Cholecystectomy:
Colon cancer, symptoms and QOL

Mr. Val Usatoff
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Cholecystectomy: and the risk of colon cancer

- Observation
  - Capron JP, Delamarre J
Cholecystectomy: colon cancer - the theory

- Theory
  - Cholecystectomy changes bile composition and flow
  - Increased bacterial degradation of bile acids to form secondary bile acids
  - Secondary bile acids carcinogenic in animal models
  - Higher levels of undigested fat in stool after cholecystectomy
  - Higher concentration of bile acids in faeces of colon cancer patients than non-cancer patients

Cholecystectomy: and the risk of colon cancer

- If true, we should observe…
  - More small bowel cancer
  - More right sided colonic cancers
  - More adenomas
- Bowel cancer common - 28,000/yr in UK
- Cholecystectomy common - 50,000/yr in UK
- Answer should be simple to derive……
Cholecystectomy: and the risk of colon cancer

- Compounding factors - clinical
  - Overlapping symptoms
  - Common risk factors - Diet, BMI
  - Abnormal bile acid metabolism may cause GS and cancers
  - “Functional cholecystectomy” ie gallstones
  - Screening
  - Surveillance after cholecystectomy

Jorgensen et al. Gallstones and colorectal cancer: there is a relationship, but it is hardly due to cholecystectomy. Dis Colon Rectum 1992;35:24
Cholecystectomy: and the risk of colon cancer

- Compounding factors - study design
  - Duration of follow-up
  - Concurrent diagnosis and resection
  - Hospital based vs population based studies
  - Lower prevalence of cholecystectomy in males
  - Null observations unlikely to be published

Jorgensen et al. Gallstones and colorectal cancer: there is a relationship, but it is hardly due to cholecystectomy. Dis Colon Rectum 1992;35:24
Cholecystectomy: and the risk of colonic adenomas

- 3 studies show **positive** association
- 2 study found **no** association
  - Small numbers
  - Poorly studied
  - Inconclusive

Cholecystectomy: and the risk of small bowel cancer

<table>
<thead>
<tr>
<th>Location of the intestinal tumor</th>
<th>Observed no. of cases</th>
<th>Cholecystectomy only SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal small bowel (adenocarcinomas)</td>
<td>68</td>
<td>1.77 (1.37–2.24)</td>
</tr>
<tr>
<td>Distal small bowel (carcinoids)</td>
<td>98</td>
<td>1.71 (1.39–2.08)</td>
</tr>
<tr>
<td>Cecum and ascending colon</td>
<td>861</td>
<td>1.16 (1.08–1.24)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>290</td>
<td>1.05 (0.93–1.17)</td>
</tr>
<tr>
<td>Descending colon</td>
<td>74</td>
<td>0.84 (0.66–1.05)</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>644</td>
<td>1.00 (0.92–1.08)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1172</td>
<td>0.95 (0.89–1.00)</td>
</tr>
</tbody>
</table>

Cholecystectomy: and the risk of colon cancer

- 13,822 autopsies - 1981
  - RR of cancer after cholecystectomy 1.59 (1.01-2.55)
    - (95% confidence interval)
  - Higher in right colon (RR 3.0)
  - Similar risk if un-operated GS

- 8563 autopsies - 1995
  - RR of cancer after cholecystectomy 0.70 (0.23-2.04)
  - RR with presence of GS 0.93 (0.58-1.48)
  - Failed to support association

Mercer et al. The relationship between cholecystectomy, unoperated GS and colorectal cancer. A necropsy study. Scan J Gastro 1995:30;1017
Cholecystectomy: and the risk of colon cancer

- Large cohort studies
  - Uppsala Health Care region, Sweden - 1993
  - 60,000 pts with cholecystectomy
  - Almost complete f/up 23 yrs
  - Overall no increased risk RR 0.99 (0.92-1.07)
    - Women increased risk RR 1.24 (1.03-1.48) >15yrs

Ekborn et al. Cholecystectomy and colorectal cancer. Gastroenterology 1993:105;142
Cholecystectomy: and the risk of colon cancer

- Large cohort studies
  - General Practice Research Data Base UK - 2005
    - 8.2 million pts, 55,960 cholecystectomy and suitable
    - Overall increased RR 1.32 (1.16-1.48)
    - Increased risk men and women
    - Also increased risk for GS without cholecystectomy

