

**LIVE the PRESENT,
ENVISION the FUTURE**

28-30 NOVEMBRE 2019 SALA CONCORDIA

Medical Therapy in Refractory IBD: When enough is enough

Crohn's Disease



Antonio Rispo

Gastroenterologia

A.O.U. "Federico II" Napoli

Their 12-track single

Donna Summer/Barbra Streisand

No More Tears (Enough Is Enough)



MEDICAL THERAPY: WHEN ENOUGH IS ENOUGH ?

- WHEN DRUGS DO NOT WORK...
- WHEN DRUGS ARE NOT ABLE TO WORK...
- WHEN SURGERY SHOULD BE THE FIRST CHOICE...
- SOMETIMES IT'S ALREADY ENOUGH AT THE BEGINNING...

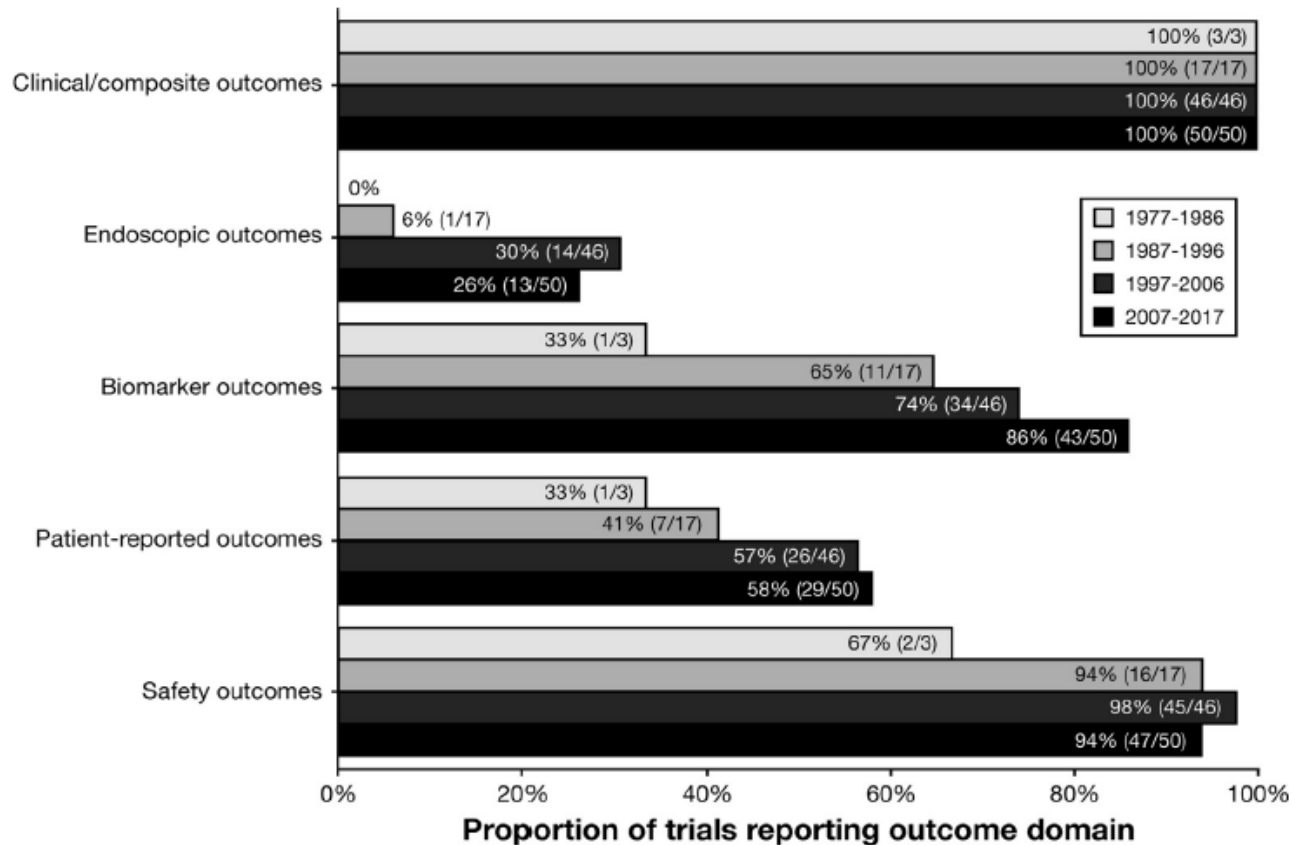
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Heterogeneity in Definitions of Efficacy and Safety Endpoints for Clinical Trials of Crohn's Disease: A Systematic Review

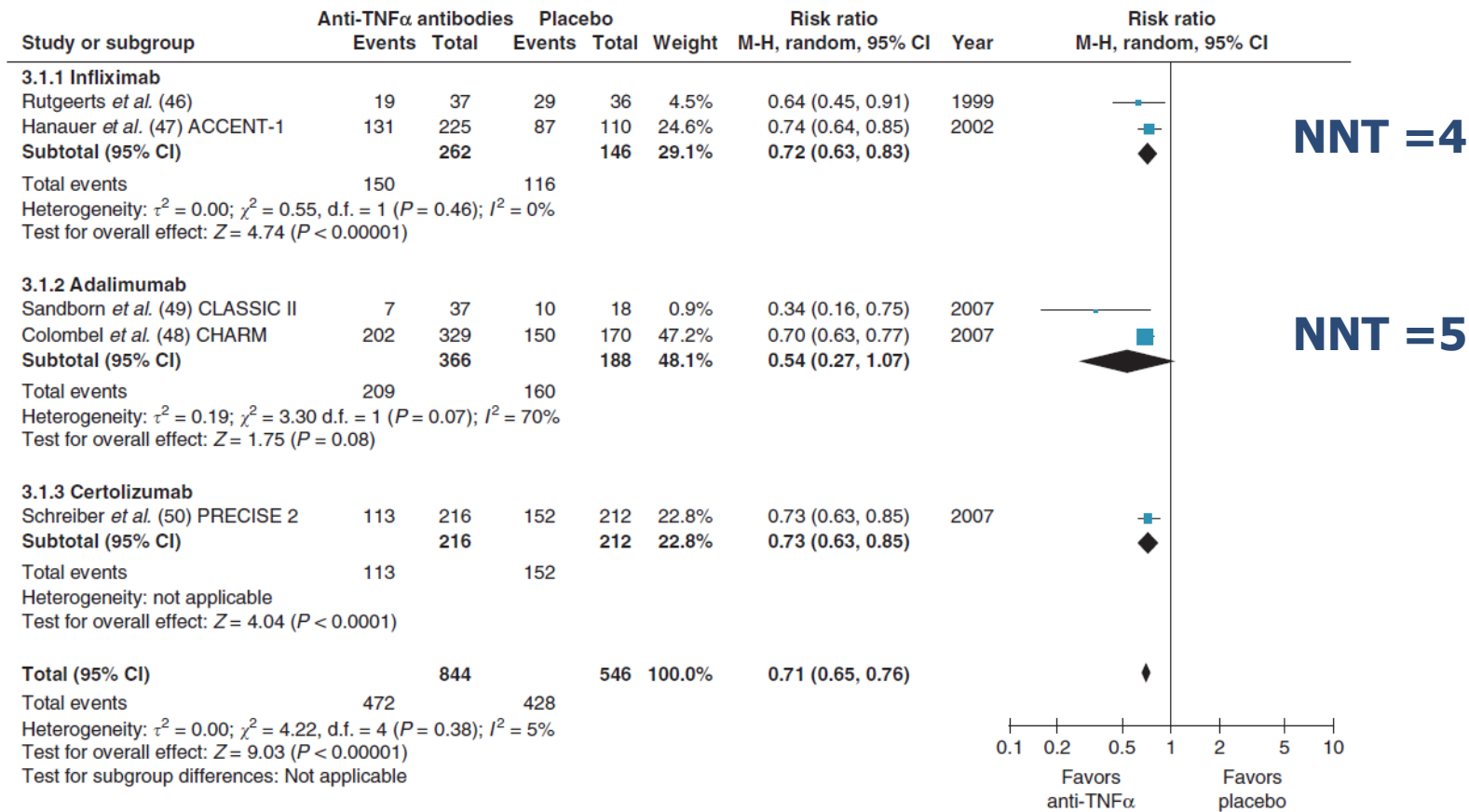


Christopher Ma,^{*,‡} Isra M. Hussein,[§] Yousef J. Al-Abbar,^{||} Remo Panaccione,^{*} Richard N. Fedorak,^{||} Claire E. Parker,[‡] Tran M. Nguyen,[‡] Reena Khanna,^{‡,#} Corey A. Siegel,^{**} Laurent Peyrin-Biroulet,^{‡‡} Rish K. Pai,^{‡,SS} Niels Vande Casteele,^{‡,|||} Geert R. D'Haens,^{‡,¶¶} William J. Sandborn,^{‡,|||} Brian G. Feagan,^{‡,#,##} and Vipul Jairath^{‡,#,##}



