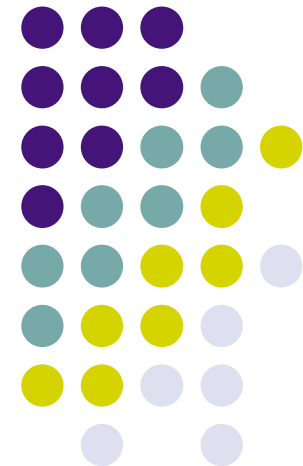


Cholecystectomy:

Colon cancer, symptoms and QOL



Mr. Val Usatoff
HPB Surgeon
Melbourne



Cholecystectomy: and the risk of colon cancer



- Observation
 - Capron JP, Delamarre J
La cholecystectomie
favorise-t-elle
l'apparition du cancer
rectocolique?
Gastroenterol Clin Biol
1978;2:383



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

Koga et al. Effect of bile acids on 1,2-dimethylhydrazine-induced colon cancer in rats. *Cancer* 1982; 50:543

Narisawa et al. Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of N-methyl-N-nitrosoguanidine. *J Natl Cancer Inst* 197; 53:1093

Hepner et al. Increased bacterial degradation of bile acids in cholecystectomized patients. *Gastroenterology* 1974; 66:556

Malagelada et al. Bile acid secretion and biliary bile acid composition altered by cholecystectomy. *Am J Dig Dis* 1973; 18:455

Brydon et al. Diet and faecal lipids following cholecystectomy in men. *Digestion* 1982;25:248



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
Gafa et al. Prevention of colorectal cancer: Role of association between gallstones and colorectal cancer. *Dis Colon Rectum* 1987;30:692

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
Gafa et al. Prevention of colorectal cancer: Role of association between gallstones and colorectal cancer. *Dis Colon Rectum* 1987;30:692

Cholecystectomy: and the risk of colonic adenomas



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

Llomas KJ et al. Cholecystectomy and adenomatous polyps of the large bowel. Gut 1986;27:1181

Mannes AG et al. Adenomas of the large bowel after cholecystectomy. Gut 1984;25:863

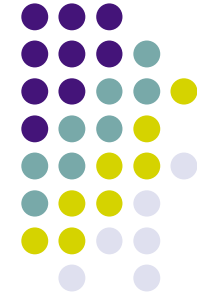
Snadler RS et al. Adenomas of the large intestine after cholecystectomy: A case controlled study. Dig Dis Sci 1988;33:1178

Neugut AI et al. Cholecystectomy and adenomatous polyps of the colon in women. Cancer 1988;61:618

Neugut AI et al. Cholecystectomy as a risk factor for colorectal adenomatous polyps and carcinoma. Cancer 1991;68:1644



Cholecystectomy: and the risk of sm bowel cancer



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

Lagergren et al. Intestinal cancer after cholecystectomy: is bile involved in carcinogenesis? *Gastroenterology* 2001;121:542

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

Turunen MJ et al. Increased risk of colorectal cancer after cholecystectomy. *Ann Surg* 1981;194:639

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

Ek bom 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

Johansen et al. Risk of colorectal cancer and other cancers in patients with gallstones. Gut 1996;39:439

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

Schernhammer et al. Cholecystectomy and the risk for developing colorectal cancer and distal adenomas. Br J Cancer 2003;88:79



Cholecystectomy: and the risk of colon cancer



Study	Year	Number	Overall RR
Uppsala	1993	60,000	0.99
GP UK	2005	55,960	1.32
Danish Hosp	1996	42,098	1.07
Nurse Health	2003	85,184	1.21

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
Reid et al. Cholecystectomy as a risk factor for colorectal cancer: a meta-analysis. Scand J Gastroenterol 1996;31:160