- Criticism
  - No adjustment for risk factors
  - Site in colon not stated

Shao et al. Cholecystectomy and the risk of colorectal cancer. Am Gastroenterol 2005:100;1813
Cholecystectomy: and the risk of colon cancer

- Large cohort studies
  - Danish National Hospital Discharge Register - 1996
  - 42,098 gallstone patients, mean f/up 7.4yrs
  - Increased risk colon cancer
    - RR 1.07 (1.0-1.1)
    - No significant difference if analysed for...
      - Sex
      - Anatomical subsite
      - Duration of f/up
      - Obesity
      - Cholecystectomy

Cholecystectomy: and the risk of colon cancer

- Large cohort studies
  - Nurse Health Study Data USA - 2003
  - 85,184 women
    - smoking, wt, ht, physical activity, aspirin use, FHx, food habits
  - 16 yrs f/up (1,308,490 person yrs follow-up!)
  - Increased risk with GS or cholecystectomy
    - Overall- age adjusted and MVA - RR 1.21 (1.01-1.46)
    - Proximal colon RR1.36 (1.00-1.86)
    - Rectum RR1.64 (1.12-2.39)
  - Increased risk remains (GS or cholecystectomy) even after adjustment for known risk factors

### Cholecystectomy: and the risk of colon cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number</th>
<th>Overall RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uppsala</td>
<td>1993</td>
<td>60,000</td>
<td>0.99</td>
</tr>
<tr>
<td>GP UK</td>
<td>2005</td>
<td>55,960</td>
<td>1.32</td>
</tr>
<tr>
<td>Danish Hosp</td>
<td>1996</td>
<td>42,098</td>
<td>1.07</td>
</tr>
<tr>
<td>Nurse Health</td>
<td>2003</td>
<td>85,184</td>
<td>1.21</td>
</tr>
</tbody>
</table>
Cholecystectomy: and the risk of colon cancer

- Meta-analysis
  - Giovannucci et al. Gastroenterology 1993
    - Harvard Medical School, USA
  - Reid et al. Scand J Gastroenterol 1996
    - King’s College, UK

Giovannucci E et al. A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterology 1993; 105;130
Cholecystectomy: and the risk of colon cancer

- Giovannucci 1993
  - 60 studies identified
  - Selected - 5 cohort studies, 33 case control studies
  - Results
    - Overall - increased risk CRC - RR 1.22 (1.08-1.38)
      - Proximal > distal RR 1.88 (1.54-2.3) c/w 1.09 (0.93-1.27)
      - Higher in hosp vs pop’n RR 2.37 (1.90-2.95) c/w 1.33 (1.09-1.62)
    - Adenomas - increased risk - esp. women > 10yrs
    - Gallstones only - mixed results, small numbers
  - Criticised
    - Small studies, variable f/up, confounding factors not controlled
Cholecystectomy: and the risk of colon cancer

- Reid 1996
  - 95 studies identified, 35 selected
  - Increased risk of cancer
    - Overall RR 1.11(1.02-1.21)
    - Women RR 1.14(1.01-1.28)
    - Right sided RR 1.86(1.31-2.65)
  - Conclusion
    - Many biases not allowed for
    - Possible observed risk but very small for individual
Cholecystectomy: and the risk of colon cancer

**Conclusions**
- Positive association confirmed
  - Higher for proximal cancers
  - Causal vs indirect - debate continues
  - Individual risk very small
  - Not a reason not to have a cholecystectomy
  - Questions of follow-up not answered
  - Implications for consent?
Cholecystectomy: and long term symptom control

- Resolution of biliary pain
- Resolution of non-biliary pain
- Post Cholecystectomy Syndrome
- Can we predict bad outcomes?
Cholecystectomy: Questions often not addressed

- Gallstone specific symptoms elusive
  - What is Biliary colic?
  - What non-pain symptoms are related to GB/GS?
  - What does cholecystectomy cure?
  - What does cholecystectomy cause?
Cholecystectomy: problems with studies

- Comparative studies difficult
  - Definition of GB/GS symptoms
  - GI symptoms difficult to measure
  - Biased “fishing” for symptoms
  - Mostly middle-aged females with other GI Sx
    - “psychoneurotic middle-aged women”
  - Background occurrence of GI symptoms
  - Symptom substitution post operatively
  - Duration of follow-up
  - Placebo effect of surgery
  - Preop consent/info will effect outcome
  - Indications for cholecystectomy softening (28-60% increase)
Cholecystectomy: and long term symptom control

