Argument of Early Surgery in Crohn’s Disease

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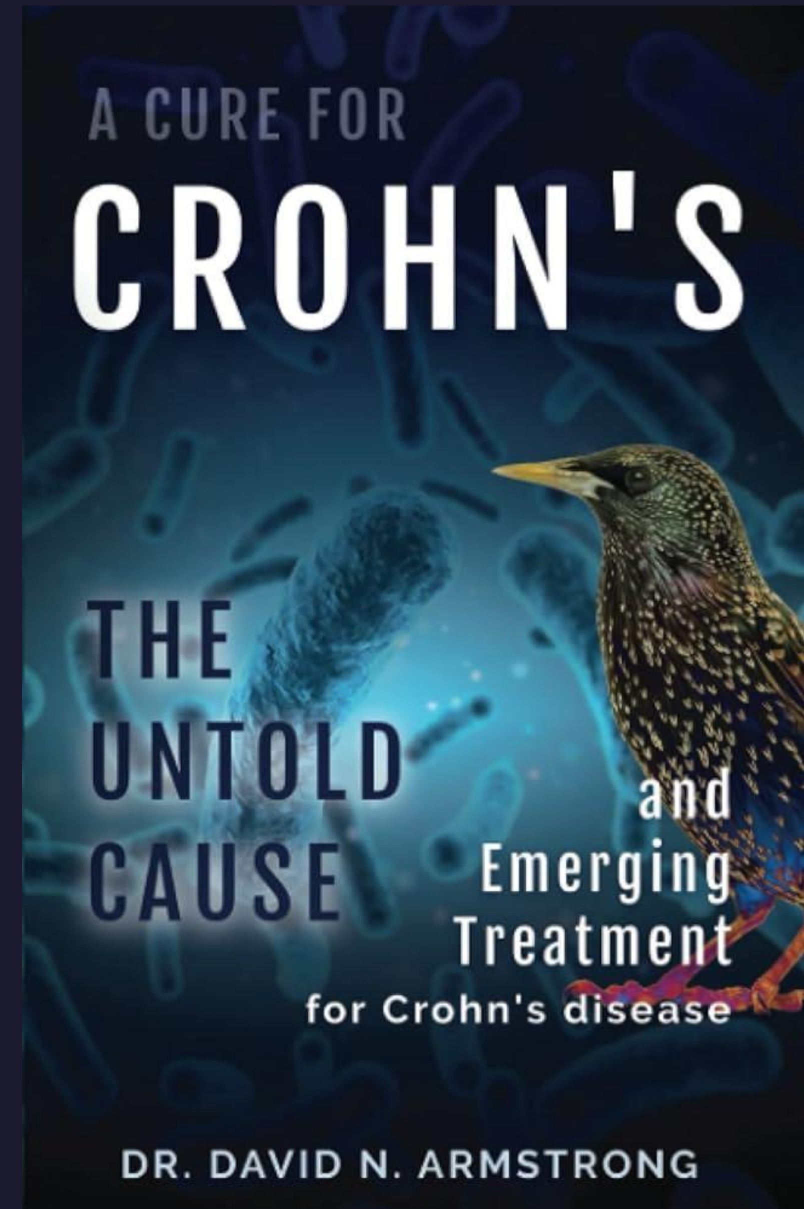
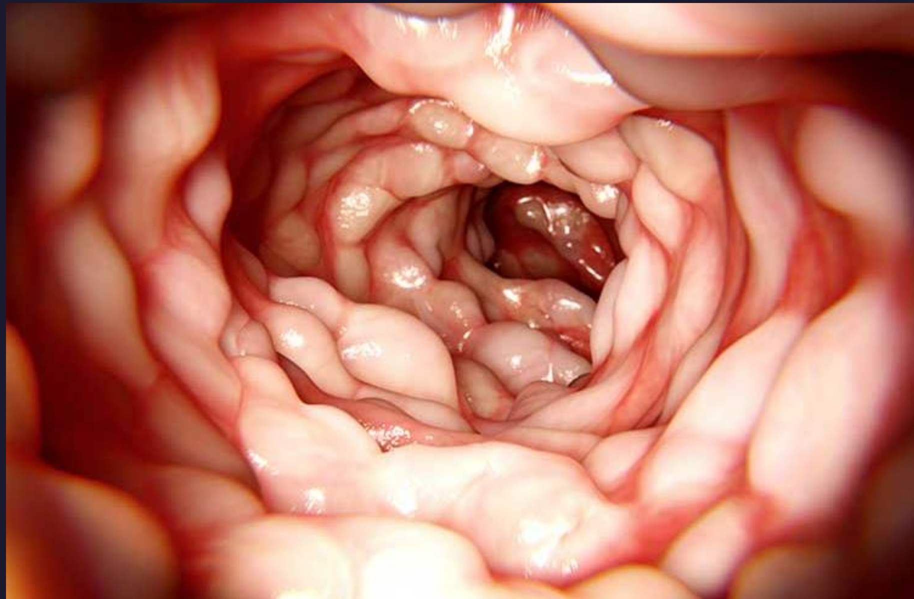
- Consultant for Touch Stone

Management of Crohn's Disease

- Early and effective treatment of CD is critical to preventing disease progression
- anti-TNF therapy is the mainstay of moderate to severe CD management
- Most often warrants indefinite continuation of treatment and is associated with loss of response, adverse events, and health care costs
- Surgical management is traditionally recommended in complicated CD or for patients nonresponsive to or intolerant of medications



Management of Crohn’s Disease



CD usually has progressive course, starting with mucosal inflammation, and can advance to transmural involvement with risk of perforation, abscesses, fistulas, & fibrotic stenosis

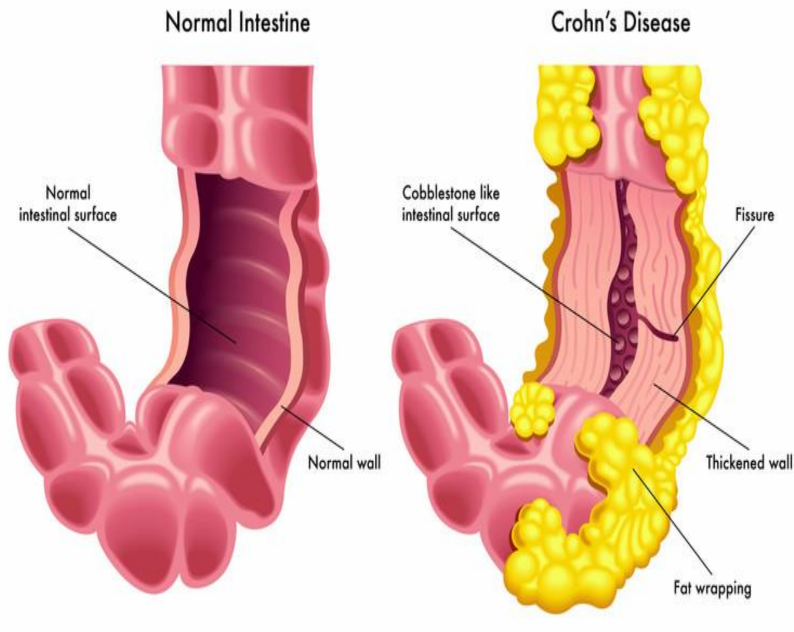
Medical treatment is the first step in the treatment, corticosteroids are commonly used for induction, while thiopurines and methotrexate can be used for maintenance

Biologics significantly improved ability to control symptoms

Anti-TNT biologics alone or in combination with other agents (e.g. azathioprine) are effective for both induction and maintenance