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



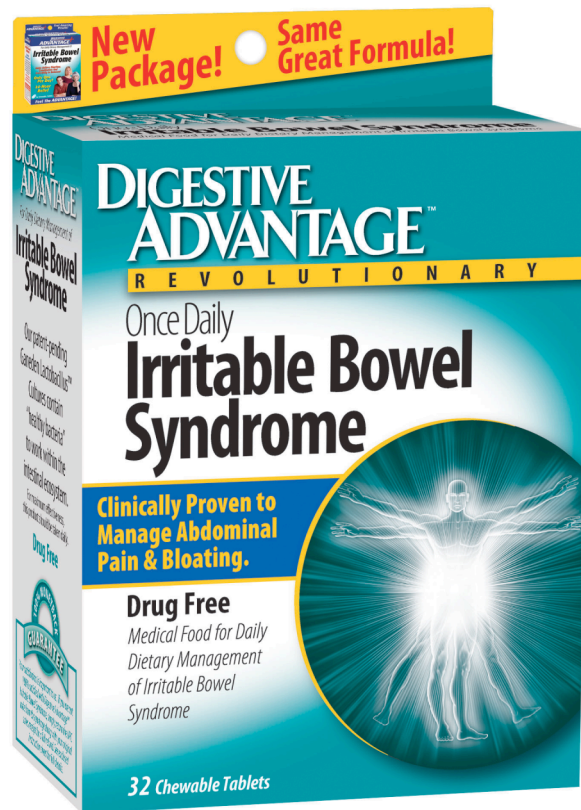
- Reid 1996
 - 95 studies identified, 35 selected
 - Increased risk of cancer
 - Overall RR 1.11(1.02-1.21)
 - Women RR 1.14(1.01-1.28)
 - Right sided RR 1.86(1.31-2.65)
 - Conclusion
 - Many biases not allowed for
 - Possible observed risk but very small for individual

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

Fenster et al. What symptoms does cholecystectomy cure? Insights from an outcome measurement project and review of the literature. Am J Surg 1995;169:533



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

Scott et al. Appropriateness of cholecystectomy: the public and private sector compared. Ann R Coll Surg Engl 1992;74;97

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

Authors	Follow-up	Cure rate%
Biliary pain		
Bates - Gut 1984	1 year	73
Bates - Br J Surg 1991	1 year	66
Gilliland - SGO 1990	15-79 mo	88
Gilliland - Am J Surg 1990	16-79 mo	79
Scriven - J R Coll Surg Edin 1993	1 yr	73
Plaisier - Am J Gastro 1994	3 mo	91
Fenster - Am J Surg 1995	3 mo	76
	Range	66-91%

Berger et al. Abdominal symptoms: do they disappear after cholecystectomy? A systematic literature review. Surg Endosc 2003;17;1723
 Konsten et al. Long term follow-up after open cholecystectomy. Br J Surg 1993;80;100