Efficacy of Biological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis

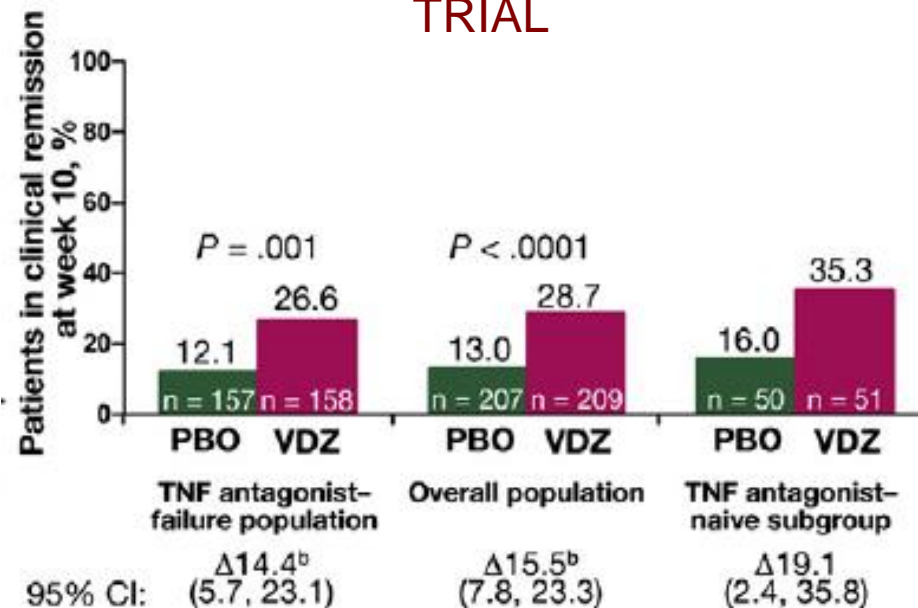
MAINTENANCE OF REMISSION IN CD USING ANTI-TNFs



Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed

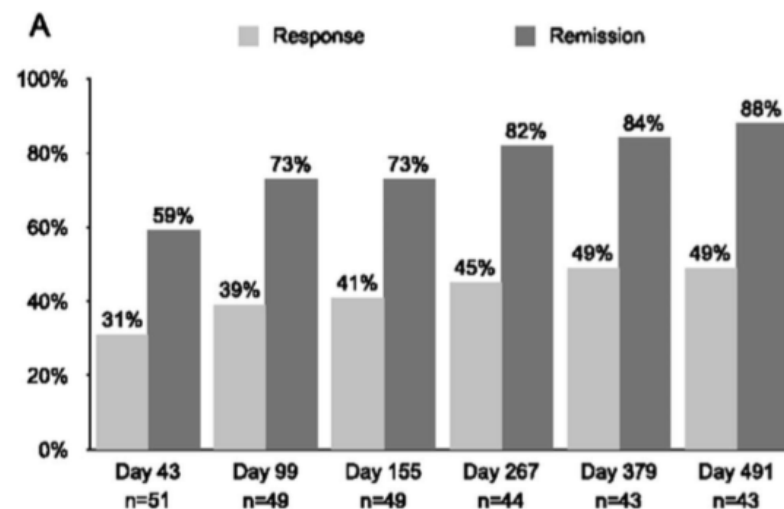
Bruce E. Sands,¹ Brian G. Feagan,² Paul Rutgeerts,³ Jean-Frédéric Colombel,^{1,4} William J. Sandborn,⁵ Richmond Sy,⁶ Geert D'Haens,⁷ Shomron Ben-Horin,⁸ Jing Xu,⁹ Maria Rosario,⁹ Irving Fox,⁹ Asit Parikh,¹⁰ Catherine Milch,⁹ and Stephen Hanauer¹¹

TRIAL





Sands, Gastroenterology 2014

RWE



Parikh, Inflamm Bowel Dis 2015

Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort

C. Ma^{*} , R. N. Fedorak[†], G. G. Kaplan^{*}, L. A. Dieleman[†], S. M. Devlin^{*}, N. Stern[†], K. I. Kroeker[†], C. H. Seow^{*} , Y. Leung[‡], K. L. Novak^{*}, B. P. Halloran[†], V. W. Huang[†], K. Wong[†], P. K. Blustein^{*}, S. Ghosh[§] & R. Panaccione^{*}

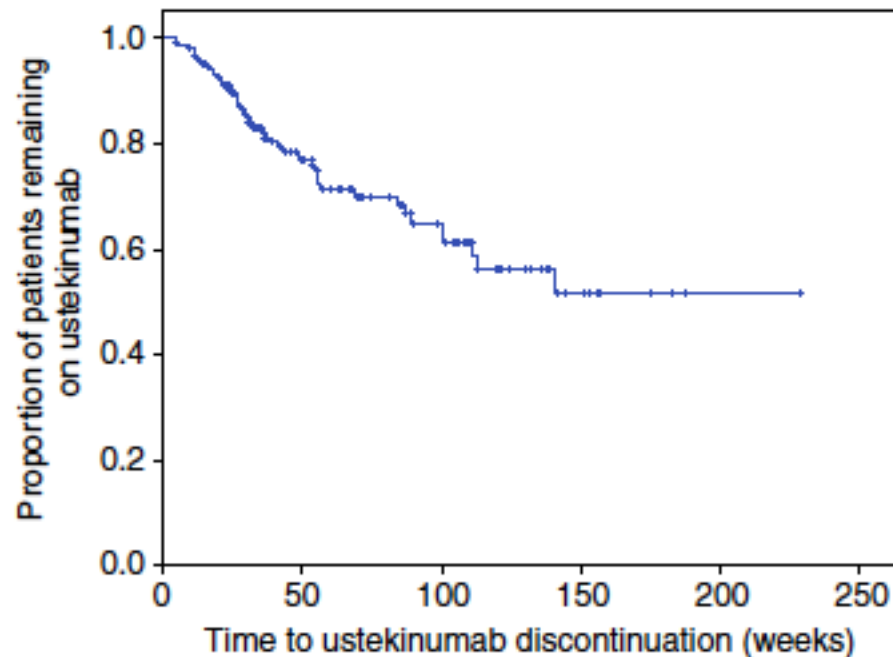


Table 3 | Adverse events related to ustekinumab among all treated patients

	n = 167
Patients with any adverse events, n (%)	53 (31.1)
Infections	20 (12.0)
Respiratory tract infections	11 (6.6)
Skin and soft tissue infections	5 (3.0)
<i>Clostridium difficile</i> infections	2 (1.2)
Other infections	2 (1.2)
Arthralgias	19 (11.4)
Headache	6 (3.6)
Injection reactions	11 (6.6)
Cutaneous rash	3 (1.8)
Hair loss	2 (1.2)
Patients with serious adverse events, n (%) [*]	11 (6.6)
Severe arthralgia	2 (1.2)
Severe infections	2 (1.2)
Severe fatigue	2 (1.2)
Severe injection reaction	3 (1.2)
Death [†]	1 (0.6)

