Clinical trial

SURVEILLANCE

Consider imaging every 6 mo for 2 y if clinically indicated, then annually up to 5 years

- Fluoropyrimidine-based chemoradiation
- Fluoropyrimidine-based or gemcitabine-based chemotherapy
- Clinical trial

Resected gross residual disease (R2)

See treatment for unresectable disease (EXTRA-1)

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Evidence Supporting Role of Radiotherapy in Biliary Tract Carcinomas

**SEER Database**
**Adjuvant RT for Extrahepatic Cholangiocarcinoma**

- **1988-2003** (4758 patients): Significant difference in overall survival between Surgery +RT vs Surgery alone (p<0.001) & between RT/Surgery/both vs none (p<0.001)


- **1973-2003** (2323 patients): Adjuvant RT is not associated with any improvement in OS/DFS.

Predictive factors for prognosis of hilar cholangiocarcinoma: Postresection radiotherapy improves survival

Q. Cheng, X. Luo, B. Zhang, X. Jiang, B. Yi, M. Wu

Abstract

Aims
Several studies have analyzed the determinants of long-term survival in hilar cholangiocarcinoma (HCCA) patients, but the majority of these have not speculated adjuvant therapy on prognosis. We conduct this study to identify potential predictive factors for prognosis of HCCA focusing on aspects dealing with adjuvant therapy.

Patients and methods
Data from 75 consecutive HCCA patients undergoing surgical resection with curative intent were recorded prospectively. The survivals of patients were comparable with respect to different factors followed by a univariate and multivariate analysis.
Chemoradiotherapy Versus Chemotherapy Alone for Unresected Nonmetastatic Gallbladder Cancer: National Practice Patterns and Outcomes.

Verma V1, Surkar SM2, Brooks ED3, Simone CB 2nd4, Lin C1.

Abstract

Purpose: Current guidelines recommend chemotherapy (CT) with or without radiotherapy for unresected nonmetastatic gallbladder cancer (GC), with little consensus. However, several small-volume, single-institution studies have documented the efficacy of local therapy for this population. This is the largest study to date evaluating outcomes of chemoradiotherapy (CRT) versus CT alone in unresected nonmetastatic GC. Methods: The National Cancer Database was queried for primary GC cases (2004-2013) receiving CT alone or CRT. Patients receiving resection or lack of CT were excluded, as were those with metastatic disease or unknown M classification. Logistic regression analysis ascertained factors associated with CRT delivery. Kaplan-Meier analysis evaluated overall survival (OS) between both cohorts. Cox proportional hazards modeling determined variables associated with OS. Results: In total, 1,199 patients were analyzed (CRT: n=327, 27%; CT: n=872, 73%). Groups were evenly balanced, with no factor on multivariate logistic regression analysis statistically predicting for receipt of a particular paradigm. Median OS in the CRT and CT groups was 12.9 versus 7.8 months, respectively (P=.001). On multivariate analysis, OS was associated with age and years of treatment (P=.001 each). Notably, receipt of CRT independently predicted for improved OS (P=.001). Conclusions: CRT, compared with CT alone, was independently associated with improved survival in unresected nonmetastatic GC. Although causation is not implied, these results support the necessity for prospective CRT evaluation.

Copyright © 2018 by the National Comprehensive Cancer Network.
Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience.
Czito BG¹, Hurwitz HI, Clough RW, Tyler DS, Morse MA, Clary BM, Pappas TN, Fernando NH, Willett CG.

➤ PURPOSE: Primary adenocarcinoma of the gallbladder is a rare malignancy. To better define the role of adjuvant radiation therapy and chemotherapy, a retrospective analysis of the outcome of patients undergoing surgery and adjuvant therapy was undertaken.

➤ METHODS AND MATERIALS: Twenty-two patients with primary and nonmetastatic gallbladder cancer were treated with radiation therapy after surgical resection. Median radiation dose was 45 Gy. Eighteen patients received concurrent 5-fluorouracil (5-FU) chemotherapy. Median follow-up was 1.7 years in all patients and 3.9 years in survivors.

➤ RESULTS: The 5-year actuarial overall survival, disease-free survival, metastases-free survival, and local-regional control of all 22 patients were 37%, 33%, 36%, and 59%, respectively. Median survival for all patients was 1.9 years.