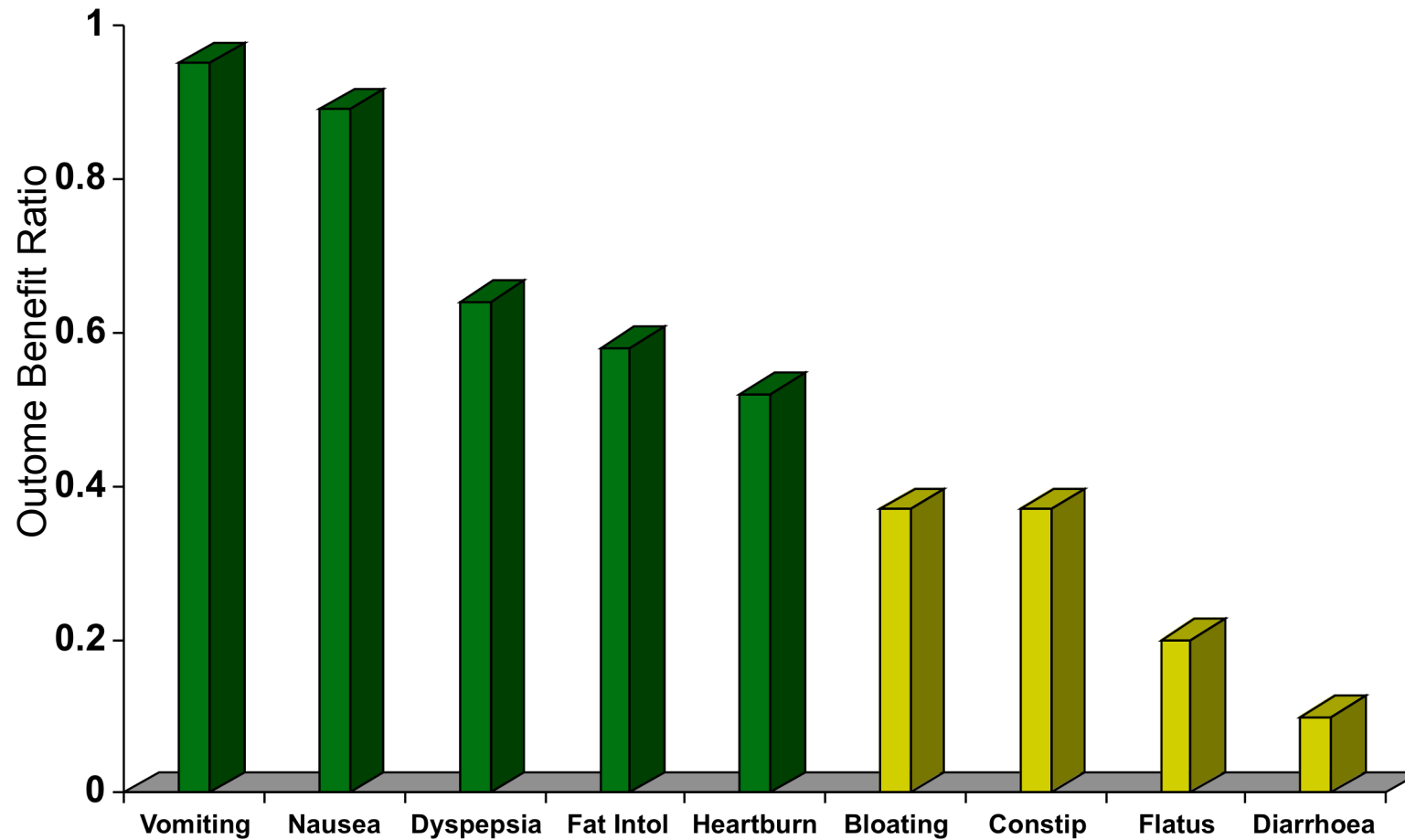
Cholecystectomy: and long term symptom control



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

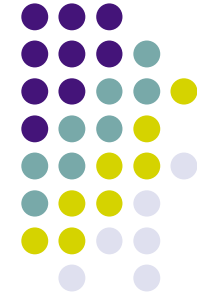
● Nausea	● Bloating
● Cramping	● Satiety
● Flatulence	● Reflux
● Constipation	● Diarrhea
● Belching	● Fatty food intolerance

Cholecystectomy: effective treatment for?



Gui et al. Is cholecystectomy effective treatment for symptomatic gallstones? Clinical outcome after long-term follow-up. Ann R Coll Surg Engl 1998;80:25

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

Authors	Follow-up	Cure rate%
Flatulent dyspepsia		
Bates - Br J Surg 1991	1 yr	33
Ros - Gut 1987	2 yrs	52
Scriven - J R Coll Surg Edin 1993	1 yr	72
Plaisier - Am J Gastro 1994	6 mo	74
Rhind - BMJ 1968	1 yr	61
Johnson - Postgrad Med J 1971	3-42 mo	46
Fenster - Am J Surg 1995	3 mo	42
	Range	33-74%

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”