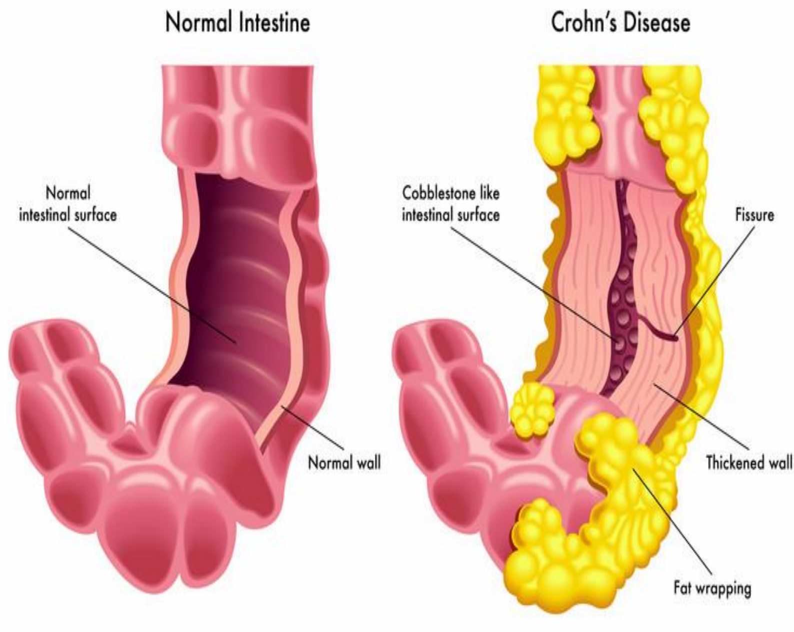
Newer biologics (vedolizumab and Ustekinumab) has increasingly important role in the management of CD

Management of Crohn's Disease

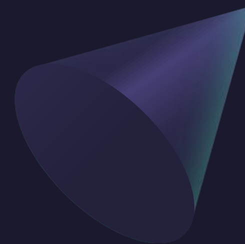


- New treatment modalities have resulted in a significant decrease in the rate of surgery requirements over the last decades
- No curative therapy available & main therapeutic goal is to induce remission in the short term and to maintain remission in the long term
- Still in the era of biologics, a considerable proportion of patients still require surgery in the course of their disease , with ileocolic resection being the most common procedure

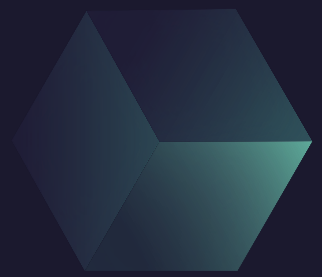
Extent of Crohn's Disease



- Extent of CD :
  - Localized : intestinal CD affecting <30 cm (usually applies to a localization in the ileocecal region) but can also be located in
  - Extensive: CD affecting >100 cm in extent independent of the localization



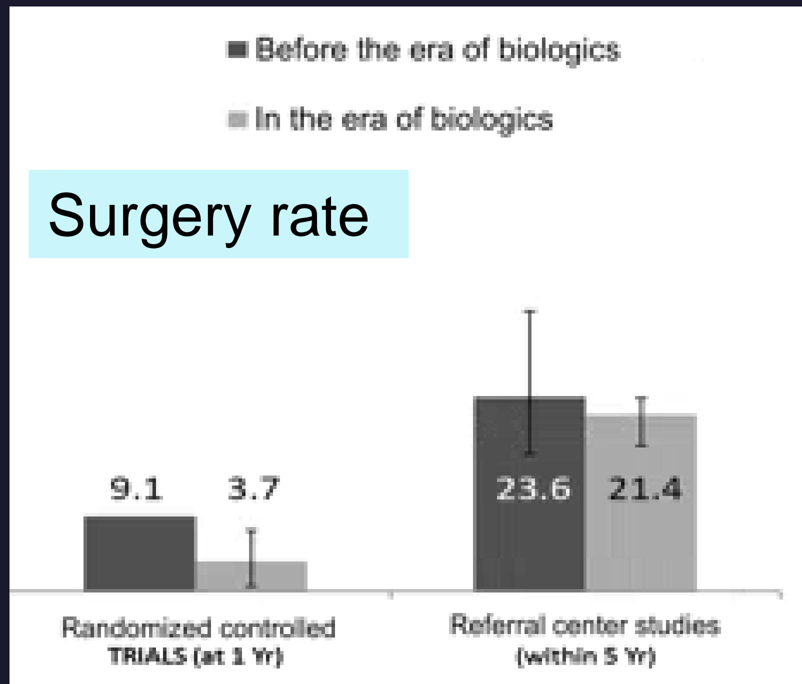
Management Strategies



- **Crohn´s disease**
  - **Extended Crohn´s disease**
    - Primary medical therapy
    - Surgery in case of complications
  - **Ileocolonic (isolated) Crohn´s disease**
    - **Predominantly inflammatory**
      - Naive (patient´s preference)
        - Surgery
        - Medical therapy
      - Refractory to medical therapy
        - Surgery
        - Medical therapy
    - **Predominantly fistulating/penetrating**
      - Asymptomatic
        - Medical therapy
        - Surgery
      - Symptomatic/with abscess
        - Surgery
    - **Predominantly fibrotic/stenotic**
      - Surgery
      - Endoscopic intervention

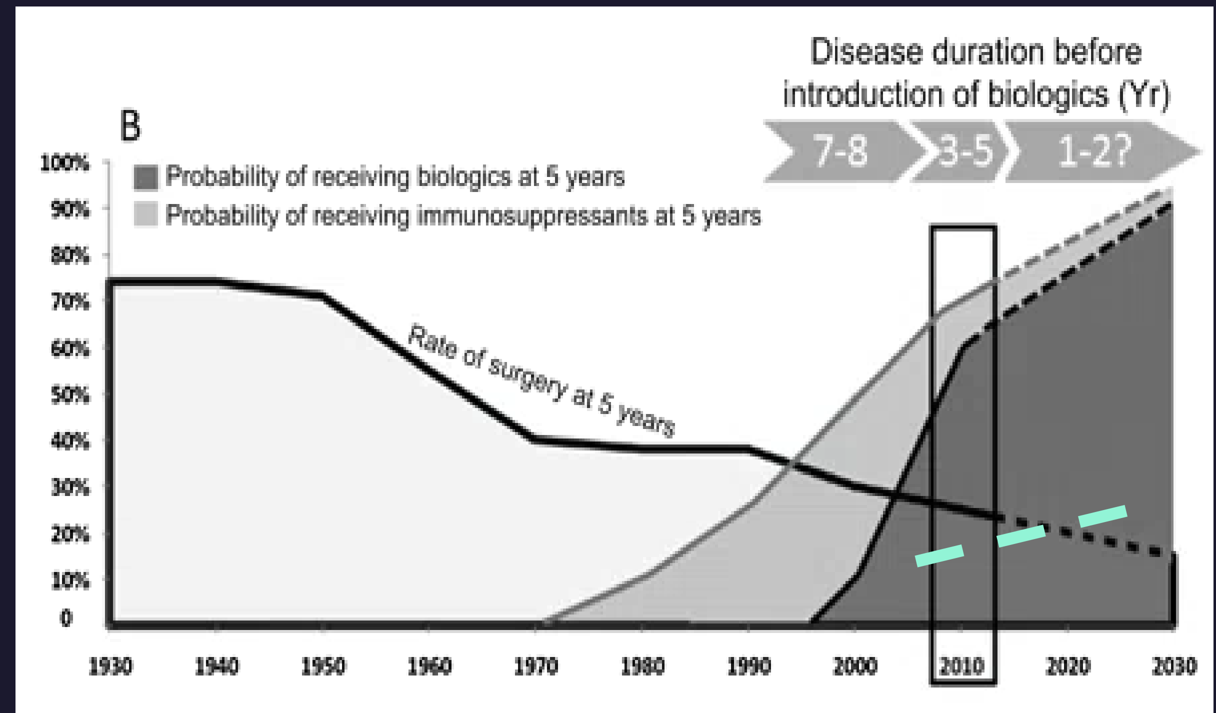
Kelm et al. Biomedicines 2021

Reduced rate of surgery in anti-TNF era?



