The following material relates to the BILCAP trial. This is in place of a journal article:


2) Pages 2-5 contain the abstract of the trial.

3) Pages 6-11 contain some slides presented at ASCO of the trial.
Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study.


GASTROINTESTINAL (NONCOLORECTAL) CANCER

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

DOI:
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WE RECOMMEND

Post-Surgery Capecitabine ‘Should Become Standard of Care’ in Biliary Tract Cancers
**Abstract**

**Background:** Despite improvements in multidisciplinary management, BTC has a poor outcome. Approximately 20% of cases are suitable for surgical resection with a 5 year survival of < 10%. BILCAP aimed to determine whether capecitabine (Cape) improves overall survival (OS) compared to observation (Obs) following radical surgery. **Methods:** Patients with completely-resected cholangiocarcinoma (CCA) or gallbladder cancer (including liver and pancreatic resection, as appropriate), with adequate biliary drainage, no ongoing infection, adequate renal, haematological and liver function, and ECOG PS ≤2, were randomized 1:1 to Cape (1250 mg/m² D1-14 every 21 days, for 8 cycles) or Obs. Randomization was minimized on tumor site, resection status, ECOG PS and surgical center. The primary outcome was OS in the intention to treat.
treat (ITT) population. 410 patients were needed to detect a hazard ratio (HR) of 0.69 (2-sided $\alpha = 0.05$ and 80% power). HR was estimated by Cox survival model with adjustment for the minimization factors. Primary analysis performed with at least 24 months (m) follow-up. **Results:**

447 participants were randomized to Cape (n = 223) or Obs (n = 224) from 44 UK sites between 2006-2014. Median age was 63y (IQR 55, 69) and 201 (45%), 232 (52%), and 14 (3%) patients were ECOG PS 0, 1 and 2 respectively. Primary site: 84 (19%) intrahepatic, 128 (28%) hilar, 156 (35%) extrahepatic CCA and 79 (18%) muscle-invasive gallbladder cancers. Resection margins: R0 in 279 (62%) and R1 in 168 (38%); 207 (46%) were node-negative. Follow up was at least 36m in > 80% of surviving patients. By ITT analysis ($n = 447$), median OS was 51m (95%CI 35, 59) for Cape and 36m (95%CI 30, 45) for Obs, HR 0.80 (95%CI 0.63, 1.04; $p = 0.097$). Sensitivity analyses with adjustment for nodal status, grade of disease and gender indicated HR 0.71 (95%CI 0.55, 0.92 $p < 0.01$). In the per-protocol analysis (Cape n = 210, Obs n = 220) median OS was 53m (95%CI 40, NR) for Cape and 36m (95%CI 30, 44) for Obs, HR 0.75 (95%CI 0.58, 0.97; $p = 0.028$). Median RFS (ITT) was 25m (95%CI 19, 37) for Cape and 18m (95%CI 13, 28) for Obs. Grade 3-4 toxicity was less than anticipated. **Conclusions:** Cape improves OS in BTC when used as adjuvant and should become standard of care. **Clinical trial information:** ISRCTN72785446.
Adjuvant capecitabine for biliary tract cancer: 
The BILCAP randomized study

John Primrose, Richard Fox, Juan Valle, Daniel Palmer, Raj Prasad, Darius Mirza, Alan Anthoney, Philippa Corrie, Stephen Falk, Harpreet Wasan, Paul Ross, Lucy Wall, Jonathan Wadsley, Jeffry Evans, Deborah Stocken, Raaj Praseedom, David Cunningham, James Garden, Clive Stubbs and John Bridgewater on behalf of the BILCAP investigators
Patients with macroscopically resected biliary tract cancer
ECOG Performance Status < 2
Liver and pancreatic resection

Control Arm
Observation
205 Patients

Treatment Arm
Capecitabine: 8 cycles 1250mg/m²
bd D1-14 of 21
205 Patients

Primary endpoint: Overall Survival

Secondary endpoints: Relapse free survival, toxicity, QoL and health economics

Statistics: To detect a 31% reduction in risk (HR 0.69) with 2-sided significance level of 5% and 80% power, required 410 patients (234 events)
Participant flow

Presented for eligibility, n=753
Excluded, n=306
  - Ineligible n=153
  - Patient declined trial n=133
  - Other n=20

Randomized, n=447

Observation, n=224
  - Premature withdrawal from study, n=6
    - Disease related, n=1
    - Patient choice, n=5
  - Lost to follow-up, n=3

Capecitabine, n=223
  - Premature withdrawal from study, n=9
    - Disease related, n=2
    - Patient choice, n=7
  - Lost to follow-up, n=4

Primary analysis population, n=224
Primary analysis population, n=223

First centre opened March 2006
First patient recruited July 2006
Accrual completion December 2014
Primary analysis (commenced) February 2017

Withdrawal from trial treatment, n=14
  - Disease related, n=2
  - Patient choice, n=6
  - Toxicity, n=4
  - Other, n=2
Overall Survival (ITT)

>80% of patients followed up for 36 months

Time from randomisation (months)

Proportion event free

Capecitabine

Observation

Median OS months (95%CI)

Capecitabine 51.1 (34.6, 59.1)

Observation 36.4 (29.7, 44.5)

HR (95%CI)

Capecitabine HR 0.81 (0.63, 1.04) p=0.097

Sensitivity analyses adjusting prognosticators $^5$

HR 0.70 95%CI (0.55, 0.91) p=0.007

$^5$Nodal status, Disease Grade, Gender
The safety population was conditional on receiving capecitabine (n=213).

There were no deaths related to chemotherapy.

<table>
<thead>
<tr>
<th>Toxicity type</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>Plantar palmar erythrema</td>
<td>44 (20.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

- Capecitabine compared to surveillance improves median overall survival in resected biliary tract cancer from 36 to 53 months
- The toxicities were modest
- Capecitabine should become the standard of care for patients following curative resection of biliary tract cancer