

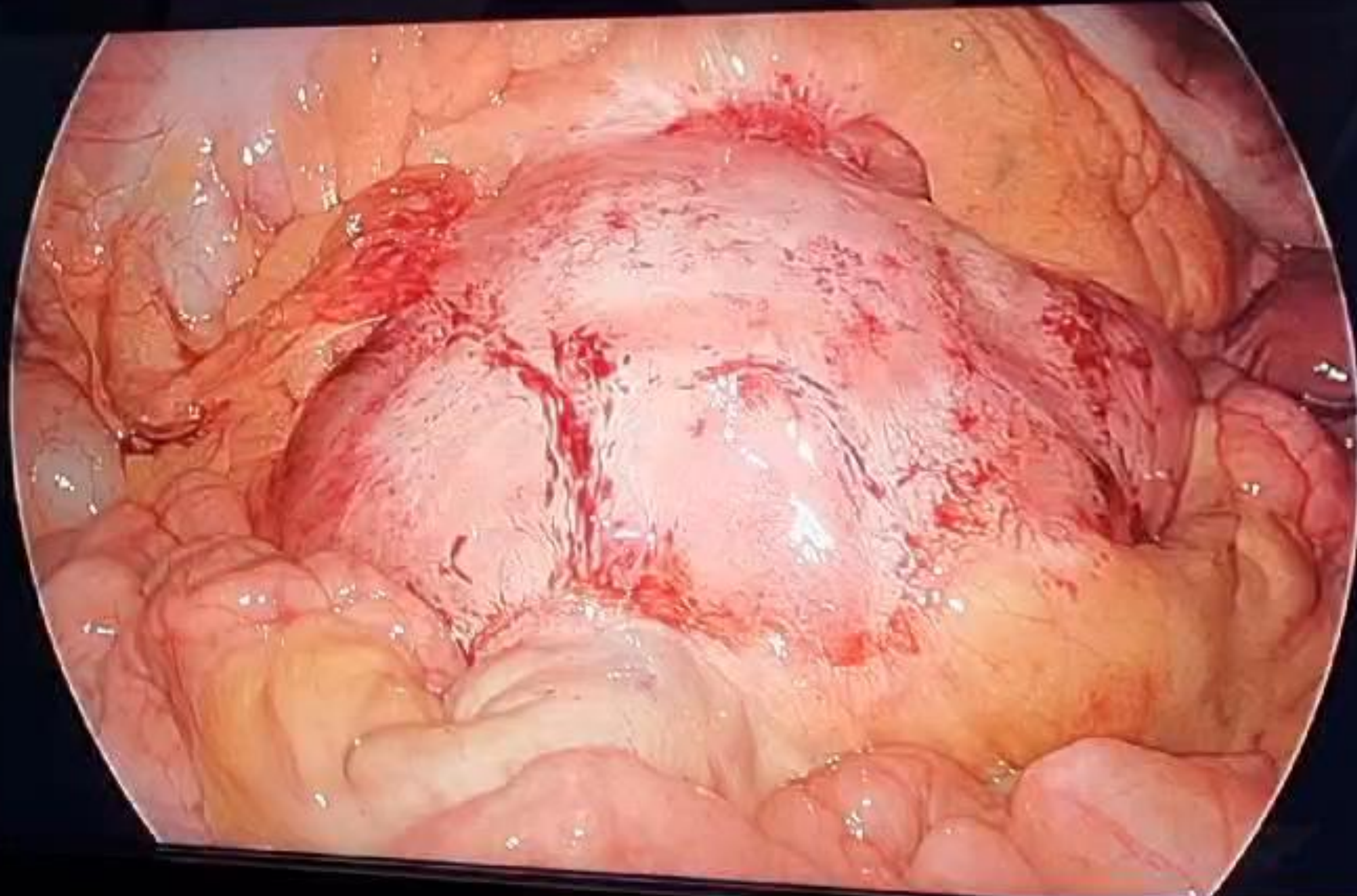


Desmoid Fibromatosis

Gabriela Moeslein