RCT data
(within 1 year)

Population-basd data
(within 5 year)



Recent studies: stable rates surgical resection: 20-35%/ 5 year

Bouguen et al. Gut 2011

Burisch et al. Gut 2019, Wong et al. Gastroenterol Rep 2019

Increased complications in the anti-TNF era

- **Delay of surgery causes inferior postoperative outcome**

TABLE 3. Drug-intake, Duration of Clinical Deterioration, and Morbidity Changes During the Study Period

Study Period	Median Duration of Clinical Deterioration, Months	Multiple-drug Combination	Preoperative Weight Loss of >5%	Inflammatory Mass Consisting of >3 Structures	Resection without an Anastomosis (Ileostomy Rate)	Postoperative IASC Rate
1992–1999 (n = 72)	5	15%	30%	28%	1.4%	7%
2000–2004 (n = 73)	4	20%	27%	23%	1.4%	18%
2005–2009 (n = 86)	6	34%	51%	46%	18.6%	36%

Statistically significant differences between group "2005–2009" compared to two other groups.

Iesalnieks et al. IBD 2010, Douglas et al. Ann Surg 2010

Isolated Ileocecal Crohn's

- Lichtenstein et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am. J. Gastroenterol.* **2018**
- Martins, R.; et al. Management of Crohn's disease: Summary of updated NICE guidance. *BMJ* **2019**,
- Preiß, J.C.; et al Updated German clinical practice guideline on "Diagnosis and treatment of Crohn's disease". *Z. Gastroenterol.* **2014**,
- Adamina, M.; et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. *J. Crohns Colitis* **2020**,

Table 1. Recommendation of international guidelines regarding isolated ileocolonic Crohn's disease.

Society/Organization	Recommendation
American College of Gastroenterology [18]	Surgery is reserved for severe enteric complications only such as bowel obstruction, abscess formation, perforation or the presence of medically refractory disease.
British National Institute for Health and Care Excellence (NICE) [27]	Surgery is recommended at an early stage of the disease as therapeutic alternative to medical therapy.
German Society of Gastroenterology (DGVS) and German Society of Visceral Surgery (DGAV) [28]	Surgery is recommended as primary treatment option in case of localized CD as an equal therapeutic alternative to biological (medical) therapy.
European Crohn's and Colitis Organization (ECCO) [29]	Surgery is recommended as primary treatment option in case of localized CD as an equal therapeutic alternative to biological (medical) therapy.

Consensus recommendations about surgery as therapeutic approach in patients with CD still heterogeneous

Arguments for Early Surgery

- Reduced risk of complications

  → *patient in better condition*

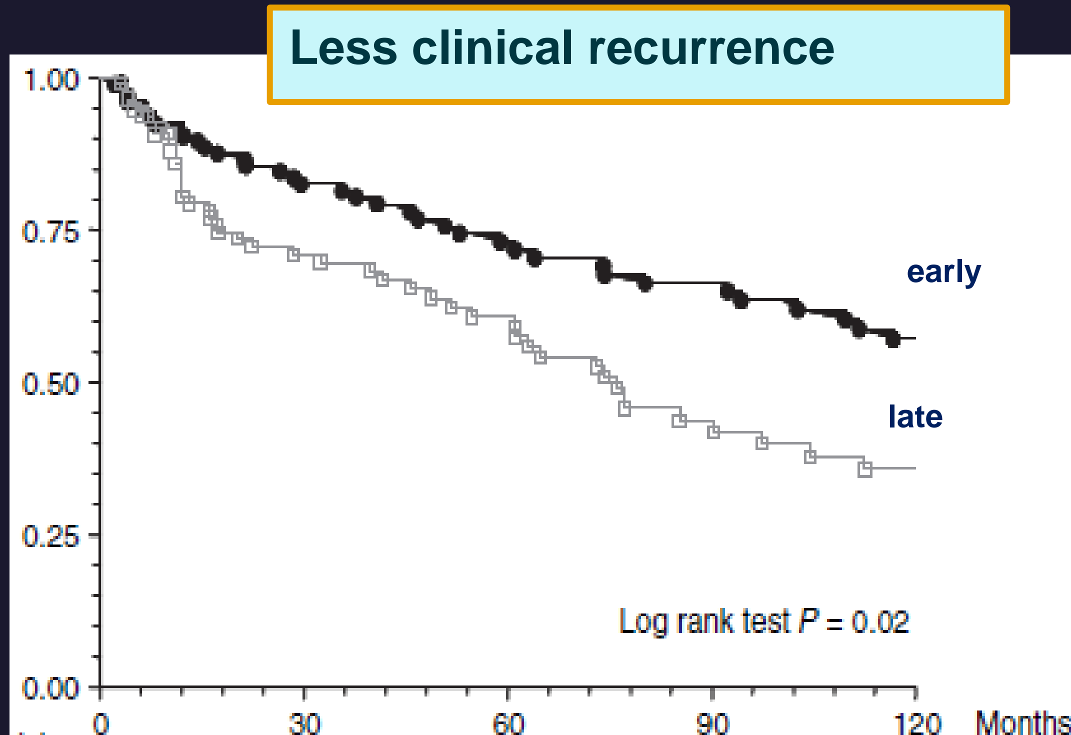
  → *reduced anastomotic leak (also associated with recurrences)*

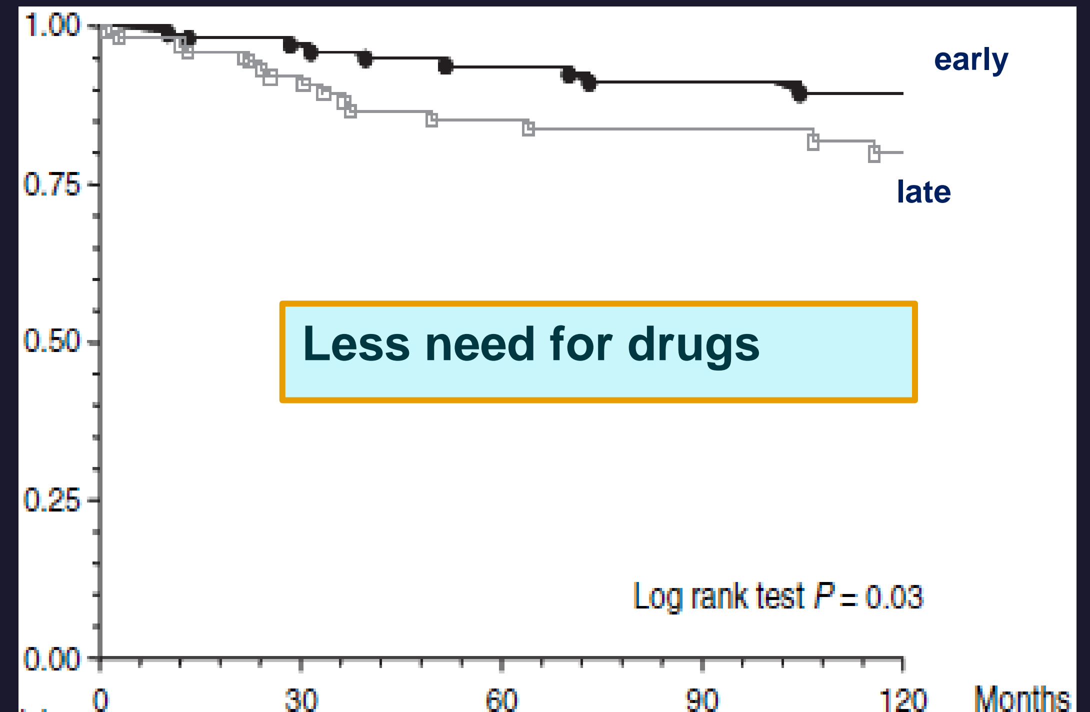
  → *reduced stoma rate*

- Reduced need for postoperative medication (>30% long-term medication free!)
- Reduced rates of re-operation
- Improved quality of life
- *Reduced costs*

Reduced need for post-operative medication

- 83 pts resection at time of diagnosis versus 124 patients therapy refractory





- Conclusion: early surgery prolongs clinical remission

Aratari et al. Aliment Pharm Ther 2007

Reduced need for post-operative medication

	Primary surgery (n=29)	Primary medication (n=74)	p-value
Laparoscopic procedure	44.8%	29.3%	0.007
Stoma rate	6.9%	5.5%	ns
Anastomotic leakage	6.9%	8.1%	ns
Medical therapy 2 years after surgery	37.9%	78.4%	<0.001
- steroids	13.8%	40.5%	
- immunomodulators	17.2%	32.4%	
- biologicals	17.2%	37.8%	