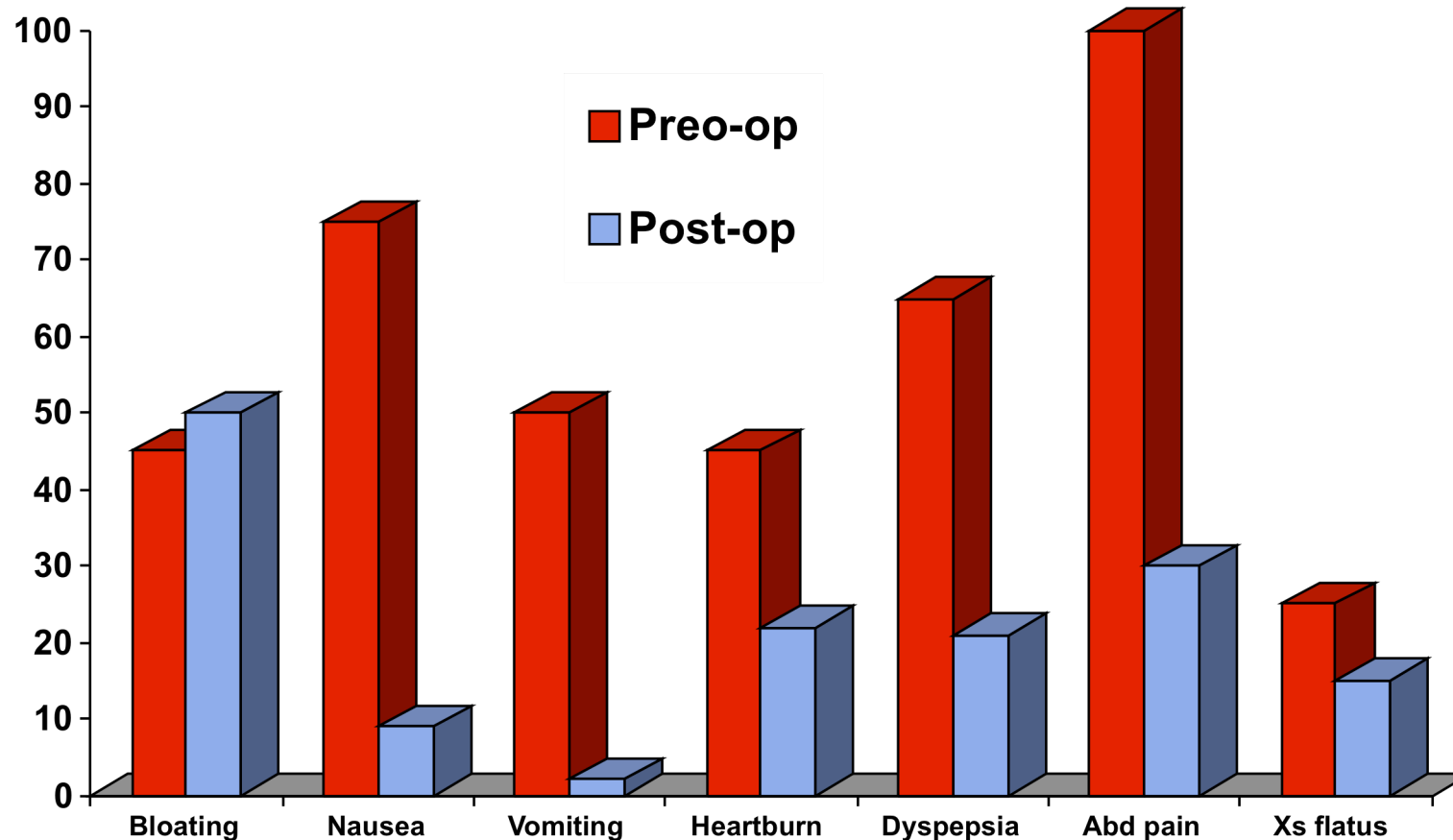
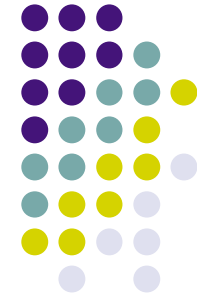
- Flatulent dyspepsia
 - Equally common with or without gallstones
- Gui 1998
 - 92 pts, 31 month follow-up
 - Control group of surgical clinic pts
 - Post chole symptoms back to control levels