- What is Biliary Colic?
  - Various important attributes
    - Not true colic, rather rises to a plateau and rarely fluctuates in intensity.
    - Typically last from 1- several hours
    - Unusual to last <15min
    - Not usually postprandial, but often nocturnal onset
    - Often radiates to upper back
    - Accompanied by nausea and vomiting

Cholecystectomy: agreement on indications

- Indications for Cholecystectomy
  - Panel of surgeons c/w other specialists
    - Unable to agree on 40% of indications
  - Audit of 252 cholecystectomy operations
    - 44% of surgeons unable to reach agreement
  - A panel of nine specialists
    - Gastroenterologists less likely to recommend surgery than either surgeons or general physicians

Scott et al. Appropriateness of cholecystectomy in the UK - a consensus panel approach. Gut 1991;32;1066
Fraser et al. Indications for cholecystectomy: The results of a consensus panel approach. Quality Ass Health Care 1993;5;75
Cholecystectomy: symptoms and outcomes

- Measuring Success
  - Resolution(Cure) of pain
  - Resolution of non-pain symptoms
  - Onset on new non-pain symptoms

- Overall satisfaction - regardless of symptoms
  - Patient satisfaction
    - 77-94% satisfaction
    - Regardless of persistence of symptoms
    - Regardless of new symptoms developing
Cholecystectomy: and long term symptom control

- Typical biliary pain
  - Pooled result - cure 90%
  - Up to 34% have pain
- Acute cholecystitis
  - Better result

<table>
<thead>
<tr>
<th>Authors</th>
<th>Follow-up</th>
<th>Cure rate%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates - Gut 1984</td>
<td>1 year</td>
<td>73</td>
</tr>
<tr>
<td>Bates - Br J Surg 1991</td>
<td>1 year</td>
<td>66</td>
</tr>
<tr>
<td>Gilliland - SGO 1990</td>
<td>16-79 mo</td>
<td>79</td>
</tr>
<tr>
<td>Scriven - J R Coll Surg Edin 1993</td>
<td>1 yr</td>
<td>73</td>
</tr>
<tr>
<td>Plaisier - Am J Gastro 1994</td>
<td>3 mo</td>
<td>91</td>
</tr>
<tr>
<td>Fenster - Am J Surg 1995</td>
<td>3 mo</td>
<td>76</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>66-91%</td>
</tr>
</tbody>
</table>

Konsten et al. Long term follow-up after open cholecystectomy. Br J Surg 1993;80;100
Cholecystectomy: and long term symptom control

What about non-pain symptoms?
- Collectively “dyspeptic symptoms”

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Bloating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramping</td>
<td>Satiety</td>
</tr>
<tr>
<td>Flatulence</td>
<td>Reflux</td>
</tr>
<tr>
<td>Constipation</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Belching</td>
<td>Fatty food intolerance</td>
</tr>
</tbody>
</table>
Cholecystectomy: effective treatment for?

Cholecystectomy: and long term symptom control

- Non-pain symptoms
  - 60% have non-pain Sx pre-op
  - Pooled results ~ 50% persist/develop
  - i.e. - 50% resolve
  - Unpredictable

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<thead>
<tr>
<th>Authors</th>
<th>Follow-up</th>
<th>Cure rate%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flatulent dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates - Br J Surg 1991</td>
<td>1 yr</td>
<td>33</td>
</tr>
<tr>
<td>Ros - Gut 1987</td>
<td>2 yrs</td>
<td>52</td>
</tr>
<tr>
<td>Scriven - J R Coll Surg Edin 1993</td>
<td>1 yr</td>
<td>72</td>
</tr>
<tr>
<td>Plaisier - Am J Gastro 1994</td>
<td>6 mo</td>
<td>74</td>
</tr>
<tr>
<td>Rhind - BMJ 1968</td>
<td>1 yr</td>
<td>61</td>
</tr>
<tr>
<td>Johnson - Postgrad Med J 1971</td>
<td>3-42 mo</td>
<td>46</td>
</tr>
<tr>
<td>Fenster - Am J Surg 1995</td>
<td>3 mo</td>
<td>42</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>33-74%</td>
</tr>
</tbody>
</table>
Cholecystectomy: and long term symptom control

- Dyspeptic symptoms apparently cured ~50%
  - WHY?
    - Placebo
    - Removal of infected bile
    - Duodenogastric reflux of bile reduced
    - Delayed gastric emptying and chronic cholecystitis
    - Pain of surgery alters reporting threshold
    - Other treatments instituted
    - Patients dietary changes
    - Desire to report “good” results
Cholecystectomy: “flatulent dyspepsia”

- Flatulent dyspepsia
  - Equally common with or without gallstones
- Gui 1998
  - 92 pts, 31 month follow-up
  - Control group of surgical clinic pts
  - Post chole symptoms back to control levels

Cholecystectomy: persistent symptoms?