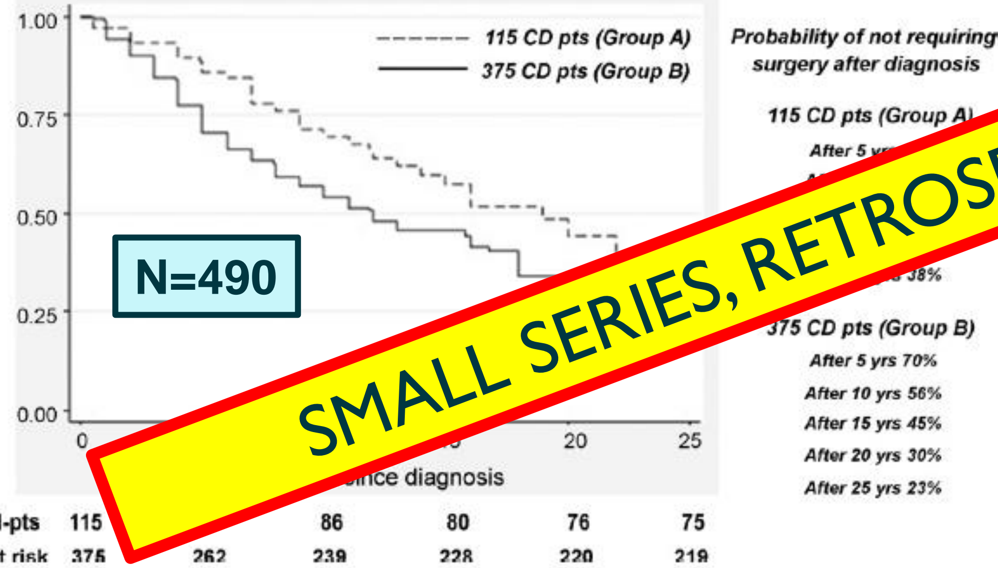
Kelm et al. J Clin Med 2021

Reduced redo surgery

ALIMENTARY TRACT | VOLUME 41, ISSUE 4, P269-276, APRIL 01, 2009

Clinical course of Crohn's disease first diagnosed at surgery for acute abdomen

G. Latella 1 • A. Cocco 1 • E. Angelucci • ... S. Bacci • S. Necozione • R. Caprilli • Show all authors •



Postoperative ... Crohn disease according to timing of ... resection

... CONNECT Study

... Moon Lee, MD, PhD[a,*], Joo Sung Kim, MD, PhD[b], You Sun Kim, MD, PhD[c], ..., MD, PhD[d], Byong Duk Ye, MD, PhD[e], Young-Ho Kim, MD, PhD[f], Dong Soo Han, MD, PhD[g], ... Kyun Lee, MD, PhD[h], Hyun-Ju Park, MD[i]

Retrospective Cohort Study

Early surgery in Crohn's disease a benefit in selected cases

Vinna An, Lauren Cohen, Matthew Lawrence, Michelle Thomas, Jane Andrews, James Moore

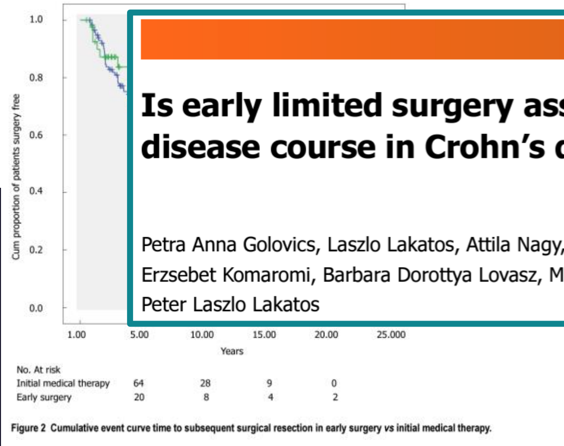


Figure 2 Cumulative event curve time to subsequent surgical resection in early surgery vs initial medical therapy.

BRIEF ARTICLE

Is early limited surgery associated with a more benign disease course in Crohn's disease?

Petra Anna Golovics, Laszlo Lakatos, Attila Nagy, Tunde Pandur, Istvan Szita, Mihaly Balogh, Csaba Molnar, Erzsebet Komaromi, Barbara Dorottya Lovasz, Michael Mandel, Gabor Veres, Lajos S Kiss, Zsuzsanna Vegh, Peter Laszlo Lakatos

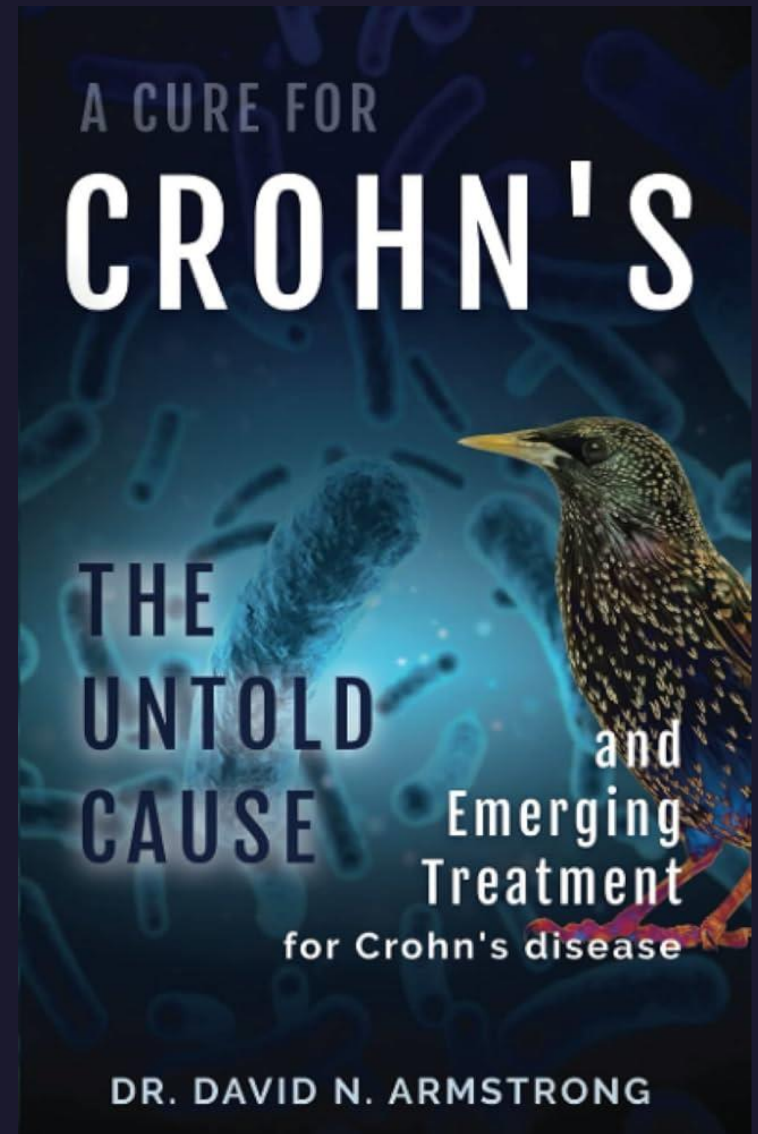
SMALL SERIES, RETROSPECTIVE, QUALITY?