Price WH. Gallbladder dyspepsia. Br J Med 1963;2:138

Gui et al. Is cholecystectomy effective treatment for symptomatic gallstones? Clinical outcome after long-term follow-up. Ann R Coll Surg Engl 1998;80:25

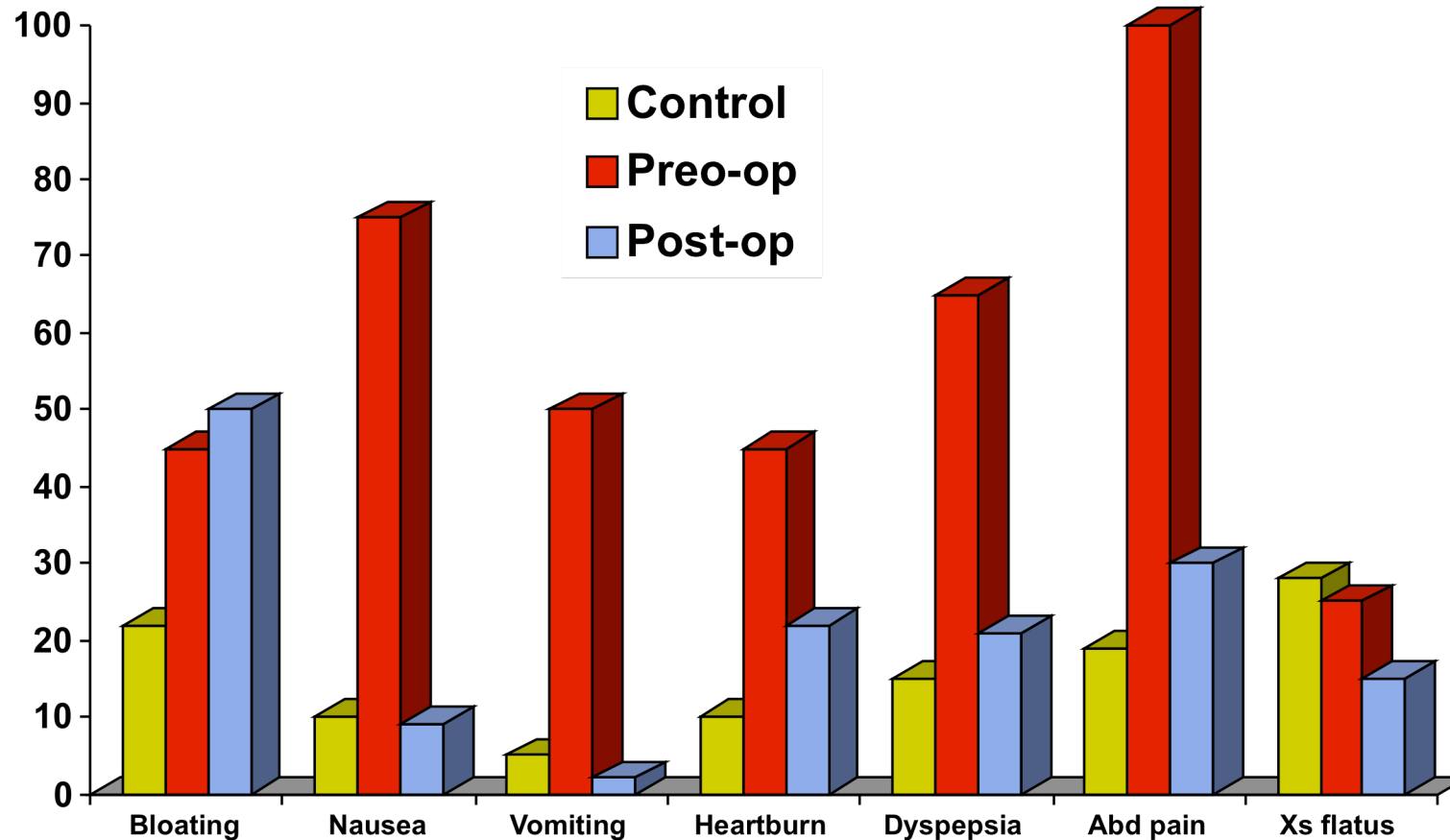


Cholecystectomy: and long term symptoms



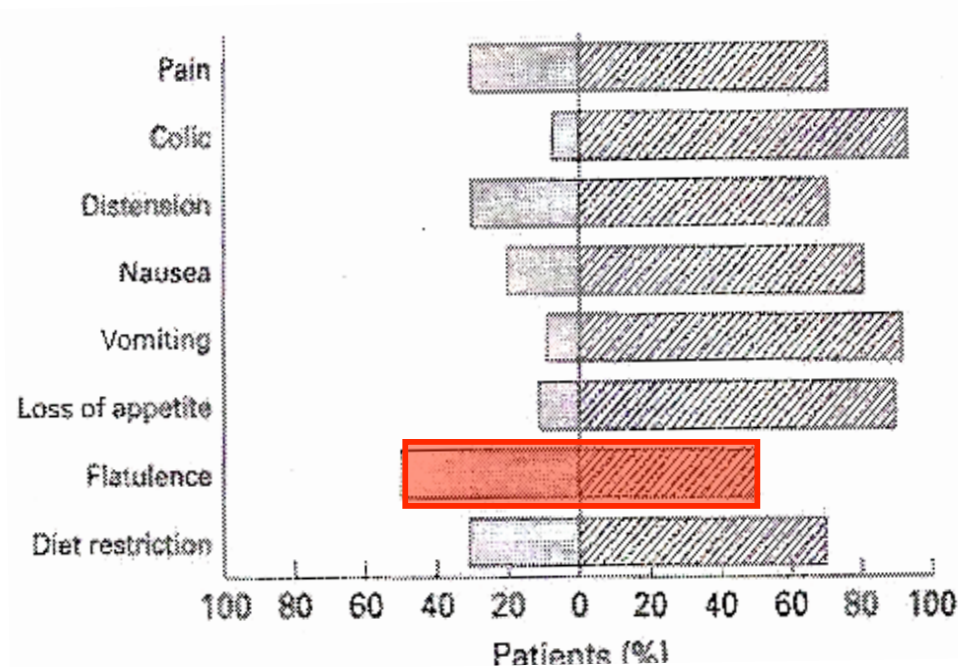
Gui et al. Is cholecystectomy effective treatment for symptomatic gallstones? Clinical outcome after long-term follow-up. Ann R Coll Surg Engl 1998;80;25

Cholecystectomy: persistent symptoms?



Gui et al. Is cholecystectomy effective treatment for symptomatic gallstones? Clinical outcome after long-term follow-up. Ann R Coll Surg Engl 1998;80;25

Cholecystectomy: persistent or new symptoms?