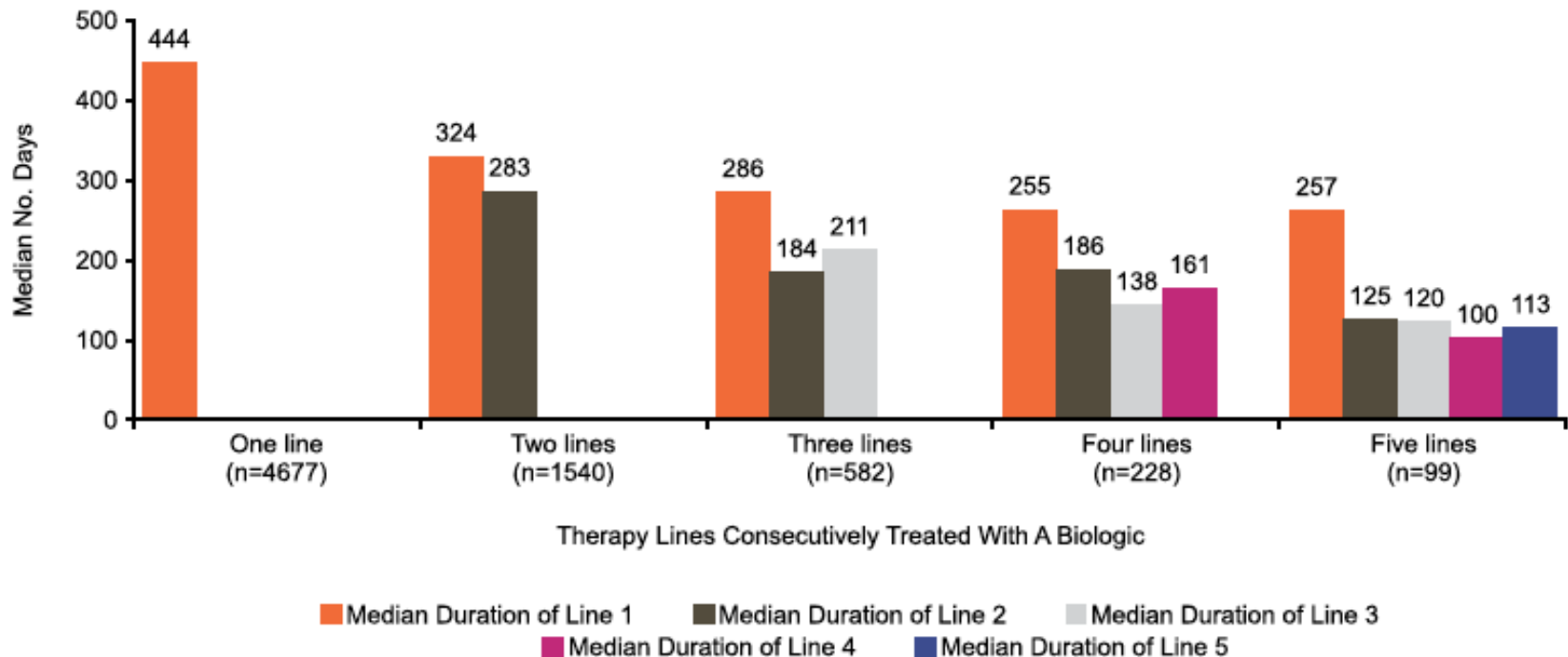
^{*} Serious adverse events defined by need for drug discontinua-

Treatment Patterns and Sequencing in Patients With Inflammatory Bowel Disease



Joanne E. Brady, PhD¹; Marni Stott-Miller, PhD²; George Mu, PhD¹; and Sue Perera, PhD²

CROHN



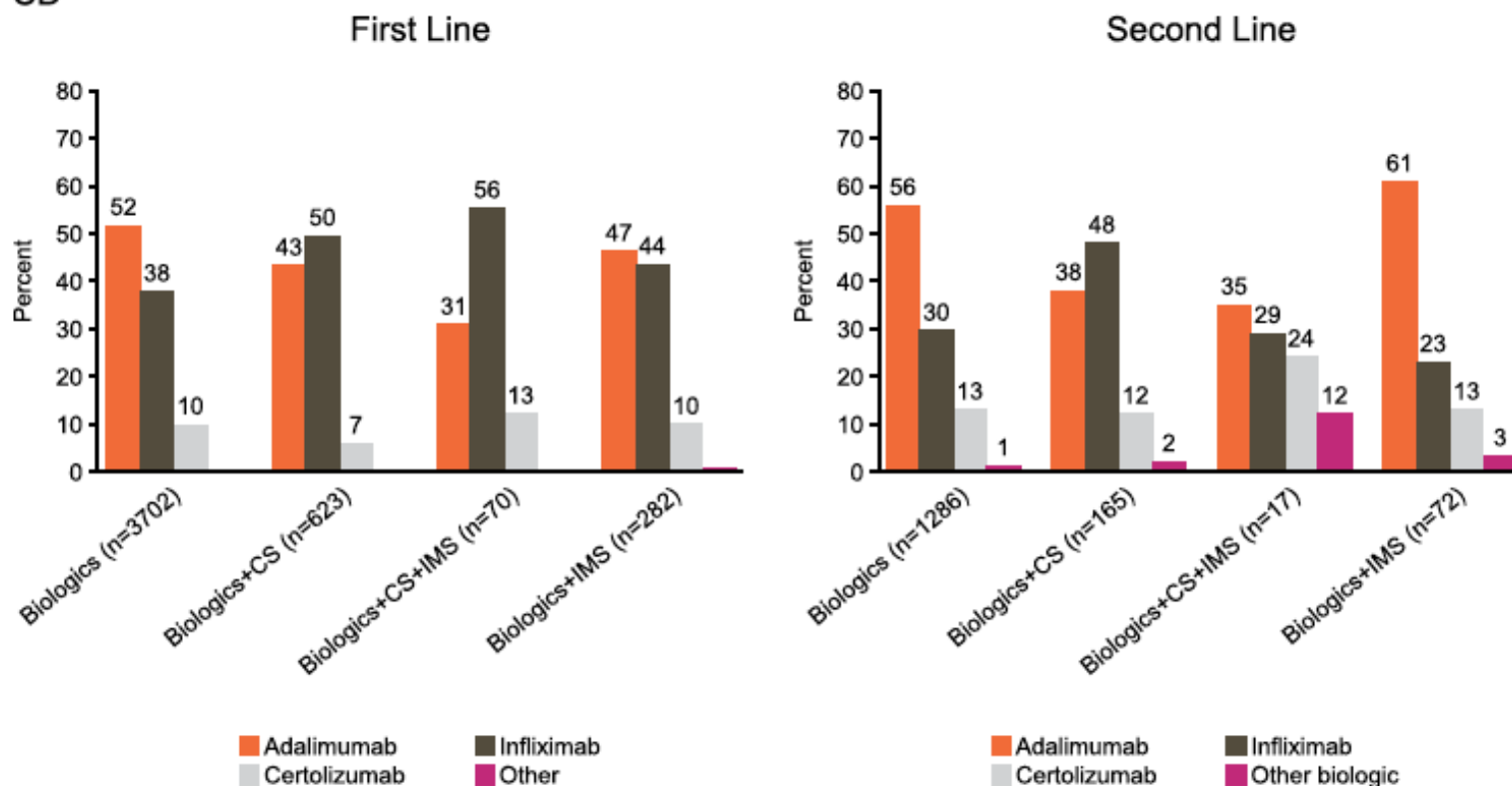
Treatment Patterns and Sequencing in Patients With Inflammatory Bowel Disease



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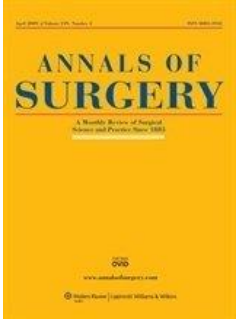
CROHN

CD



MODIFICATION OF SURGERY RATES AFTER ANTI-TNF?