➤ CONCLUSION: Our series suggests that an approach of radical resection followed by external-beam radiation therapy with radiosensitizing 5-FU in patients with locally advanced, nonmetastatic carcinoma of the gallbladder may improve survival. This regimen should be considered in patients with resectable gallbladder carcinoma.
NRG GI-001 Phase III Trial (unresectable CC)

**Unresectable Cholangiocarcinoma**
- liver confined
- no cirrhosis or CPC A
- up to 2 satellite lesions
- $12\text{ cm}$ or less

**Stratify:**
- Largest tumor $> 6\text{ cm}$
- satellite y/n

**Liver Directed Radiation Therapy**
Followed by maintenance Gem/Cis x 4

**Gem/Cis x 4**

**Re-staging AND Randomization**
after cycle 3
Radiation Planning
during cycle 4

**Gem/Cis x 4**
CONTOURING
RT Contouring Guidelines in Hepatic Cholangiocarcinoma

- Conventional radiotherapy for unresectable cases covers the gross tumour volume (GTV) with a 1.0-cm margin for CTV.

- Niska et al., assessed if the GTV varies between various phases of multiphasic CT imaging in the case of IHCC. The results showed that the IHCC lesions were best identified on the portal venous phase in 64% and the arterial phase in 29% of the cases.

Practice Radiat Oncol 2016 Jan-Feb;6(1):e9-16.
An atlas for clinical target volume definition, including elective nodal irradiation in definitive radiotherapy of biliary cancer

SILVIA BISELLO¹, MATTEO RENZULLI², MILLY BUWENGE¹, LUCIA CALCULLI², GIUSEPPINA SALLUSTIO³, GABRIELLA MACCHIA⁴, FRANCESCO DEODATO⁴, GIANCARLO MATTIUCCI⁵, SILVIA CAMMELLI¹, ALESSANDRA ARCELLI¹, LUCIA GIACCHERINI¹, FRANCESCO CELLINI⁵, GIOVANNI BRANDI⁶, SARA GUERRI², SAVINO CILLA⁷, RITA GOLFIERI², LORENZO FUCCO⁸, ALESSIO G. MORGANTI⁹ and ALESSANDRA GUIDO¹⁰

¹Radiation Oncology Unit, Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital; ²Radiology Unit, Department of Diagnostic and Preventive Medicine, S. Orsola-Malpighi Hospital, I-40138 Bologna; ³Radiology Unit; ⁴Radiation Oncology Unit, Catholic University of The Sacred Heart, I-86100 Campobasso; ⁵Radiation Oncology Department, Sacred Heart Catholic University, I-00168 Rome; ⁶Department of Experimental, Diagnostic and Specialty Medicine, ‘L. e. A. Seragnoli’ Institute of Hematology and Medical Oncology, S. Orsola-Malpighi Hospital, I-40138 Bologna; ⁷Medical Physics Unit ‘Giovanni Paolo II’ Foundation, Catholic University of the Sacred Heart, I-86100 Campobasso; ⁸Department of Medical and Surgical Sciences, University of Bologna, I-40138 Bologna, Italy

Received June 7, 2018; Accepted October 31, 2018
RTOG contouring guidelines for adjuvant RT

CTV must include:

1. **Post-operative bed**
   - Based on location of initial tumor from pre-operative imaging and pathology reports

2. **Anastomoses**
   - Pancreaticojejunostomy (PJ)
   - Choledochal or hepaticojejunostomy

3. **Abdominal nodal regions**
   - Peripancreatic
   - Celiac
   - Superior mesenteric
   - Porta hepatis
   - Para-aortic
<table>
<thead>
<tr>
<th>Delineation type</th>
<th>JSHBPS classification</th>
<th>Recommended margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor delineation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>-</td>
<td>GTV + 10 mm radially</td>
</tr>
<tr>
<td>Lymph node group, nodes delineation</td>
<td></td>
<td></td>
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<tr>
<td>Hepatoduodenal ligament lymph nodes</td>
<td>12</td>
<td>10 mm margin around the segment of portal vein from the confluence between the right and left hepatic ducts and the upper border of the pancreas</td>
</tr>
<tr>
<td>Common hepatic artery lymph nodes</td>
<td>8</td>
<td>10 mm margin around the common hepatic artery</td>
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<tr>
<td>Para-aortic lymph nodes</td>
<td>16</td>
<td>10 mm margin around the abdominal aorta, from the diaphragmatic aortic hiatus to the upper border of the origin of the inferior mesenteric artery</td>
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<tr>
<td>Posterior pancreaticoduodenal lymph nodes</td>
<td>13</td>
<td>10 mm around the posterior pancreaticoduodenal artery</td>
</tr>
<tr>
<td>Left gastric artery lymph nodes</td>
<td>7</td>
<td>10 mm around the trunk of the left gastric artery</td>
</tr>
<tr>
<td>Lesser gastric curvature lymph nodes</td>
<td>3</td>
<td>The area around the lesser curvature of the stomach</td>
</tr>
<tr>
<td>Right paracardial lymph nodes</td>
<td>1</td>
<td>The narrowed anatomic space identified between gastric cardia and the liver, extending posteriorly to the aorta and inferiorly to the lesser curvature LNs</td>
</tr>
<tr>
<td>Left paracardial lymph nodes</td>
<td>2</td>
<td>The anatomic space defined medially by the gastric fundus, anteromedially by the visceral peritoneum, posteriorly by the spleen, superiorly by the hemi diaphragm, and inferiorly by the great curvature LNs</td>
</tr>
</tbody>
</table>