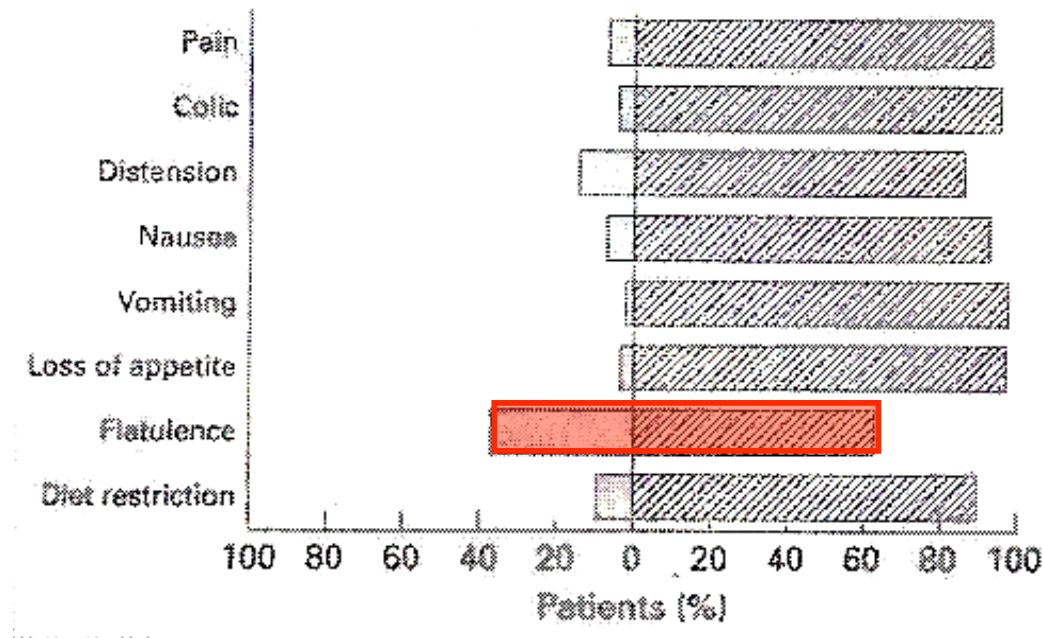
- Ure, Germany 1995
 - 468 pts, 19mo f-up
 - Existing pre-op symptoms
 - Left - persist
 - Right - cured

Ure et al. Long-term results after laparoscopic cholecystectomy. Br J Surg 1995;82:267

Cholecystectomy: what symptoms does it cause?



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



Ure et al. Long-term results after laparoscopic cholecystectomy. Br J Surg 1995;82:267

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. *Scand J Gastro* 1999;34:1144

Ros et al. Postcholecystectomy symptoms. A prospective study of gall stone patients before and two years after surgery. *Gut* 1987;28:1500

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.