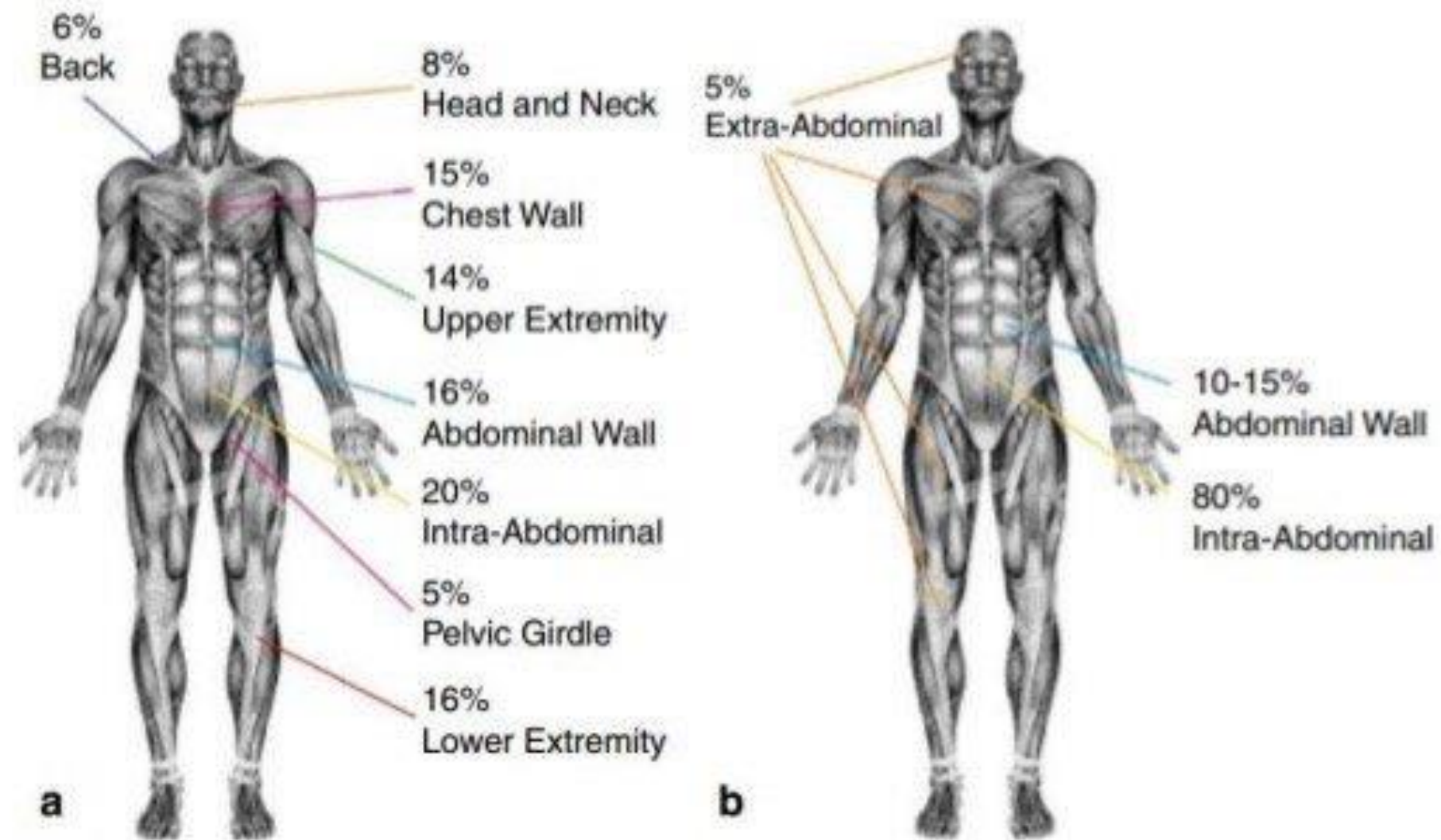
gmoeslein@outlook.de

Is this a desmoid?