Diagnosis at surgery only independent predictor of reduced further surgery

Management of Crohn's Disease

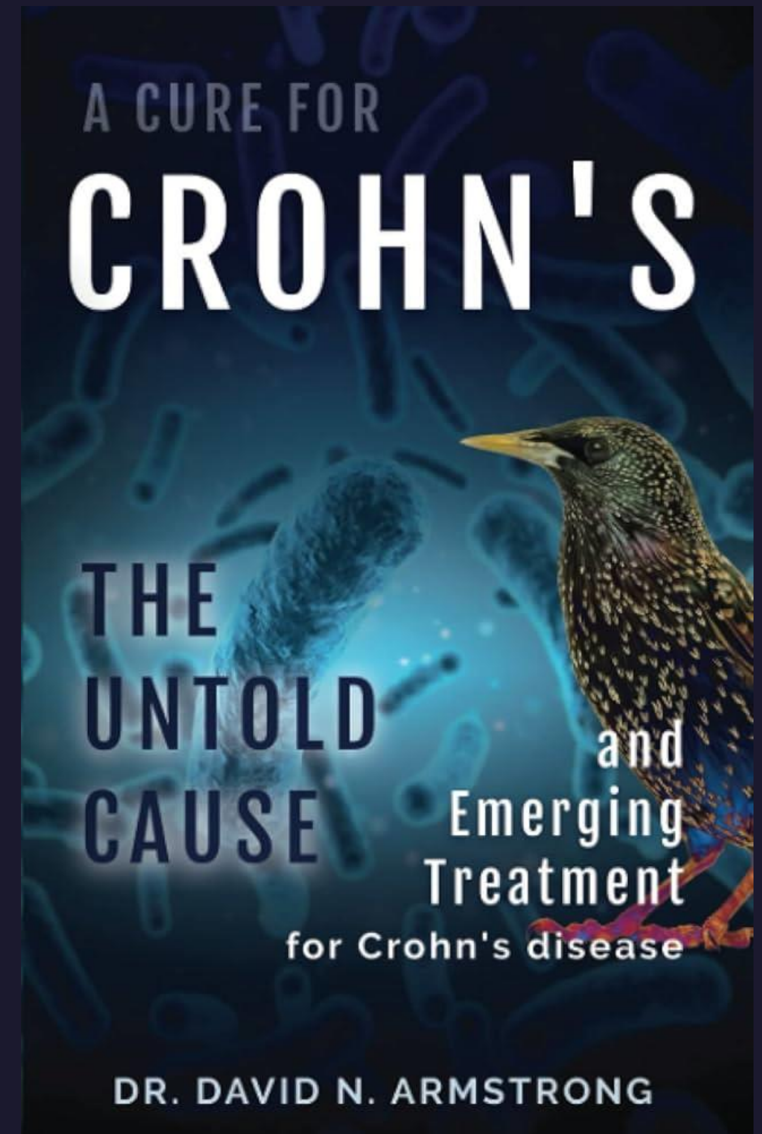
- Retrospective analysis of long-term data (median, 5 years) demonstrated that individuals in the ICR group (n = 69) did not require repeat surgery and, furthermore, that most were on no medical treatment, contrary to the anti-TNF group (n = 65), of whom 31 (48%) required surgery and the remaining were maintained on a biologic medication

Agarwal et al : Gastroentrology 2023

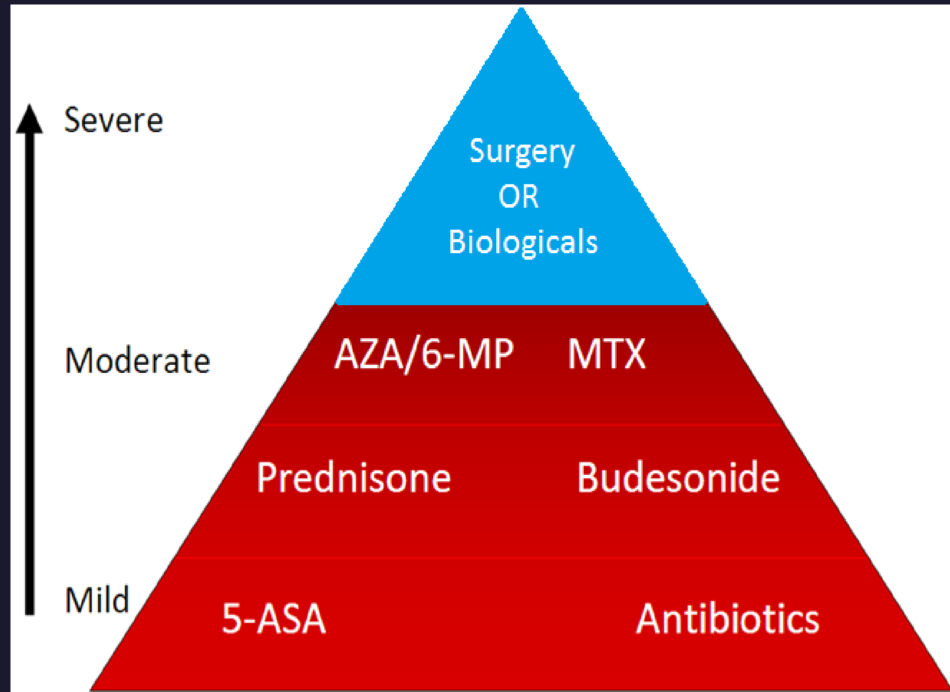


Management of Crohn's Disease

- Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Recurrent Distal Ileitis in Crohn's Disease (LIR!C) randomized clinical trial
-

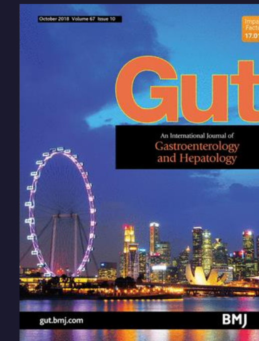


LIR!C trial

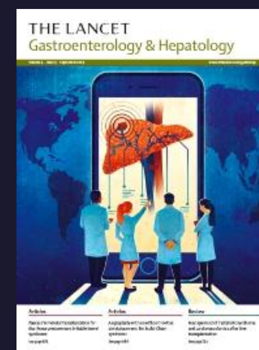


RCT patients failing immunomodulator

Lap ileocaecal resection versus infliximab for terminal ileitis in CD.
Ponsioen et al. 2017

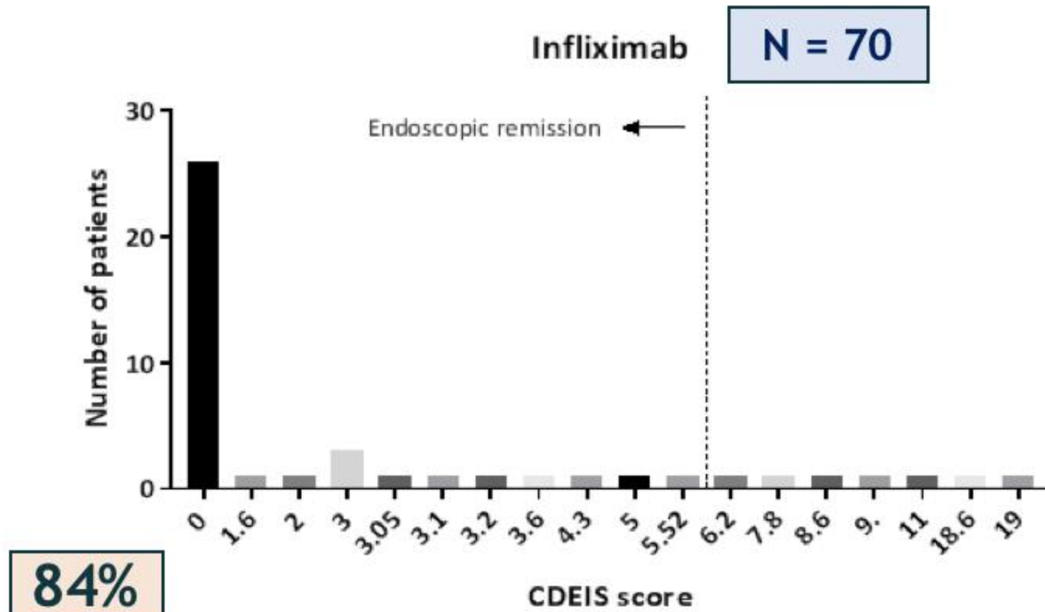


Cost-effectiveness of ileocaecal resection versus infliximab
De Groof et al. 2019

