This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Gallbladder Cancer
GI Practice Guideline

Background/Incidence

• Most common biliary malignancy. High incidence in Chile, other South American countries, SW U.S. Native Americans – also in India, Pakistan, Korea, Japan, Israel. M:F = 1:3

• Risk factors:
  • gallstones (but incidence in patients with gallstones = 0.5-3% only), calcified gallbladder, gallbladder polyps, anomalous pancreatic duct drainage (esp. in Japanese pts), infections such as S. typhi, ?H.P.
  • Medications: INH, methyldopa
  • Exposures: paper, oil workers; Radon

• Presentation
  • often initially like gallstone pain, then anorexia, malaise, wt loss. Later: obstructive jaundice (esp. if stone and Mirizzi syndrome [hepatic duct compression]), ascites, acanthosis nigricans.

• Histological subtypes (%)
  • Adenocarcinoma (76)
  • Papillary (6) – best prognosis
  • Mucinous (5)
  • Adenosquamous (4)
  • Squamous (2)
  • Small cell (0.5)
  • Not otherwise specified (8)
### TNM Staging

**Definition of TNM**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or muscle layer</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades muscle layer</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extrahepatic bile ducts.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades main portal vein or hepatic artery, or invades multiple extrahepatic organs or structures.</td>
</tr>
</tbody>
</table>

**Regional lymph nodes (N)**

| N0                        | No regional lymph node metastasis |
| N1                        | Regional lymph node metastasis |

**Distant metastasis (M)**

| M0                        | No distant metastasis |
| M1                        | Distant metastasis |

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Gallbladder Cancer - GI Practice Guideline
Approved September 2006

Presentation

• Mass on imaging
• Incidental finding during cholecystectomy
• Incidental finding on pathology review of resected gallbladder

T1a tumour: observe
No need for LRCP referral

Other stage, or unknown

Required Work-up

• CT abdomen / pelvis
• Liver profile, CBC, Creatinine (blood work)
• CXR
• Biopsy/path report

Surgical Assessment

Surgical opinion: Unresectable or residual disease

Extensive metastasis (clearly unresectable)

• No need for surgical assessment unless for relief of obstruction/jaundice

LRCP referral
MO + RO

Palliative Rx

• Local therapy
• Chemoradiation
• Intra-arterial chemotherapy

• Systemic therapy
• Trial
• Epirubicin/Cisplatin/5FU chemotherapy
• Gemcitabine/Capecitabine chemotherapy

Surgical opinion resectable, or cholecystectomy already done

• Cholecystectomy (if not already done) + local hepatic resection + lymphadenectomy with or without bile duct excision.

• If laparoscopic surgery done: consider port site resection re:

Potentially curative surgery

LRCP referral
MO + RO

Adjuvant Rx

• Consider adjuvant therapy if more advanced than T1 N0, however not standard currently
• Clinical trial
• Chemotherapy (5FU or gemcitabine-based)
• Chemoradiation (5FU/radiation) especially if positive margins
• Observation. Followup q3-6 months with history/physical. ?CT q6months if potential re-resection candidate

LRCP referral
MO + RO

Other stage, or unknown

Required Work-up

• CT abdomen / pelvis
• Liver profile, CBC, Creatinine (blood work)
• CXR
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Surgical Assessment

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• Observation. Followup q3-6 months with history/physical. ?CT q6months if potential re-resection candidate
References

1. **Chemotherapy**: Only one randomized trial: Takada et al Cancer 2002 Oct 15;95(8):1685-95 also including pancreatic and bile duct cancer; Mitomycin-C, then 5FU infusion then oral 5FU: 26 vs 14 % 5YS. **Chemoradiation**: Conflicting historical series. Most positive Kresl et al Int J Radiat Oncol Biol Phys 2002 Jan 1;52(1):167-75, 64% 5YS with adj 5FU/radiation. Need to individualize in discussion with patient. Options as indicated.


4. Systemic therapy: Epirubicin/Cisplatin/ 5FU is standard at LRCP. Evolving evidence favours gemcitabine or capecitabine combinations however. See Table 1 below

5. Gemcitabine/Capecitabine regimen not yet funded.

6. No evidence to indicate that detecting asymptomatic recurrences translates into prolonged survival

### Table 1. Palliative Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>N</th>
<th>RR (%)</th>
<th>Median Surv. (Mos)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>Patt et al J Clin Oncol 1996 Aug;14(8):2311-5</td>
<td>32</td>
<td>0-34</td>
<td>~6</td>
<td>34% RR if interferon added</td>
</tr>
<tr>
<td>PIAF (Cisplatin, interferon, doxorubicin, 5FU)</td>
<td>Patt et al Clin Cancer Res 2001 Nov;7(11):3375-80</td>
<td>19</td>
<td>35</td>
<td>11.5</td>
<td>Toxicity significant</td>
</tr>
<tr>
<td>Epirubicin 60mg/m² q21d + Cisplatin 50mg/m² q21d + Fluorouracil 200mg/m² daily continuous infusion</td>
<td>Ellis et al Eur J Cancer 1995 Sep;31A(10):1594-8</td>
<td>20</td>
<td>19-40</td>
<td>~9</td>
<td>Used at LRCP. Less toxic than Leukovorin/ etoposide/ 5FU</td>
</tr>
<tr>
<td>Docetaxel 100 mg/m² q21 days</td>
<td>Papakostas et al Eur J Cancer 2001 Oct;37(15):1833-8</td>
<td>25</td>
<td>20</td>
<td></td>
<td>Small series (25 pts), 56% severe toxicity</td>
</tr>
<tr>
<td>Gemcitabine (1000 mg/m² day 1) and oxaliplatin (100 mg/m² day 2) q14 d</td>
<td>Andre et al Ann Oncol 2004 Sep;15(9):1339-43</td>
<td>33</td>
<td>22-36</td>
<td>7.6 – 14.3</td>
<td>Range: poor PS – good PS.</td>
</tr>
<tr>
<td>Gemcitabine (1000 mg/m² days 1 and 8, and cisplatin (70 mg /m² day 1, q21d)</td>
<td>Doval et al Br J Cancer 2004 Apr 19;90(8):1516-20, others</td>
<td>30</td>
<td>25-64</td>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>Capecitabine 650 mg/m² bid x 14 days/21, gemcitabine 1,000 mg/m² d1 and 8</td>
<td>Knox et al, J Clin Oncol 2005 Apr 1;23(10):2332-8</td>
<td>21</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine alone</td>
<td>Patt et al Cancer 2004 Aug 1;101(3):578-86</td>
<td>8</td>
<td>50</td>
<td></td>
<td>Early data suggesting some benefit</td>
</tr>
<tr>
<td>Capecitabine (1000 mg/m² twice daily on days 1 to 14) and oxaliplatin (130 mg/m²)</td>
<td>Nehls et al, Abstract, Proc Am Soc Clin Oncol 2003; 22:280a</td>
<td>29</td>
<td>23</td>
<td>Includes cholangiocarcinoma patients</td>
<td></td>
</tr>
</tbody>
</table>
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