Desmoid = aggressive fibromatosis

MAJOR ANATOMIC SITES



a. Locations of all desmoid tumors b. FAP-associated desmoid tumors

Desmoid Tumor: Some facts

- Desmoid tumors comprise 3% of soft tissue tumors
- Desmoids are the most common primary tumor of the mesentery and can mimic a malignant bowel or mesenteric neoplasm
- Do not metastasize, but fulfill criteria of malignancy for local growth
- Related to trauma (also surgical trauma)
- Occur in approx. 30% of FAP patients (75% after colectomy)
- Spontaneous regression in 5 – 10% of cases
- Recurrence rates after surgical resection, radiation therapy and aggressive chemotherapy are approximately 60 – 70%

Desmoid Tumor: Some examples



Desmoid Tumor: Some examples

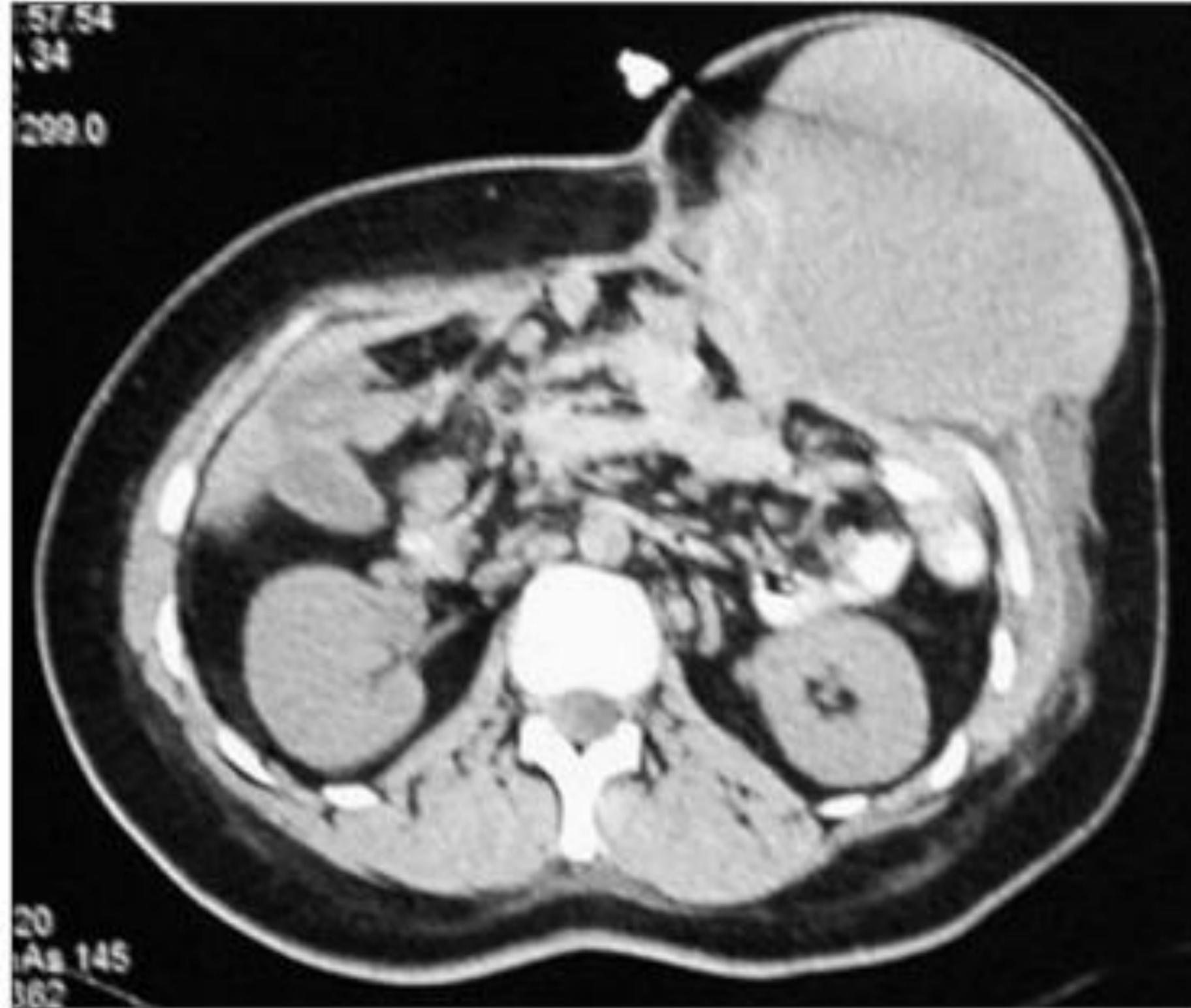
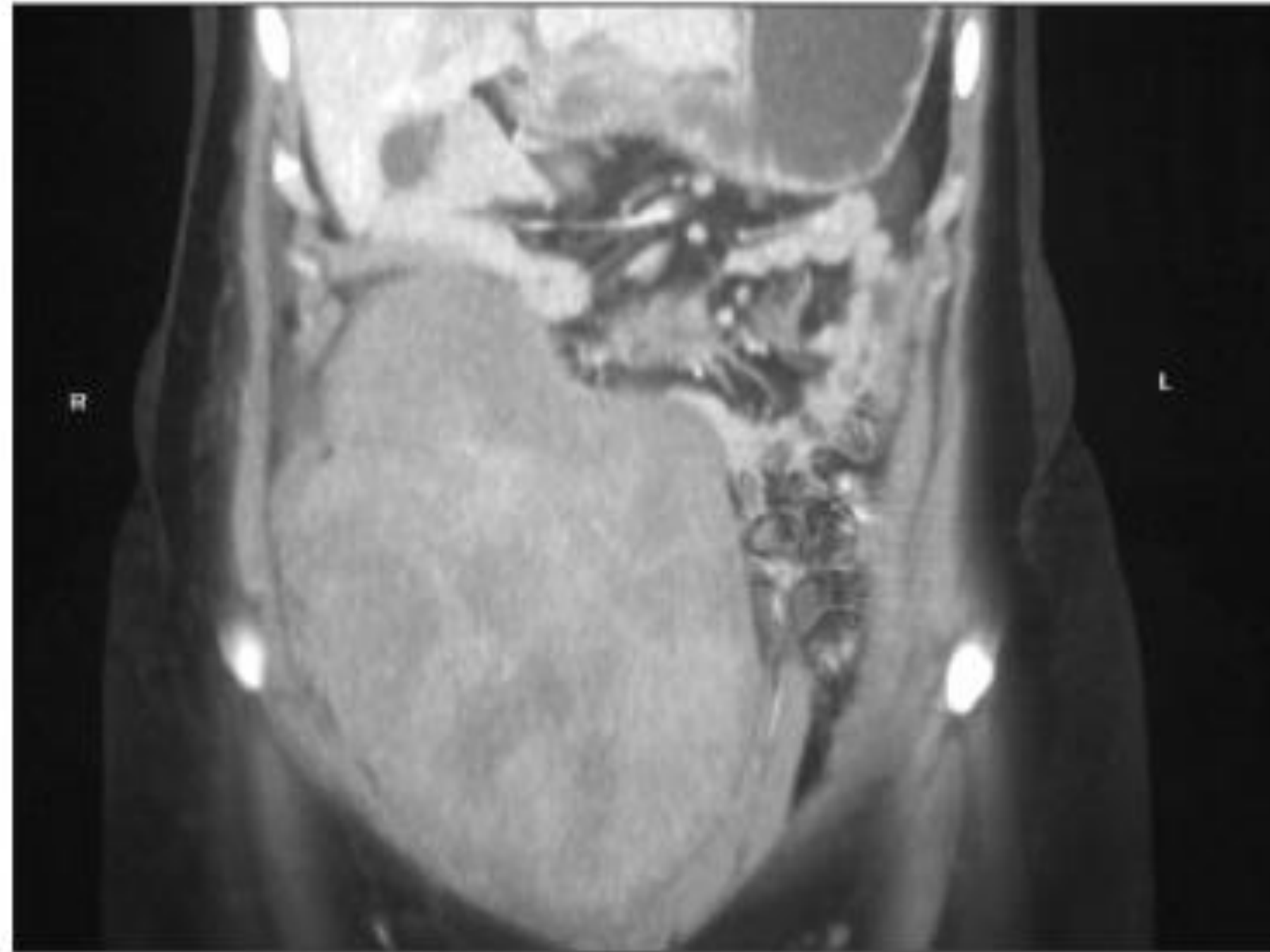