ORIGINAL ARTICLES

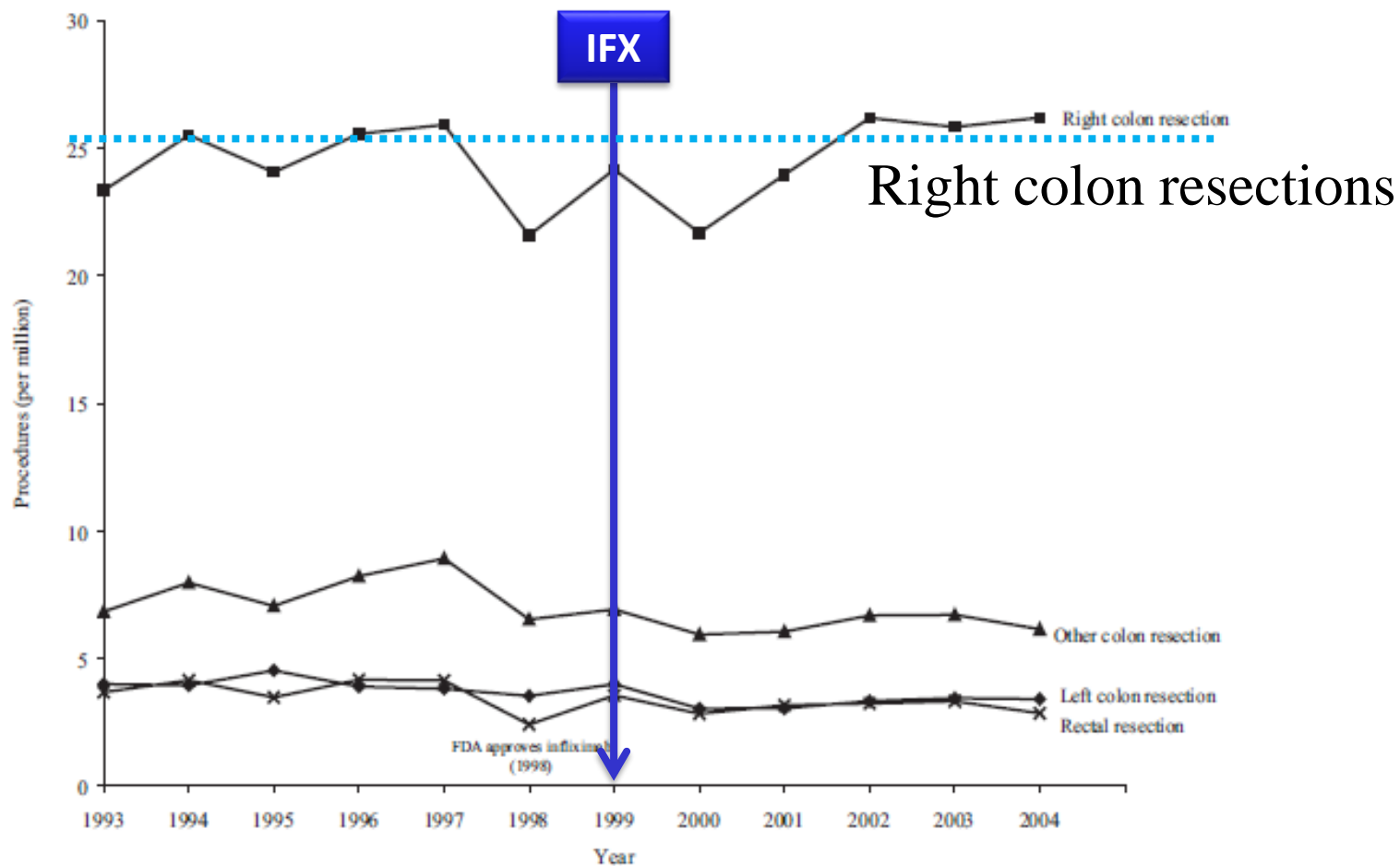


Trends in Surgery for Crohn's Disease in the Era of Infliximab

Douglas W. Jones, MD, and Samuel R. G. Finlayson, MD, MPH†‡*

- **USA: Nationwide populational study**
- **Hospital admissions for CD between 1993 and 2004**
- **Tendency analysis for the number of specific operations**
- **1000 hospitals – 8 million admissions/year**

CROHN'S DISEASE: SURGERY AND ANTI-TNF



Risk of Surgery for Inflammatory Bowel Diseases Has Decreased Over Time: A Systematic Review and Meta-analysis of Population-Based Studies

Frolkis, Gastroenterology 2013

Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management: Results from the Population-Based IBDSL Cohort

Jeuring, Am J Gastroenterol 2016

REVIEW ARTICLE

Are Surgical Rates Decreasing in the Biological Era In IBD?

Francesca Di Candido^{1,*}, Gionata Fiorino^{2,3}, Marco Spadaccini², Silvio Danese^{2,3} and Antonino Spinelli^{1,3}

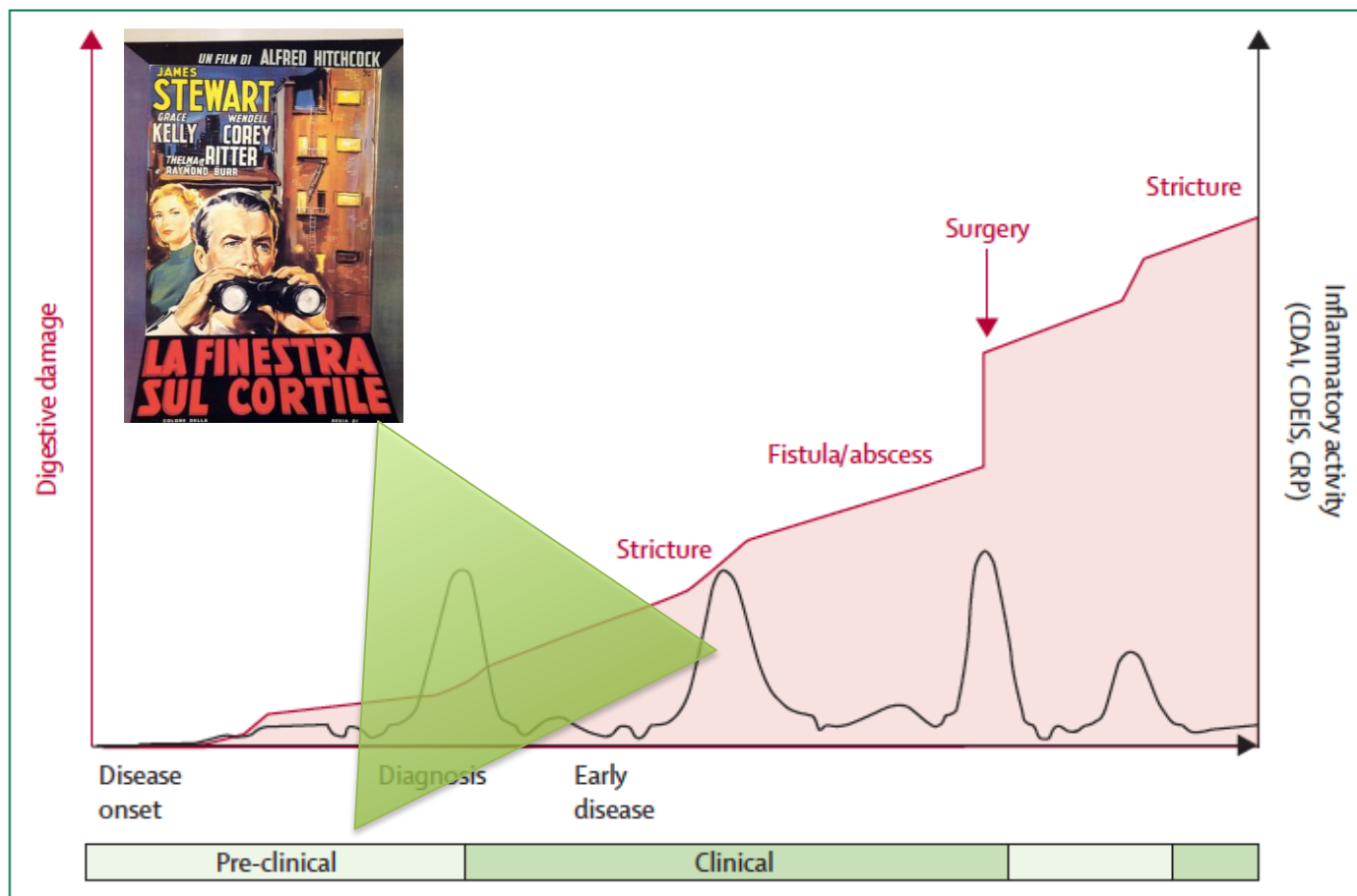
Di Candido, Curr Drug Target 2019

MEDICAL THERAPY: WHEN ENOUGH IS ENOUGH ?

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CLINICAL—ALIMENTARY TRACT

Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease

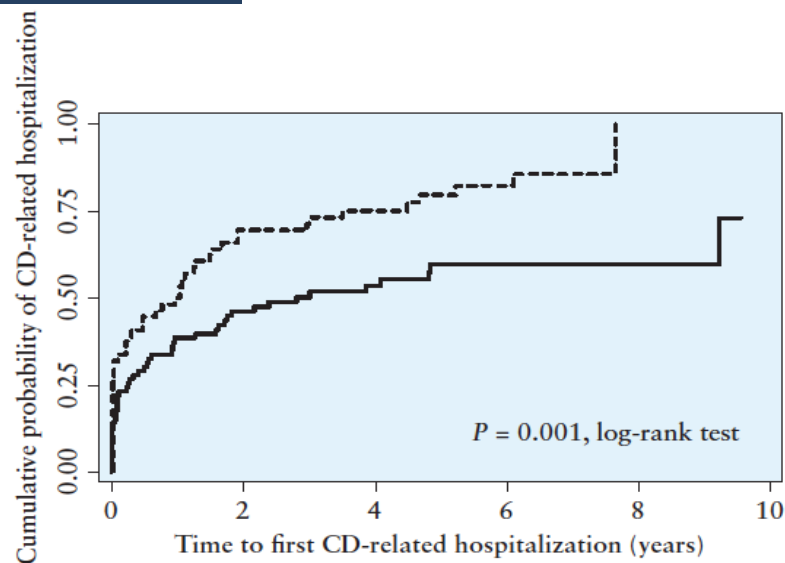
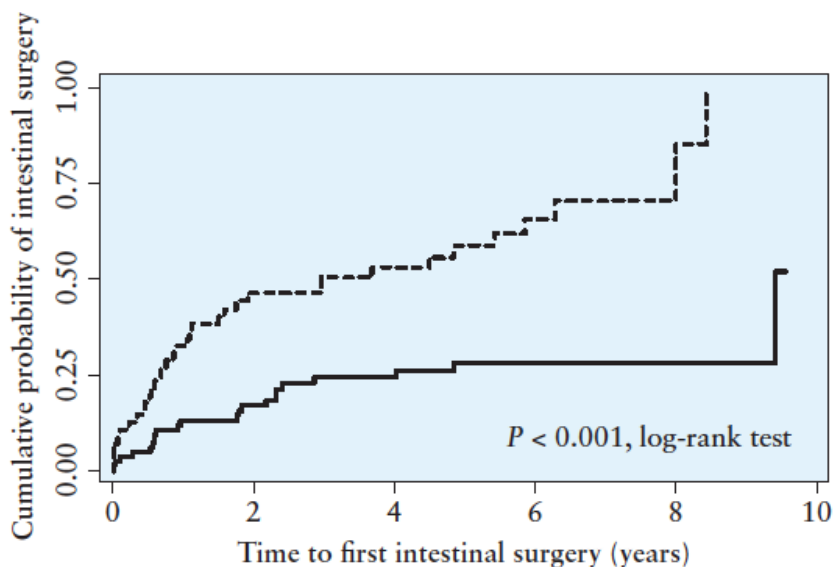