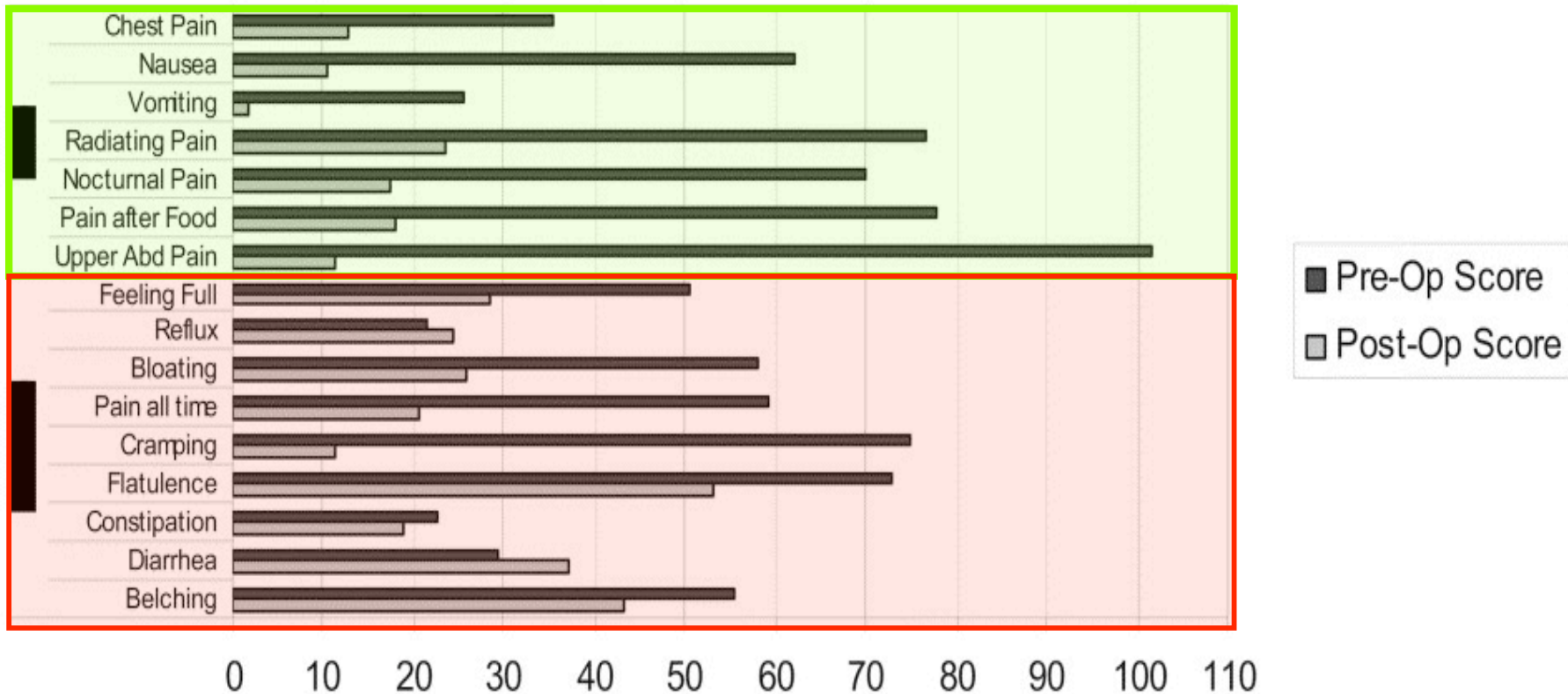


- 104 patients, prospective
 - GI symptom score - University Alabama
 - 16 GI complaints
 - frequency, severity, distressfulness
 - HRQOL survey - SF36
 - 8 domains - physical , social, vitality etc.

Finan et al. Improvement in gastrointestinal symptoms and quality of life after cholecystectomy . Am J Surg 2006:192;196

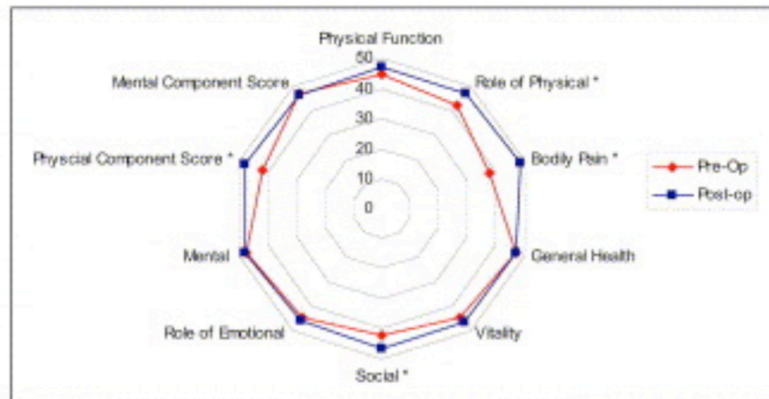


Cholecystectomy: and quality of life.



Finan et al. Improvement in gastrointestinal symptoms and quality of life after cholecystectomy. Am J Surg 2006;192;196

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

Finan et al. Improvement in gastrointestinal symptoms and quality of life after cholecystectomy. Am J Surg 2006;192;196

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

Quintana et al. Health-related quality of life and appropriateness of cholecystectomy. *Annals of Surgery* 2005;241;110



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 Menten 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

Fort et al. Bowel habit after cholecystectomy: physiological changes and clinical implications. Gastroenterology 1996;111;617

Victorzon et al. Short and long term outcome after laparoscopic cholecystectomy. Ann Chir Gynaecol 1999;88;259.



Cholecystectomy:

Colon cancer, symptoms and QOL



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