Fig. 6. CT scan showing a large desmoid tumor of the left rectus abdominis.

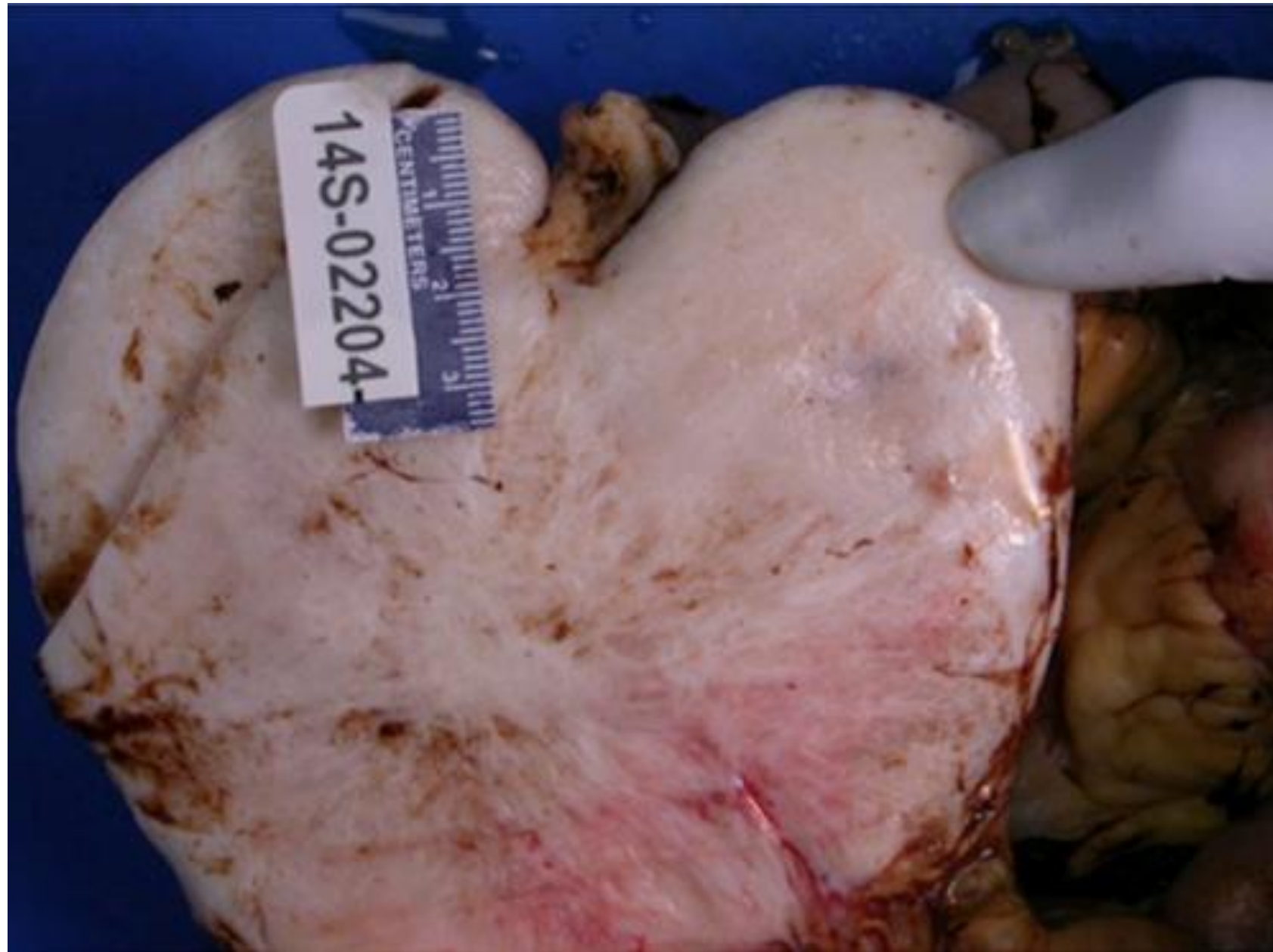
Desmoid Tumor: Some examples



Desmoid Tumor: Some examples



Desmoid Tumor: Specimen characteristics

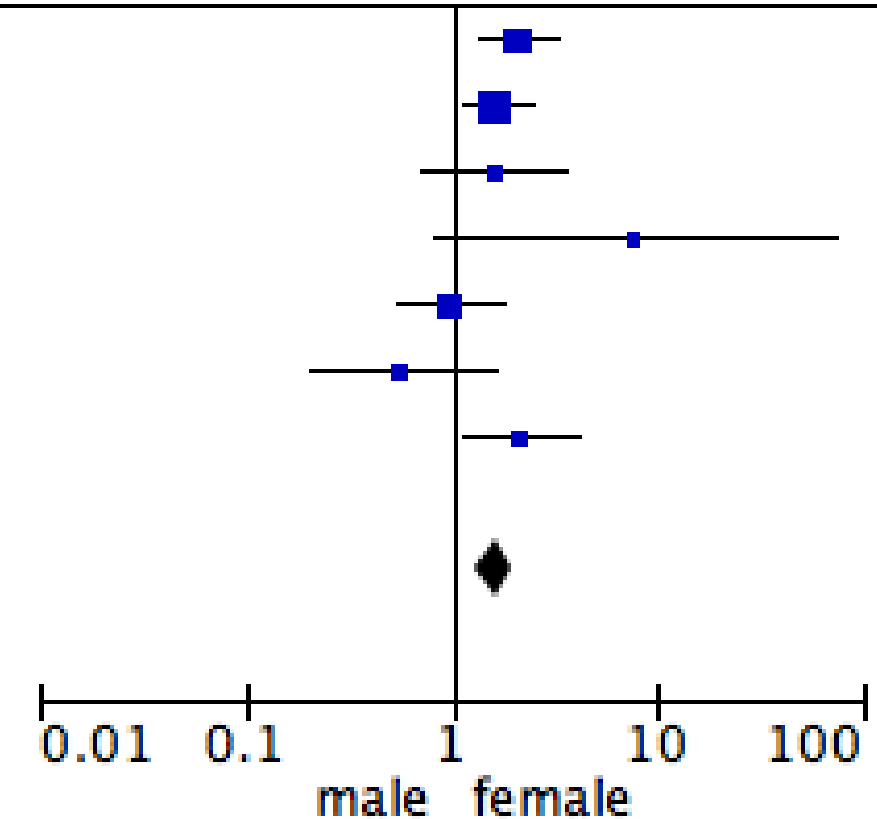


Aetiological factors

- Oestrogens
- Trauma
- Genetics

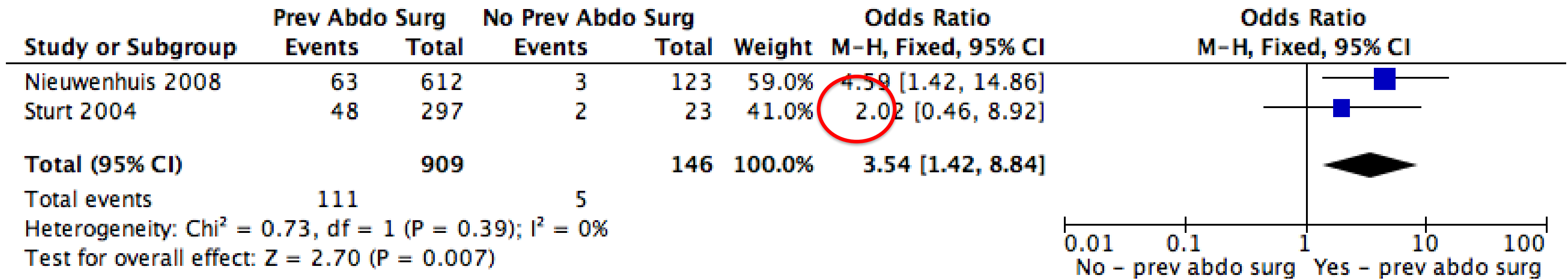
Oestrogens

| Study or Subgroup | female | | male | | Weight | Odds Ratio | Odds Ratio |
|--|--------|-------------|--------|-------------|---------------|--------------------------|--------------------|
| | Events | Total | Events | Total | | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Bertario 2001 | 65 | 403 | 42 | 494 | 24.8% | 2.07 [1.37, 3.13] | |
| Durno 2007 | 71 | 420 | 51 | 467 | 31.4% | 1.66 [1.13, 2.44] | |
| Heiskanen 1996 | 17 | 98 | 12 | 104 | 7.5% | 1.61 [0.73, 3.57] | |
| Hizawa 1997 | 5 | 22 | 1 | 27 | 0.5% | 7.65 [0.82, 71.29] | |
| Lefevre 2008 | 25 | 225 | 25 | 220 | 17.6% | 0.97 [0.54, 1.76] | |
| Rodriguez-Bigas 1994 | 9 | 29 | 15 | 34 | 7.5% | 0.57 [0.20, 1.61] | |
| Sturt 2004 | 33 | 161 | 17 | 159 | 10.7% | 2.15 [1.14, 4.05] | |
| Total (95% CI) | | 1358 | | 1505 | 100.0% | 1.64 [1.32, 2.04] | |
| Total events | 225 | | 163 | | | | |
| Heterogeneity: Chi ² = 10.75, df = 6 (P = 0.10); I ² = 44% | | | | | | | |
| Test for overall effect: Z = 4.46 (P < 0.00001) | | | | | | | |