Prevalence of Bowel Damage Assessed by Cross-Sectional Imaging in Early Crohn's Disease and its Impact on Disease Outcome

Gionata Fiorino,^{a,*} Mathilde Morin,^{b,*} Stefanos Bonovas,^a
 Cristiana Bonifacio,^c Antonino Spinelli,^{d,e} Adeline Germain,^f
 Valérie Laurent,^g Camille Zallot,^b Laurent Peyrin-Biroulet,^b
 Silvio Danese^{a,e}

Bowel Damage L.I. > 4.8

142 CD pts



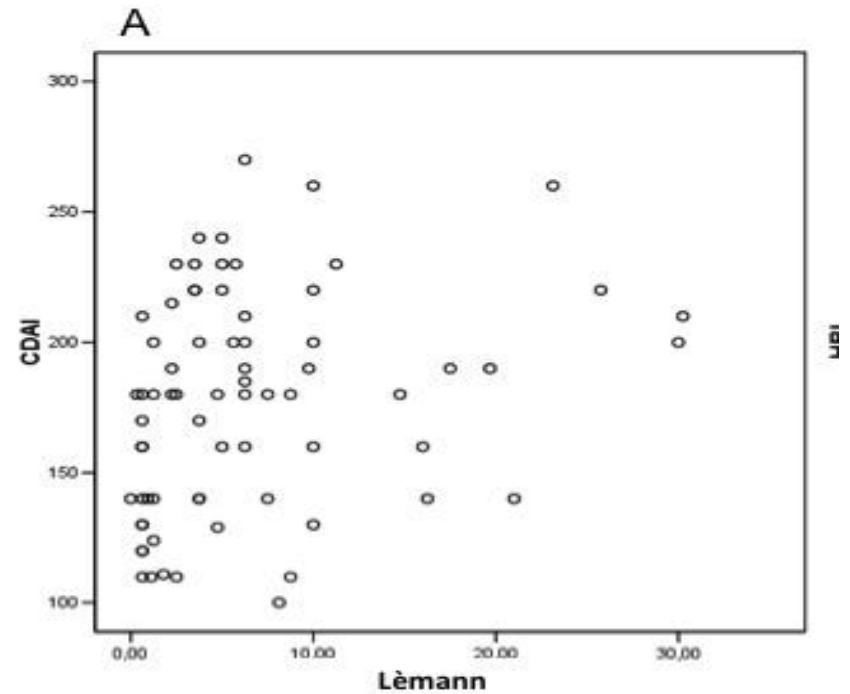
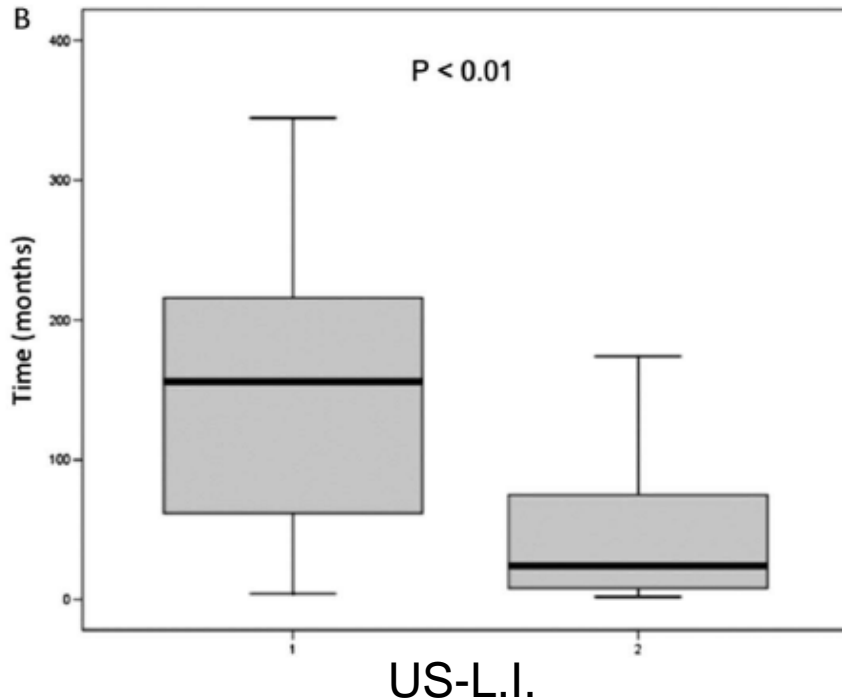
39% of CD patients showed bowel damage at diagnosis

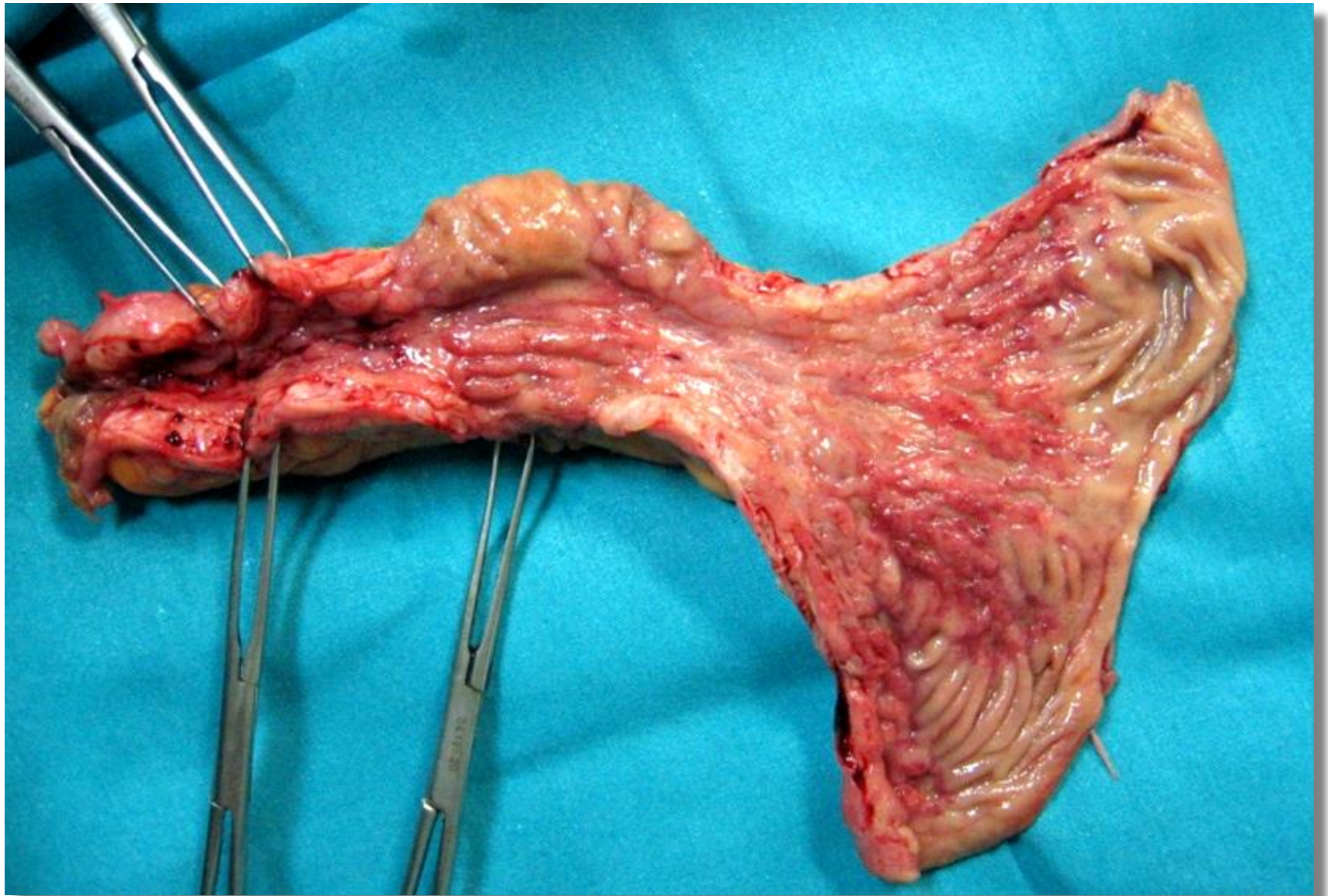
Bowel Damage in Crohn's Disease: Direct Comparison of Ultrasonography-based and Magnetic Resonance-based Lemann Index