Lymph node nomenclature is based on the 3rd English Edition of Classification of biliary tract cancers established by the JSHBPS. The anatomical structures of interest and the abdominal vessels of reference were identified for each lymph node region. JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; CTV, clinical target volume; GTV, gross tumor volume.
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<tr>
<td>Peri-choledochal nodes</td>
<td>12b2</td>
<td><strong>10 mm margin around the choledochal duct</strong></td>
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Table III. CTV for gallbladder carcinoma.

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<td>-</td>
<td>GTV + 25 mm radially in hepatic direction + gallbladder residual volume</td>
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<td>Cystic duct lymph nodes</td>
<td>12c</td>
<td>10 mm around the cystic duct</td>
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</tbody>
</table>

Lymph node nomenclature is based on the 3rd English Edition of Classification of biliary tract cancers established by the JSHBPS. The anatomical structures of interest and the abdominal vessels of reference were identified for each lymph node region. JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; CTV, clinical target volume; GTV, gross tumor volume.
Contouring

- Contour both target and normal structures on EACH breath hold scan; As you flip through scans, add but do NOT subtract from your volume. The goal is to cover everywhere the tumor or normal structures might be.
- If dose escalating, will contour avoidance structure (PRV) subtracted from high dose region (Right).

Tao et al; 2016
Radiation Simulation

- Fiducials placed for daily imaging
- Upper Vaclock with arms overhead
- NPO 3 hours prior to simulation and treatment (to standardize duodenal and gastric filling)
- Multi-phase contrast-enhanced 4DCT simulation with 2-3mm slices; Free breathing scan and 3-5 Breath hold scans during contrast administration
SBRT Plan

DVH constraints to these structures: bowel: 24 Gy in three fractions to no more than a third of the circumference of the bowel with a maximum point dose of 30 Gy in 3 fractions;

Liver: at least 750 cc of healthy Liver $V_{21} = <30\%$ and $V_{15} < 50\%$.

3 daily fractions were typically used,
### OAR Dose Constraints

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>$D_{\text{max}} &lt; 30 \text{ Gy}$; $D_{\text{max}} &lt; 45 \text{ Gy}$</td>
</tr>
<tr>
<td>Heart</td>
<td>$V_{40} \text{ Gy} &lt; 10%$</td>
</tr>
<tr>
<td>Liver-GTV</td>
<td>$700\text{cc} &lt; 24 \text{ Gy}$; $\text{Mean} &lt; 24 \text{ Gy}$</td>
</tr>
<tr>
<td>Kidneys</td>
<td>$V_{20} &lt; 33%$ for each</td>
</tr>
<tr>
<td>Stomach</td>
<td>$D_{\text{max}} &lt; 45 \text{ Gy}$</td>
</tr>
<tr>
<td>Duodenum</td>
<td>$D_{\text{max}} &lt; 45 \text{ Gy}$</td>
</tr>
<tr>
<td>Esophagus</td>
<td>$D_{\text{max}} &lt; 45 \text{ Gy}$</td>
</tr>
<tr>
<td>Common/ Main Bile duct</td>
<td>$D_{\text{max}} &lt; 70\text{Gy}$</td>
</tr>
<tr>
<td>Chest Wall</td>
<td>$V_{40} &lt; 150\text{cc}$</td>
</tr>
</tbody>
</table>
2D and 3D Planning of ILBT
Contouring Guidelines in ILBT

- GTV is defined as any visible tumor by CT and/or MRI.
- CTV = 1-1.5 cm margin to the GTV, especially along the bile duct and to the target depth
- PTV = 0.5 to 1 cm to the CTV. 1 to 3 mm slice thickness is recommended, with contrast medium
- Not possible to treat nodes.
- PTV = defined by adding in the longitudinal direction a margin of 1 cm both, distally and proximally to the CTV.
- The dose-limiting surrounding organs (both for EBRT and BT) include the liver, pancreas, duodenum, small bowel, stomach, and spinal cord.
Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis.