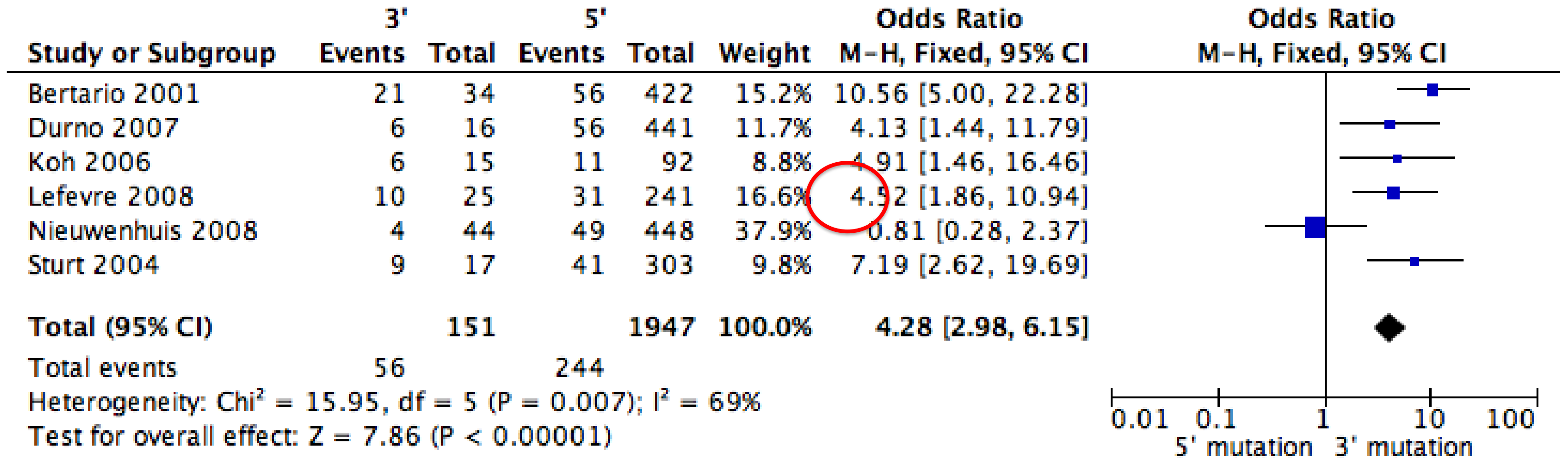


Trauma

- most within 2-3 years of surgery

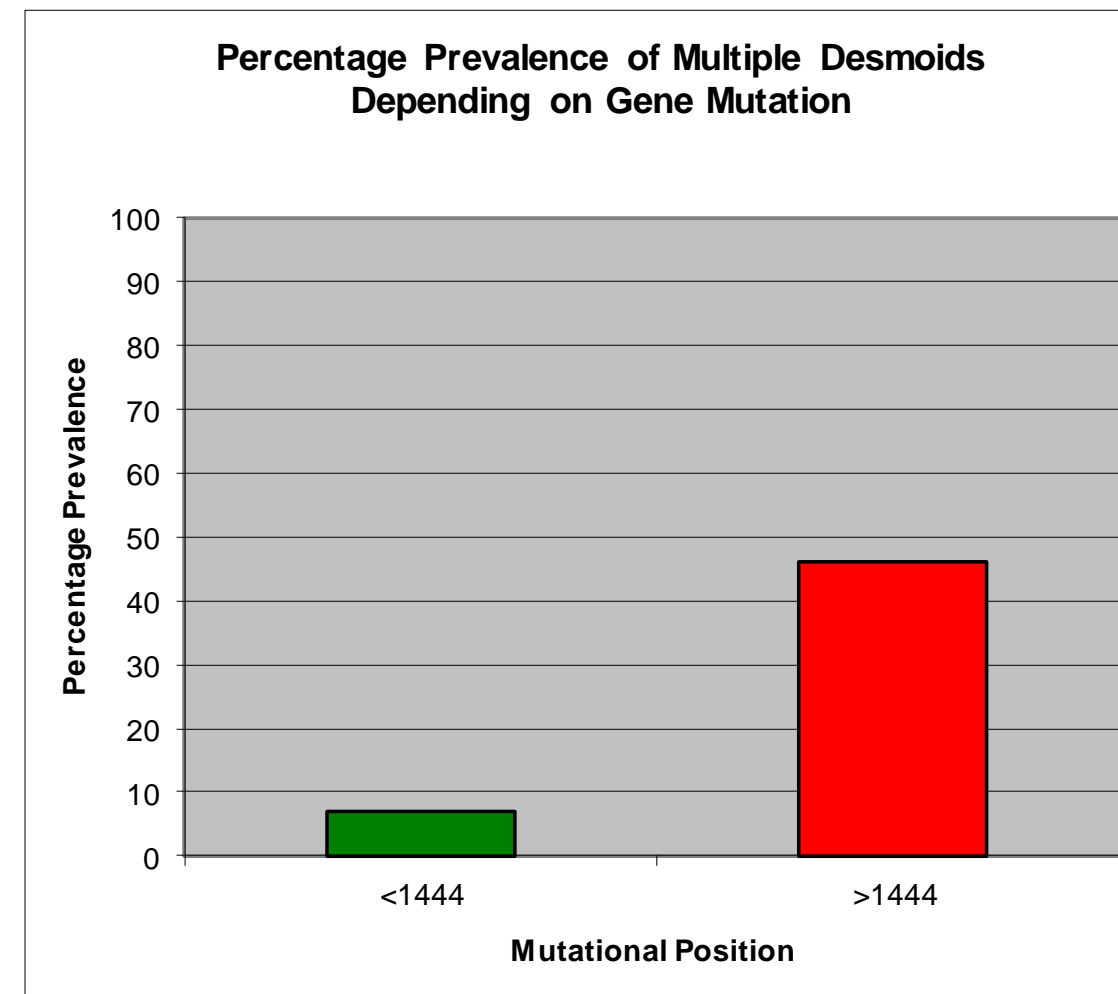


Genetics