Antonio Rispo, MD, PhD,* Nicola Imperatore, MD,* Anna Testa, MD, PhD,* Pierpaolo Mainenti, MD,[†] Giovanni Domenico De Palma, MD,[‡] Gaetano Luglio, MD,[§] Simone Maurea, MD,^{||} Olga Maria Nardone, MD,* Nicola Caporaso, MD,* and Fabiana Castiglione, MD*

Bowel Damage L.I. > 4.8

71 CD pts





Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review

Dominik Bettenworth,¹ Arne Bokemeyer,¹ Mark Baker,² Ren Mao,^{3,4} Claire E Parker,⁵ Tran Nguyen,⁵ Christopher Ma,^{5,6} Julián Panés,⁷ Jordi Rimola,⁸ Joel G Fletcher,⁹ Vipul Jairath,^{5,10,11} Brian G Feagan,^{5,10,11} Florian Rieder,^{4,12} on behalf of the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium.

Study ID	Radiographic modality	Wall thickness (mm)	Luminal narrowing (mm)	Wall thickening (mm)	Criteria required for stricture diagnosis
Ultrasound (US)	Baumgart <i>et al</i> ¹⁴	✓	✓	✓ >3mm	Not further specified
	Kumar <i>et al</i> ¹⁵	✓	✓	✓	Wall thickening
	Maconi <i>et al</i> ¹⁶	✓ >25 mm	✓ Markedly narrowed lumen	✓ >4mm	All criteria required
	Onali <i>et al</i> ¹⁷	✓	✓ <10 mm	✓	Luminal narrowing
	Pallotta <i>et al</i> ¹⁸	✓ >25 mm	✓ <10 mm	✓	Luminal narrowing
	Ripollès <i>et al</i> ¹⁹	✓	✓	✓	Not further specified
	Serra <i>et al</i> ²⁰	✓	✓	✓ >4mm	All criteria required
	Stidham <i>et al</i> ²¹	Not Indicated	Not Indicated	Not Indicated	Not further specified
	Wilkens <i>et al</i> ²²	✓	✓	✓	Not further specified
	CT	Adler <i>et al</i> ²³	✓	✓	✓ ≥3mm
Chorean <i>et al</i> ²⁴		✓	✓ Luminal narrowing ≤50%	✓	Luminal narrowing
Pellino <i>et al</i> ²⁶		✓	✓	✓ >3mm	Not further specified
Vogel <i>et al</i> ²⁵		✓ >3 cm	✓ <10 mm	✓ >5mm	Luminal narrowing and wall thickening
MRI		Kumar <i>et al</i> ¹⁵	✓	✓	✓
	Li <i>et al</i> ²⁷	Not Indicated	Not Indicated	Not Indicated	Not further specified
	Pellino <i>et al</i> ²⁶	✓	✓	✓ >3mm	Not further specified
	Pous-Serrano <i>et al</i> ²⁸	Not Indicated	Not Indicated	Not Indicated	Not further specified
	Punwani <i>et al</i> ²⁹	✓	✓	✓	Not further specified
	Rimola <i>et al</i> ³⁰	✓	✓ Luminal narrowing ≤50%	✓	Luminal narrowing ≤50% and prestenotic dilation
	Sinha <i>et al</i> ³⁴	✓	✓	✓ >3mm	Not further specified
	Steward <i>et al</i> ²⁵	✓	✓	✓	Not further specified
	Tielbeek <i>et al</i> ³¹	✓	✓	✓	Not further specified
	Wagner <i>et al</i> ³²	✓	✓	✓	Not further specified
	Wilkens <i>et al</i> ²²	✓	✓	✓	Not further specified
	Zappa <i>et al</i> ³³	✓ >1.5 of normal loop	✓	✓	Not further specified

CEUS, contrast-enhanced ultrasound; MT, magnetisation transfer; PET, positron emission tomography; SICUS, small Intestinal contrast ultrasonography; TUS, transabdominal ultrasonography; US, ultrasound.

Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review

Dominik Bettenworth,¹ Arne Bokemeyer,¹ Mark Baker,² Ren Mao,^{3,4} Claire E Parker,⁵ Tran Nguyen,⁵ Christopher Ma,^{5,6} Julián Panés,⁷ Jordi Rimola,⁸ Joel G Fletcher,⁹ Vipul Jairath,^{5,10,11} Brian G Feagan,^{5,10,11} Florian Rieder,^{4,12} on behalf of the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium.

While MRE has excellent capability to assess the degree of inflammation, fibrosis detection is likely problematic.

Combined Endoscopic/Sonographic-based Risk Matrix Model for Predicting One-year Risk of Surgery: A Prospective Observational Study of a Tertiary Centre Severe/Refractory Crohn's Disease Cohort

Antonio Rispo,^a Nicola Imperatore,^a Anna Testa,^a Luigi Bucci,^b Gaetano Luglio,^b Giovanni Domenico De Palma,^c Matilde Rea,^a Olga Maria Nardone,^a Nicola Caporaso,^a Fabiana Castiglione^a

		SMALL BOWEL CD EXTENSION			
		EXT < 33	EXT ≥ 33		
ENDOSCOPY	SES-CD ≥ 9	15.9% (8.32–31.63)	87.5% (78.3–94.5)	B 2-3	BEHAVIOR
	SES-CD < 9	1.65% (0.66–3.46)	23.7% (14.4–39.3)	B 1	
		BWT < 7	BWT ≥ 7		
BOWEL SONOGRAPHY					

MEDICAL THERAPY: WHEN ENOUGH IS ENOUGH ?

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ECCO-ESCP Consensus on Surgery for Crohn's Disease

3.1.1.1. ECCO-ESCP Statement 2A

Free perforation with peritonitis and massive haemorrhage unresponsive to other therapies are indications for emergency surgery in CD [EL3]

3.1.1.2. ECCO-ESCP Statement 2B

Patients with CD who present with acute severe colitis should be under daily and interdisciplinary surveillance by a specialised gastroenterologist and surgeon, in haemodynamically stable patients without peritonitis. [EL5]. Any clinical deterioration or failure to improve within approximately 1 week despite optimal medical treatment should prompt consideration for an emergent surgery [EL3]