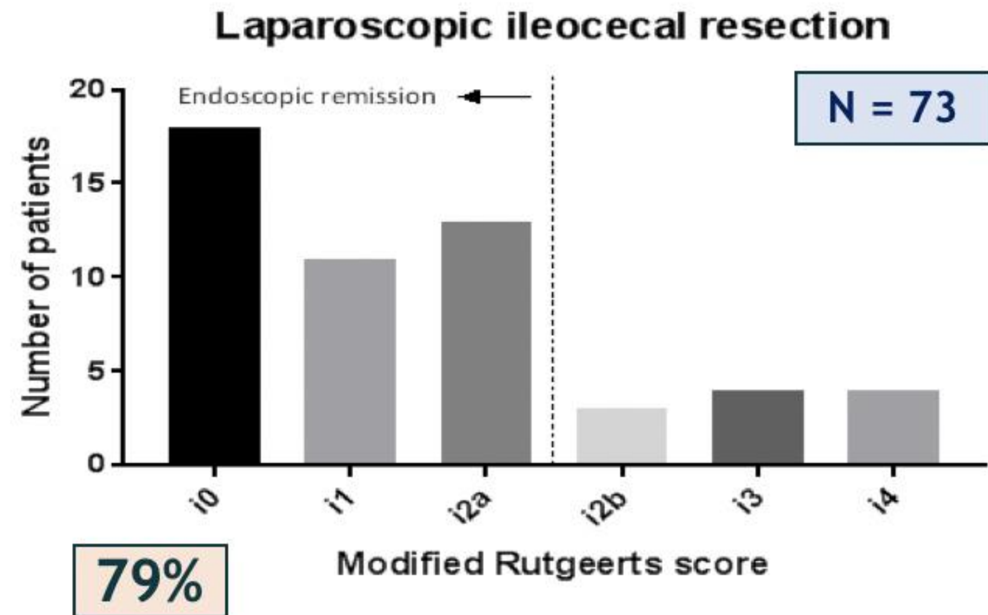


Long-term results (median FU 64 months)
Stevens et al. 2020

LIR!C TRIAL



84%



Endoscopic remission after 1 year

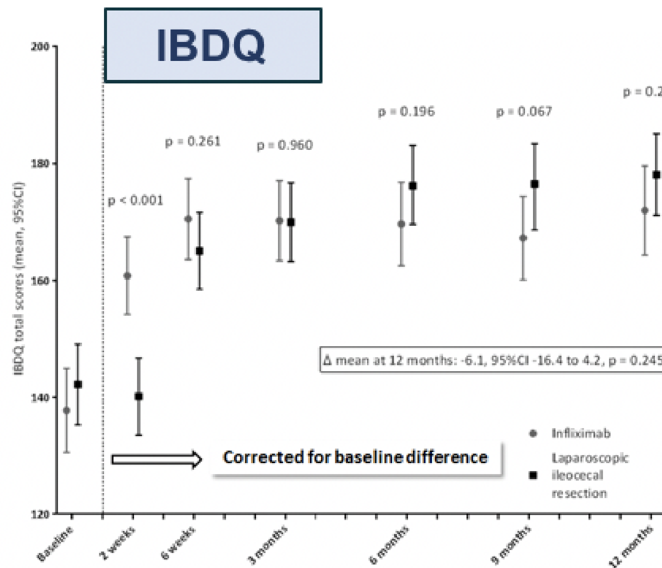
79%

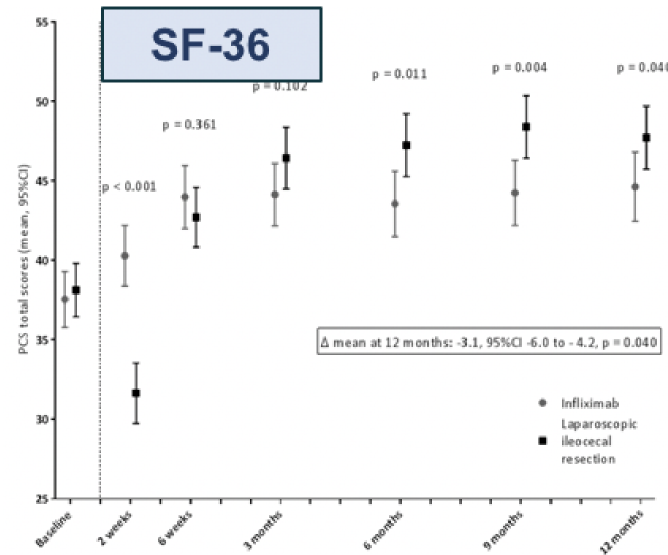
Ponsioen et al. Lancet Gastro&Hepatol 2017

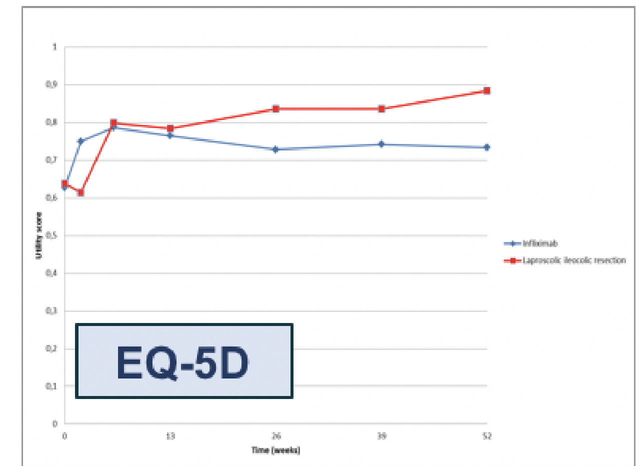
LIR!C long-term results (FU > 5 years)