Yoshioka Y1, Ogawa K2, Oikawa H3, Onishi H4, Kanesaka N5, Tamamoto T6, Kosugi T7, Hatano K8, Kobayashi M9, Ito Y10, Takayama M11, Takemoto M12, Karasawa K13, Nagakura H14, Imai M15, Kosaka Y16, Yamazaki H17, Isohashi F1, Nemoto K18, Nishimura Y19; Japanese Radiation Oncology Study Group (JROSG).

Author information

Abstract

PURPOSE: To determine whether adding intraluminal brachytherapy (ILBT) to definitive radiation therapy (RT) for unresectable biliary tract cancer has a positive impact on survival outcome.

METHODS AND MATERIALS: The original cohort comprised 209 patients, including 153 who underwent external beam RT (EBRT) alone and 56 who received both ILBT and EBRT. By matching propensity scores, 56 pairs (112 patients) consisting of 1 patient with and 1 patient without ILBT were selected. They were well balanced in terms of sex, age, performance status, clinical stage, jaundice, and addition of chemotherapy. The impact of ILBT on overall survival (OS), disease-specific survival (DSS), and local control (LC) was investigated.

RESULTS: The 2-year OS rates were 31% for the ILBT+ group and 40% for the ILBT- group (P=.862). The 2-year DSS rates were 42% for the ILBT+ group and 41% for the ILBT- group (P=.288). The 2-year LC rates were 65% for the ILBT+ group and 35% for the ILBT-group (P=.094). Three of the 4 sensitivity analyses showed a significantly better LC for the ILBT+ group (P=.010, .025, .049), and another showed a marginally better LC (P=.068), and none of the sensitivity analyses showed any statistically significant differences in OS or DSS.

CONCLUSIONS: In the treatment for unresectable biliary tract cancer, the addition of ILBT to RT has no impact on OS or DSS but is associated with better LC. Therefore, the role of ILBT should be addressed by other measures than survival benefit, for example, by less toxicity, prolonged biliary tract patency decreasing the need for further palliative interventions, or patient quality of life.
Can We Dose Escalate??

- How far is tumor from gastrointestinal mucosa? Would a 5mm expansion on gastrointestinal mucosa still allow you to cover >50% of the tumor in the high dose region?
- How big is tumor and how is patient’s overall liver function, and therefore how much normal liver will you cover with high dose? Remember, a small volume of normal liver can tolerate a high dose, but a high volume of normal liver cannot tolerate even a low dose
- 700cc <24Gy; mean dose <24Gy for CP class A
- 700cc <20Gy; mean dose <20Gy for CP class B
# The Aftermaths

## Radiation Induced Liver Disease (RILD)

### Classic RILD
- Occurs 2-3 months post-RT
- Associated with hepatomegaly, ascites +/- jaundice
- Due to veno-occlusive disease
- Seen in healthy livers

### Non-classic RILD
- Occurs 1wk-3 months post-RT
- Seen in cirrhotic livers
- Rise of SGOT/SGPT with worsening of liver function
- Without features of classic RILD

**Treatment:** Once established, RILD is difficult to manage and is invariably fatal in the absence of transplant therapy. Medical management with diuretics, etc is only symptomatic.
5 Year Survival of GBC and Cholangiocarcinoma

Table 5

Distribution and Survival for Each Stage (Nevin Stage of Gallbladder Cancer)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage of Patients at Presentation</th>
<th>1-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6.5%</td>
<td>83%</td>
<td>59%</td>
</tr>
<tr>
<td>II</td>
<td>9%</td>
<td>71%</td>
<td>40%</td>
</tr>
<tr>
<td>III</td>
<td>18%</td>
<td>33%</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>11%</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>V</td>
<td>55.5%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adapted from Gagner et al.29

INTRAHEPATIC

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>15%</td>
</tr>
<tr>
<td>Regional</td>
<td>6%</td>
</tr>
<tr>
<td>Distant</td>
<td>2%</td>
</tr>
</tbody>
</table>

EXTRAHEPATIC

<table>
<thead>
<tr>
<th>Stage</th>
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</table>

American Cancer Society. Bile Duct Cancer (Cholangiocarcinoma). 2014
Future Directions

- A Phase III trial aims to compare adjuvant CRT vs chemotherapy in EHCC and gall bladder cancer (NCT02798510) evaluating induction gemcitabine followed by 5-FU-based CCRT and maintenance capecitabine prior to LT.

- Need to test sequencing of adjuvant CCRT and chemotherapy in Phase III trials for EHCC and IHCC (NCT02798510)

- Cholangiocarcinoma - radiosensitization with oncolytic viral therapy (NV1023 virus strain).
“You cannot hope to build a better world without improving the individuals. To that end, each of us must work for our own improvement.”

Marie Curie