ECCO-ESCP Consensus on Surgery for Crohn's Disease

3.1.1.3. ECCO-ESCP Statement 2C

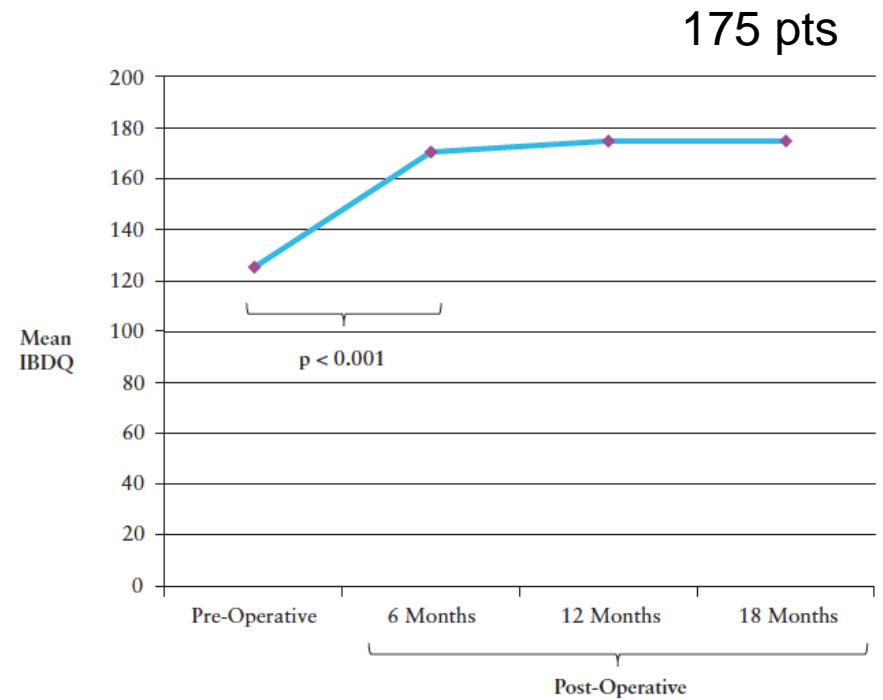
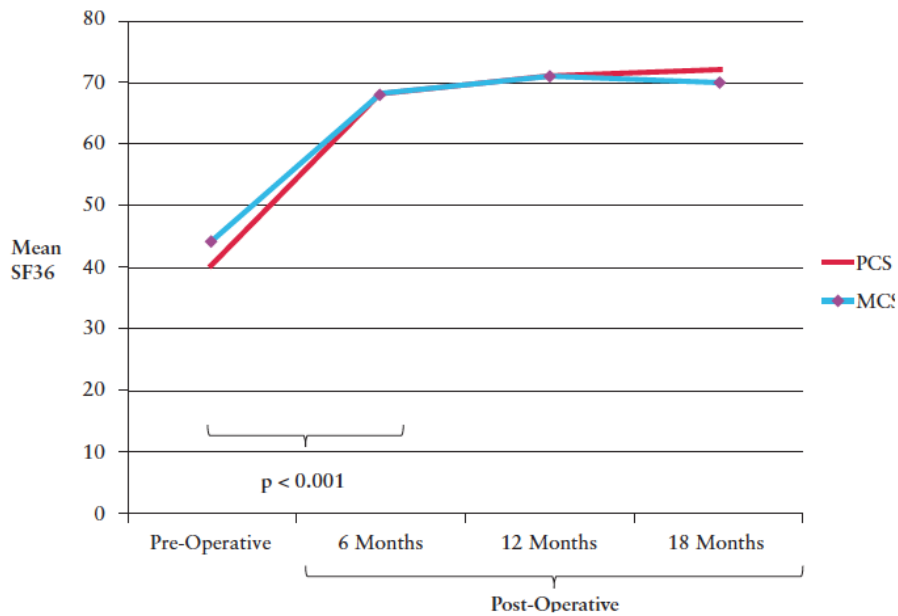
Acute intestinal obstruction caused by an inflamed or fibrotic segment should be initially treated with conservative measures. Emergency surgery is indicated in rare cases of complete bowel obstruction, or if bowel ischaemia is suspected. In cases of partial bowel obstruction nonresponsive to medical therapy, surgery can usually be scheduled after the patient is optimised [EL4]

3.1.2.1. ECCO-ESCP Statement 2D

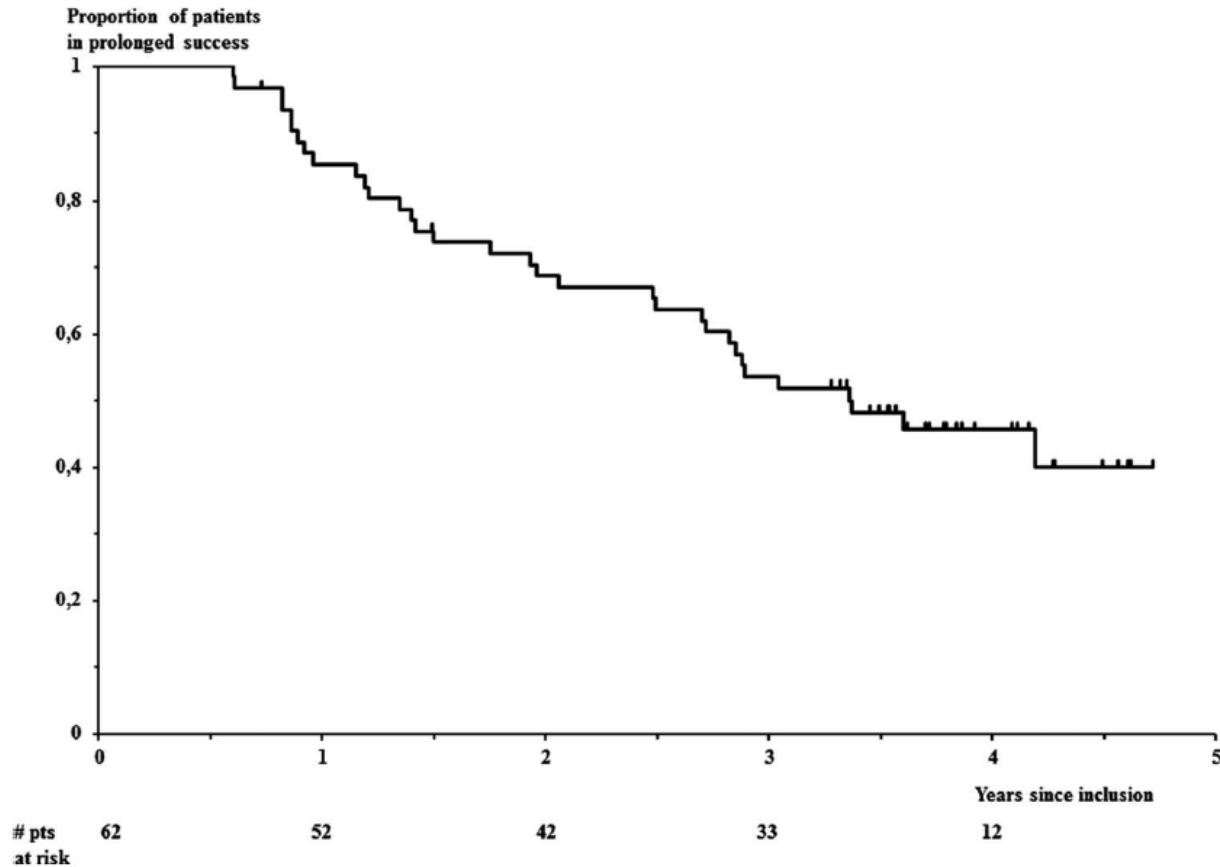
Surgery is the preferred option in patients with localised ileocaecal CD with obstructive symptoms but no significant evidence of active inflammation [EL4]



Effect of Intestinal Resection on Quality of Life in Crohn's Disease



Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study



Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study

Table 3 Baseline magnetic resonance enterography features of the 97 patients with Crohn's disease and symptomatic small bowel stricture(s) (maximal or more severe characteristic across strictures, except if otherwise indicated)

Characteristics	n, frequency (%) or median (IQR)
Maximum wall thickness (mm)	8 (7–10)
Stricture(s) length (mm)*	15 (7–25)
Degree of enhancement	
Parenchymatous phase	
At least mild to moderate	94 (97)
Severe	57 (59)
Delayed phase†	
At least mild to moderate	91 (98)
Severe	53 (57)
Pattern of enhancement	
Parenchymatous phase (90 s after gadolinium injection)	
Homogeneous (>70%)	46 (47)
Layered (>70%)	52 (54)
Mixed pattern	10 (10)
Delayed phase (8 min after gadolinium injection)	
Homogeneous	58 (62)
Layered	33 (35)
Mixed pattern	7 (8)
T2 wall hypersignal	61 (63)
Deep ulceration	26 (27)
Inflammatory change of mesenteric fat	
Blurred wall at least	36 (37)
Mass or phlegmon without abscess	4 (4)
Luminal diameter in the segment proximal to the narrowing (mm)	25 (18–29)
Luminal diameter in the most narrowed segment (mm)	2 (1–3)
Comb sign‡	64 (66)
Fistula	
Blind	17 (18)
Internal	7 (7)
Cutaneous	0 (0)
Abscess	0
Fibro-fatty proliferation	59 (61)
Lymph nodes§	
Size >3 mm	58 (60)
Enhancement	54 (56)

Table 5 Serious adverse events in 97 patients registered during the study

Variable	From week 0 to week 24	After week 24	Total
Patients with at least one serious adverse event, n (%)	31 (32)	39 (40)	70 (72)
Patients with serious adverse events, n			
Surgery for Crohn's disease	18	30	48
Endoscopic dilation	2	2	4
Hospitalisation for Crohn's disease complication*	9	4	13
Neurological disorder	0	1	1
Myelodysplasia†	1	0	1
Basal cell carcinoma	1	1	2
Lymphoma	0	1	1

*Occlusive syndrome (seven), severe abdominal pain (three), fever and nausea (one), severe acute diarrhoea (one) and subacute folliculitis (one).

†The patient died at the age of 82 years, 12 months later of myelodysplasia, diagnosed 1 month after adalimumab initiation in combination with azathioprine, initiated 12 months before.

ECCO-ESCP Consensus on Surgery for Crohn's Disease

3.1.2.3. ECCO-ESCP Statement 2F

In patients with symptomatic perforating/fistulising disease, surgery should be considered at an early stage [EL4]

Perforating Crohn's Ileitis: Delay of Surgery Is Associated with Inferior Postoperative Outcome

Igors Iesalnieks, MD,* Alexandra Kilger, MD,* Heidi Glaß, MD,* Florian Obermeier, MD,[†]
Ayman Agha, MD,* and Hans J. Schlitt, Prof.*

Inflamm Bowel Dis 2010.