Stevens et al. Lancet Gastro&Hepatol 2020

Primary outcome parameter LIR!C: QoL







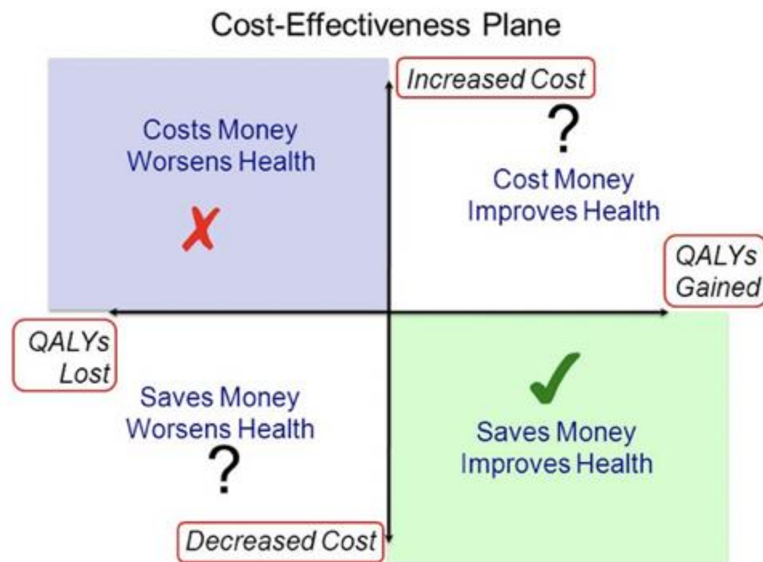
IBDQ: Surgery at least as good

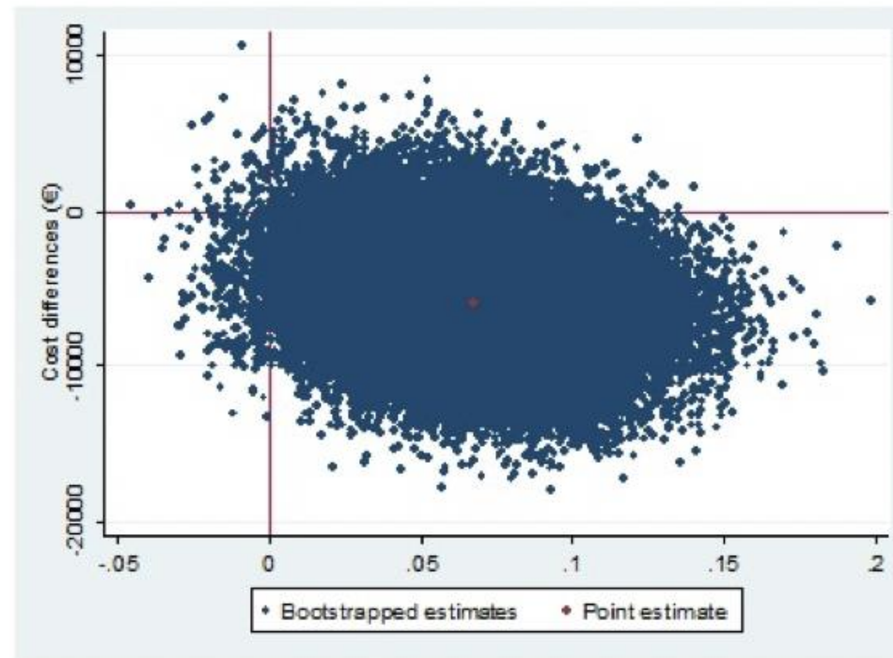
SF-36: Surgery better

SF-36: Surgery better

Ponsioen et al. Lancet Gastro&Hepatol 2017

Ileocoecal resection: LIR!C costs





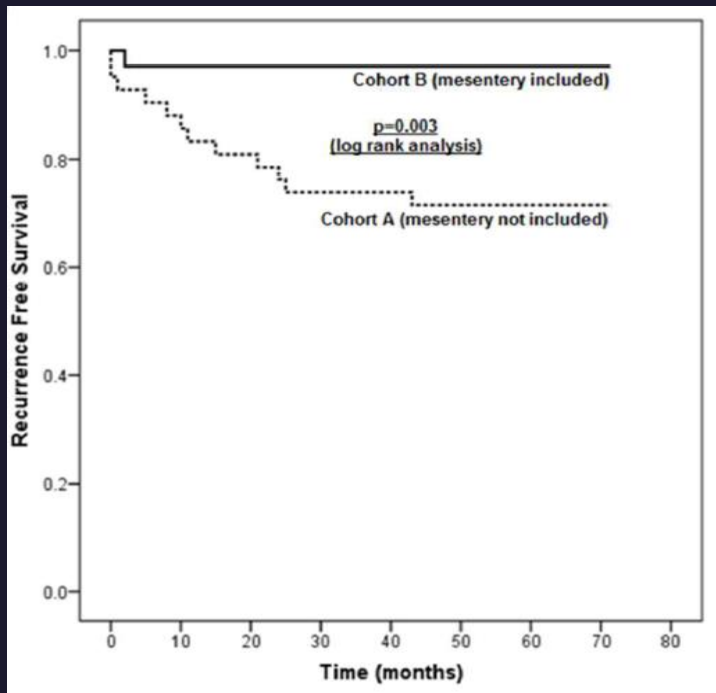
Lap ileocoecal resection more effective than anti-TNF, and less costly

Groof et al. Gut 2019

Additional Benefits of Surgery?

Improved surgical techniques to further reduce recurrence?

- Mesenteric resection

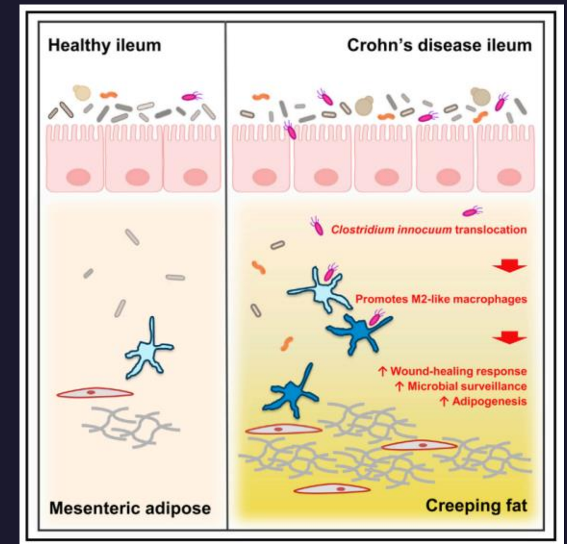


Surgical recurrence

- Close bowel resection: 40%
- Oncological resection: 2.9%

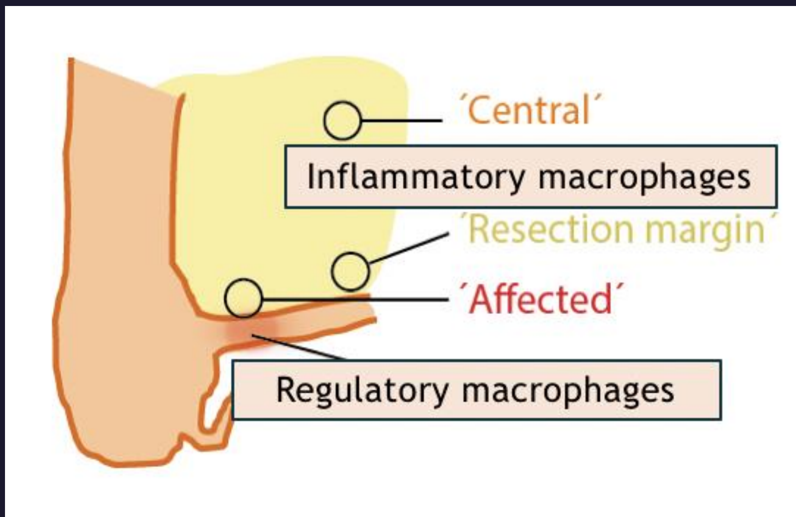
Coffey et al. J Crohn Colitis 2018

Additional Benefits of Surgery?

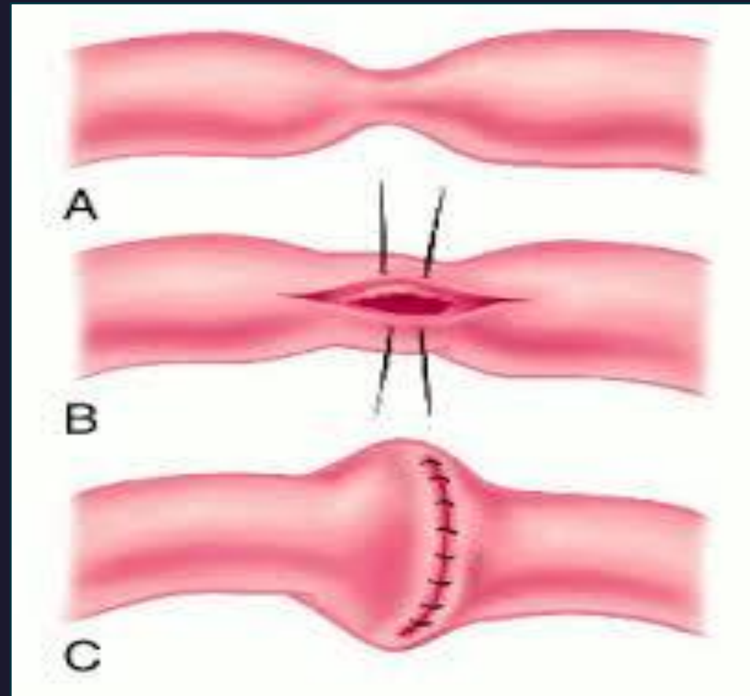


Improved surgical techniques to further reduce recurrence?

- Mesenteric resection? CD = systemic disease



Meer et al. Clin Gastroenterol 2019



In Brief

Ha et al. provide evidence that, in humans with inflammatory bowel disease, the phenomenon known as "creeping fat" is a protective response where mesenteric adipose tissue migrates (or "creeps") to sites of gut barrier dysfunction to prevent systemic dissemination of potentially harmful bacterial antigens that have translocated across the barrier from the gut lumen.

Ha et al. Cell 2020

Coffey et al. J Crohn Colitis 2018

Additional benefits of surgery?

Improved surgical techniques to further reduce recurrence?