Cholecystectomy: persistent or new symptoms?

- Ure, Germany 1995
  - 468 pts, 19mo f-up
  - **Existing** pre-op symptoms
  - Left - persist
  - Right - cured

Cholecystectomy: what symptoms does it cause?

- Ure Germany 1995
  - 468 pts, 19mo f-up
  - Absent symptom pre-op
  - Left - appearance
  - Right - stayed absent

Cholecystectomy: long term symptom prediction

- Durations of symptoms prognostic indicator
  - Duration of problem
    - Symptoms >5 yrs - 43% cured
    - Symptoms <3 mo - 72% cured
  - Duration of pain episodes
    - Pain lasting hrs better than pain lasting days/weeks
  - Possible argument for early intervention

- Psychological vulnerability
  - Determined by questionnaire
  - Associated with poor outcome
  - Related to visceral hyperalgesia (sim Irr BS)

Borly et al. Preoperative prediction model of outcome after cholecystectomy for symptomatic gallstones. Scan J Gastro 1999:34;1144
Cholecystectomy: long term symptom prediction

- Predictors of “poor” outcome
  - Flatulent dyspepsia
  - Bloating
  - Long duration of symptoms
  - No previous episode of Acute Cholecystitis
  - Absence of thick walled GB
  - “Psychoneurotic middle aged females”
  - Psychiatric medications
  - Patient expectations
Cholecystectomy: and quality of life.

- Difficult area to study
- Few good QOL studies
- Overlapping symptoms
- Pre-existing symptoms
- Changes in diet/drug use
- Related to length of f/up
Cholecystectomy: and quality of life.

- 104 patients, prospective
  - GI symptom score - University Alabama
    - 16 GI complaints
      - frequency, severity, distressfulness
  - HRQOL survey - SF36
    - 8 domains - physical, social, vitality etc.

Cholecystectomy: and quality of life.

Cholecystectomy: and quality of life.

- Sig better after LC
  - Physical role activities
  - Bodily pain
  - Social function
- No change
  - Physical function
  - Perceived general health
  - Vitality
  - Emotional role activities
  - Mental health score

Cholecystectomy: and quality of life.

- 650 patients, prospective, 3 month follow-up
- SF-36 (8 domains) and GIQLI (5 domains)
- All pts independently assigned as:
  - (based on 414 indications)
  - appropriate
  - uncertain
  - inappropriate
- “Appropriate” pts did better
- Conservative approach for asymptomatic pts

Cholecystectomy: and quality of life.

- Symptomatic vs asymptomatic pts
  - i.e. Biliary colic as primary Sx
- GIQLI (36 criteria) at 4 months post op
- No sig diff in post op scores
- Sig improvement in 30/36 criteria in Sx group
- Sig improvement in 9/36 criteria in ASx group
  - Truly asymptomatic?

Bulent Mentes et al. Gastrointestinal QOL in patients with symptomatic or asymptomatic cholelithiasis before and after lap chole. Surg Endos 2001:15;1267
Cholecystectomy: and quality of life - conclusions

- Patients with “true” biliary colic have an excellent outcome after surgery
- Some patients with “soft symptoms” also do well
Cholecystectomy: and post-op diarrhoea.

- Often perceived and reported
- Especially by women - report urgency
- Mixed evidence
- Careful records vs patient reports
  - No change in frequency, form or defecatory symptoms
- Some evidence suggests rectal irritability
  - Colonic transit may be accelerated
- Reports of diarrhoea improved after LC

Hearing et al. Effect of cholecystectomy on bowel function: a prospective, controlled study. Gut 1999:45;889
Heaton et al. Bowel function and irritable bowel symptoms after hysterectomy and cholecystectomy-a population based study. Gut 1993:34;1108
Cholecystectomy:
Colon cancer, symptoms and QOL

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