197 patients (cohort) undergoing bowel resection for penetrating ileitis

Correlation between «***duration of preoperative deterioration***» which led to surgery and ***perioperative outcomes***

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 (<i>n</i> = 72)	5	15%	30%	28%	1.4%	7%
2000–2004 (<i>n</i> = 73)	4	20%	27%	23%	1.4%	18%
2005–2009 (<i>n</i> = 86)	6	34%	51%	46%	18.6%	36%

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

Sponsor:

Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives

Predictive Factors of ANTI-TNF Response in Luminal Crohn's Disease Complicated by Abscess (MICA)

Study Design

Go to

Study Type ⓘ : Observational

Actual Enrollment ⓘ : 125 participants

Observational Model: Cohort

Time Perspective: Prospective

Official Title: Predictive Factors of ANTI-TNF Response in Luminal **Crohn's** Disease Complicated by Abscess A Multicenter Prospective, Observational Cohort Study

Actual Study Start Date ⓘ : April 2013

Actual Primary Completion Date ⓘ : January 2019

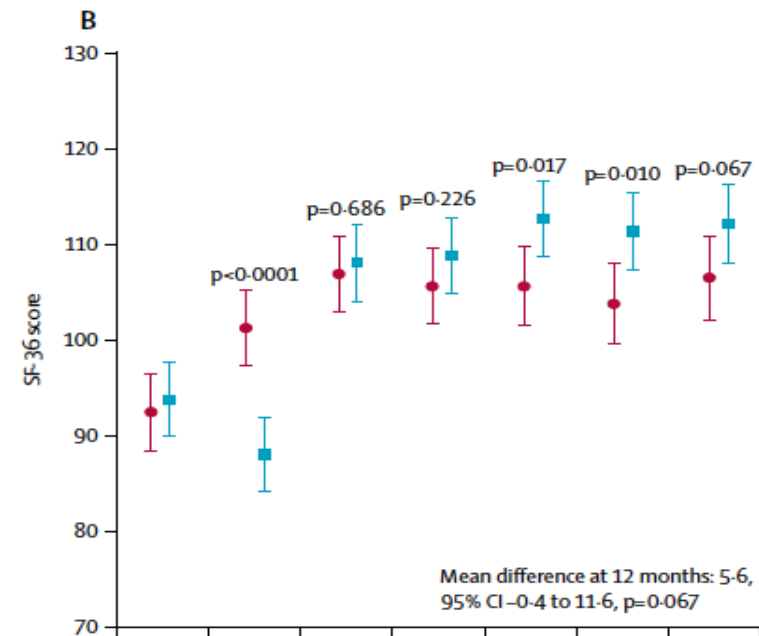
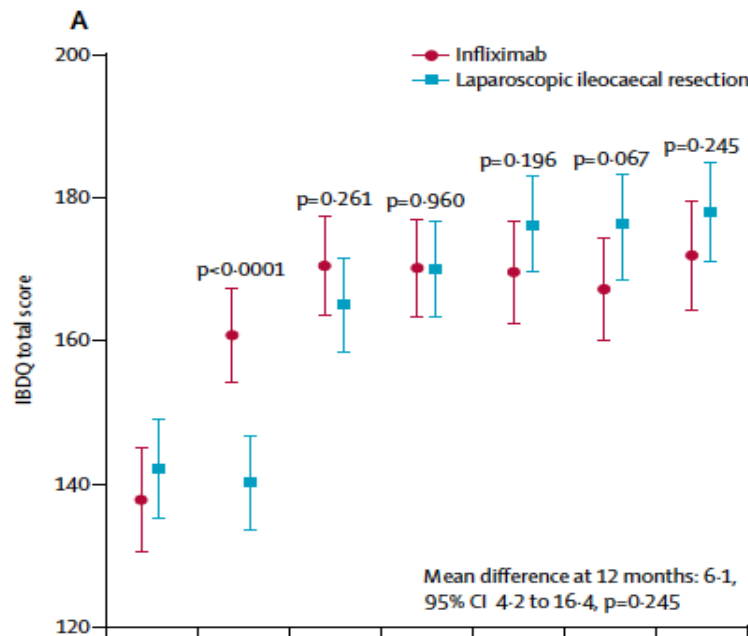
Estimated Study Completion Date ⓘ : May 2019

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Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial

Cyriel Y Ponsioen, E Joline de Groof, Emma J Eshuis, Tjibbe J Gardenbroek, Patrick M M Bossuyt, Ailsa Hart, Janindra Warusavitarne, Christianne J Buskens, Ad A van Bodegraven, Menno A Brink, Esther C J Consten, Bart A van Wagenveld, Marno C M Rijk, Rogier M P H Crolla, Casper G Noomen, Alexander P J Houdijk, Rosalie C Mallant, Maarten Boom, Willem A Marsman, Hein B Stockmann, Bregje Mol, A Jeroen de Groof, Pieter C Stokkers, Geert R D'Haens, Willem A Bemelman, on behalf of the LIR!C study group*



ECCO-ESCP Consensus on Surgery for Crohn's Disease

2.2.1. ECCO-ESCP Statement 1A

Laparoscopy, when feasible, should be the preferred approach in surgery for CD. It results in reduced morbidity, shorter hospital stay, reduction in adhesions and hernia formation, and improved cosmesis [EL1]

3.3.1. ECCO-ESCP Statement 20

Application of the principles of enhanced recovery after elective intestinal surgery [ERAS] is recommended for CD, and conveys advantage in postoperative recovery [EL 2]

Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C Trial

	Unit	Laparoscopic ileocaecal resection		Infliximab		Mean Difference	95% CI
		n=73		n=70			
		Mean (SD) units	Mean (SD) costs	Mean (SD) units	Mean (SD) costs		
Index treatment							
Ileocaecal resection	Procedure	0.96 (0.17)	€4240 (880)	0.00 (0.00)	€0 (0)	€4240	€4025 to €4421
Infliximab	Infusions	0.00 (0.00)	€0 (0)	6.46 (259)	€14 197 (6727)	€-14197	€-15 781 to €-12 613
Admission (ward)	Days	6.45 (3.76)	€3540 (240)	6.76 (3.18)	€3527 (1891)	€-13	€-652 to €661
Admission (intensive care unit)	Days	0.47 (0.32)	€1117 (7826)	0.00 (0.00)	€0 (0)	€1117	€215 to €3365
Surgical re-intervention	Procedure	0.04 (0.17)	€177 (863)	0.00 (0.00)	€0 (0)	€117	€42 to €415
	<i>Subtotal</i>	–	€9074 (1145)	–	€17 724 (944)	€-8650	€-11 398 to €-5147
Readmissions and re-interventions							
Readmission (ward)	Days	2.03 (7.69)	€1056 (3742)	1.74 (4.27)	€923 (2435)	€1056	€-904 to €1251
Readmission (intensive care unit)	Days	0.00 (0.00)	€0 (0)	0.00 (0.00)	€0	€ 0	€0 to €0
Ileocaecal resection	Procedure	0.00 (0.00)	€0 (0)	0.20 (0.41)	€886 (1799)	€-886	€-1318 to €497
Stoma closure	Procedure	0.05 (0.17)	€138 (572)	0.01 (0.08)	€36 (302)	€102	€-36 to €256
Surgical (re)intervention	Procedure	0.03 (0.17)	€24 (145)	0.01 (0.08)	€46 (385)	€-21	€-136 to €51
Radiological intervention	Procedure	0.09 (0.42)	€19 (85)	0.00 (0.00)	€0 (0)	€19	€3 to €41
Balloon dilatation	Procedure	0.00 (0.00)	€0 (0)	0.01 (0.08)	€10 (83)	€-10	€-36 to €8
Infliximab/adalimumab	Infusions	0.18 (0.85)	€413 (2008)	0.01 (0.08)	€30 (251)	€383	€-27 to €911
	<i>Subtotal</i>	–	€1650 (4862)	–	€1931 (4041)	€-280	€-1701 to €1159
Mean total costs at 12 months		–	€10 724 (12 483)	–	€19 655 (7254)	€-8931	€-12 087 to €-5097

CONCLUSIONS: WHEN ENOUGH IS ENOUGH ?

- WHEN DRUGS DO NOT WORK...

“Strategic” trials – HeadToHead trials – “Targeted” therapy - Addresses of Authorities

- WHEN DRUGS ARE NOT ABLE TO WORK...

Early diagnosis – Better definition of fibrosis

- WHEN SURGERY SHOULD BE THE FIRST CHOICE...

“Chi è causa del suo mal pianga se stesso...”

- SOMETIMES IT’S ALREADY ENOUGH AT THE BEGINNING...

Better strategies for post-operative recurrence

THANK YOU FOR YOUR ATTENTION...