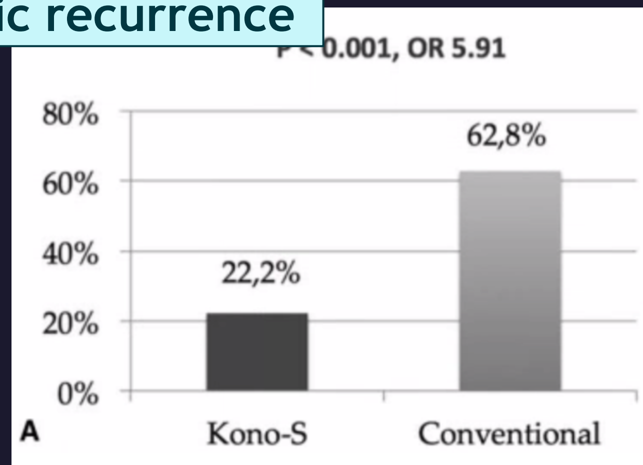
- Mesenteric resection
- Kono-S anastomosis (anti-mesenteric functional E-E vs standard E-E)

  - Surgical recurrence: 3.4% vs 24.4% (Follow-up: 38 months vs 89 months)

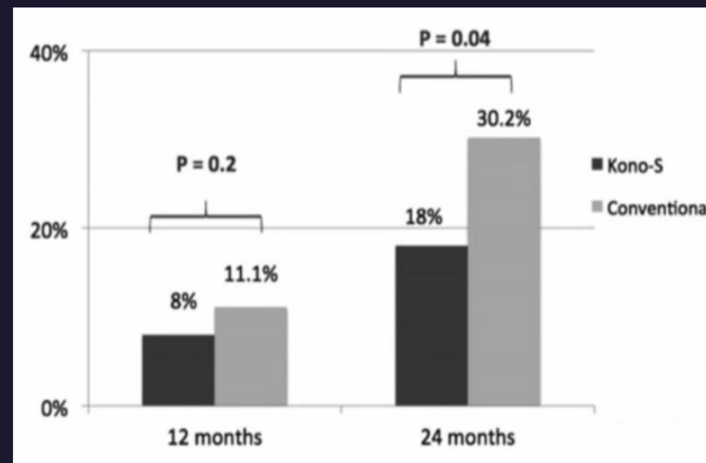
Supreme study (n=79)

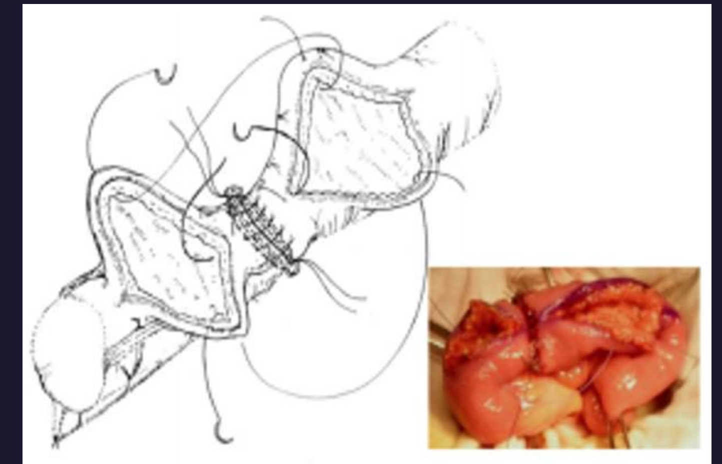
- Kono-S vs S-S stapled anastomosis

Endoscopic recurrence



Clinical recurrence





Kono T et al. J Gastrointest Surg 2016

Kono-S

Arguments against early surgery?

- **Surgical complications:** reducing over time
- **Short bowel syndrome:**
  - due to iatrogenic complications
  - predominantly redo surgery

Results: AMC + AZ leuven

Dindo–Clavien grade	Leuven (*n* = 354)	Amsterdam (*n* = 184)	All patients (*n* = 538)
0	262 (74·0)	155 (84·2)	417 (77·5)
I	23 (6·5)	5 (2·7)	28 (5·2)
II	53 (15·0)	14 (7·6)	67 (12·5)
IIIa	6 (1·7)	3 (1·6)	9 (1·7)
IIIb	7 (2·0)	6 (3·3)	13 (2·4)
IVa	3 (0·8)	1 (0·5)	4 (0·7)

Extra argument to operate early (before fistulizing disease)

De Buck van Overstraeten BJS 2017

Tailored treatment approach

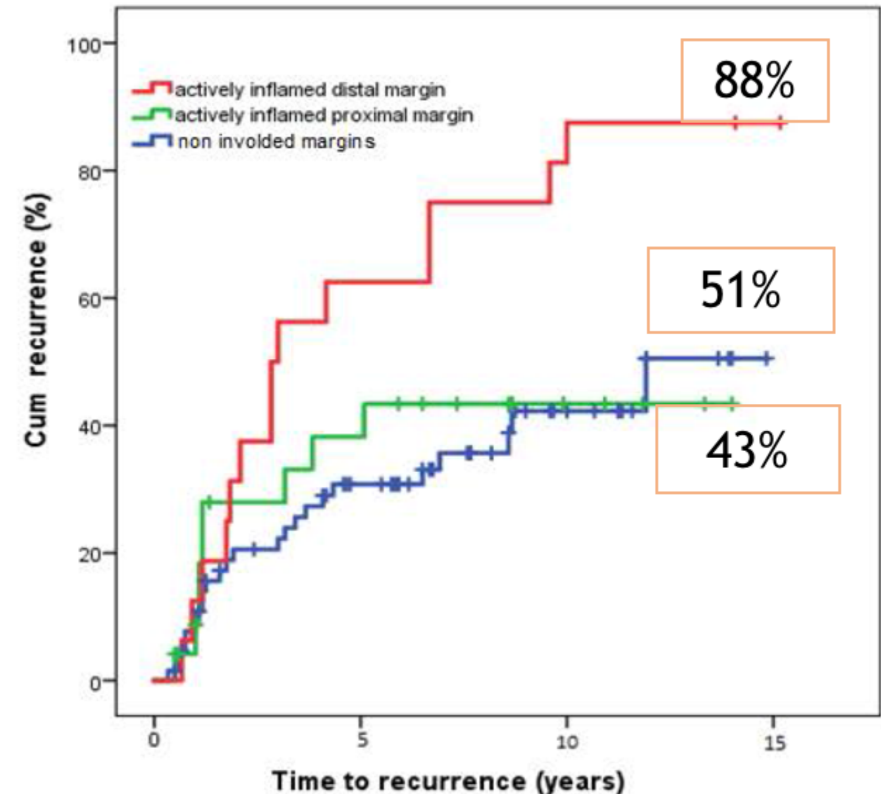
Surgery perhaps not first choice in:

- Long affected segment (>40cm?)
- Extensive perianal disease
- Patient in poor condition
- L3 disease

  → clinical recurrence >80%

  → different phenotype?

- **Patient that prefers medication?**



Wasmann et al. Inflamm Bowel Dis 2020

Conclusions

Early surgery in ileocoecal Crohn's disease: a good alternative! → discuss with patient

- Reduced complications
- Reduced need for postoperative medication
- Reduced rates of re-operation
- Improved quality of life
- Reduced costs

Surgery should not be the primary outcome parameter in studies

PATIENT TAILORED TREATMENT APPROACH!

Let's not get over-confident

Summary

Based on the current evidence, all available therapeutic alternatives (medical versus surgical) should be discussed with patients with localized ileocecal CD early, considering the risks and benefits as well as the personal preferences of patients

This is an important and relevant development since surgery was indicated only in case of therapeutic refraction or enteric complications in the past

Optimal treatment regimens remain controversial and not only medical but also surgical improvements are necessary to improve long-term outcome for patients with CD

Summary

A major difficulty for the adequate interpretation and comparison of studies about therapies in patients with CD remains the heterogeneity of patient cohorts as well as the complexity of the disease with multiple confounders

Operative strategies and surgical techniques such as the Kono-S anastomosis and minimally-invasive/robotic-assisted surgery needs to be developed including aspects such as the role of positive resection margins and resection of the mesentery, which will be part of future analysis and might provide the potential to decrease postoperative recurrence rates

Conclusions

There has been a renaissance of surgical approaches in the multidisciplinary treatment of isolated Crohn's disease with improved quality of life and fewer side effects based on new evidence in recent years

Further efforts are still needed to develop and introduce novel medical and surgical therapy options to continuously improve the outcome of patients suffering from Crohn's disease

To do so, sufficient cooperation between medical and surgical therapeutic approaches is critical

THANK YOU!