Risk of multiple desmoid tumours related to germline mutation

- 5' to 1444
 - 10/136 (7%)
- 3' to 1444
 - 6/13 (46%)
- $p < 0.001$

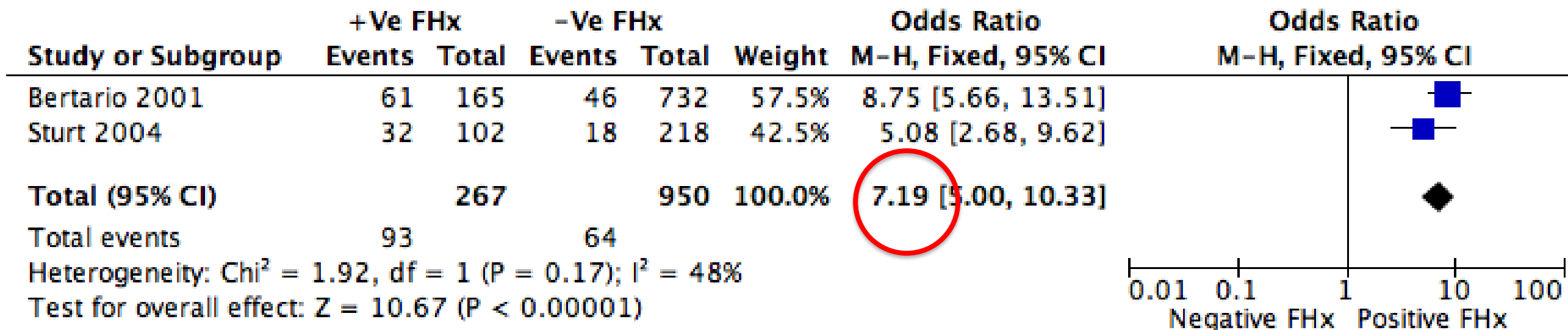


COLON CANCER

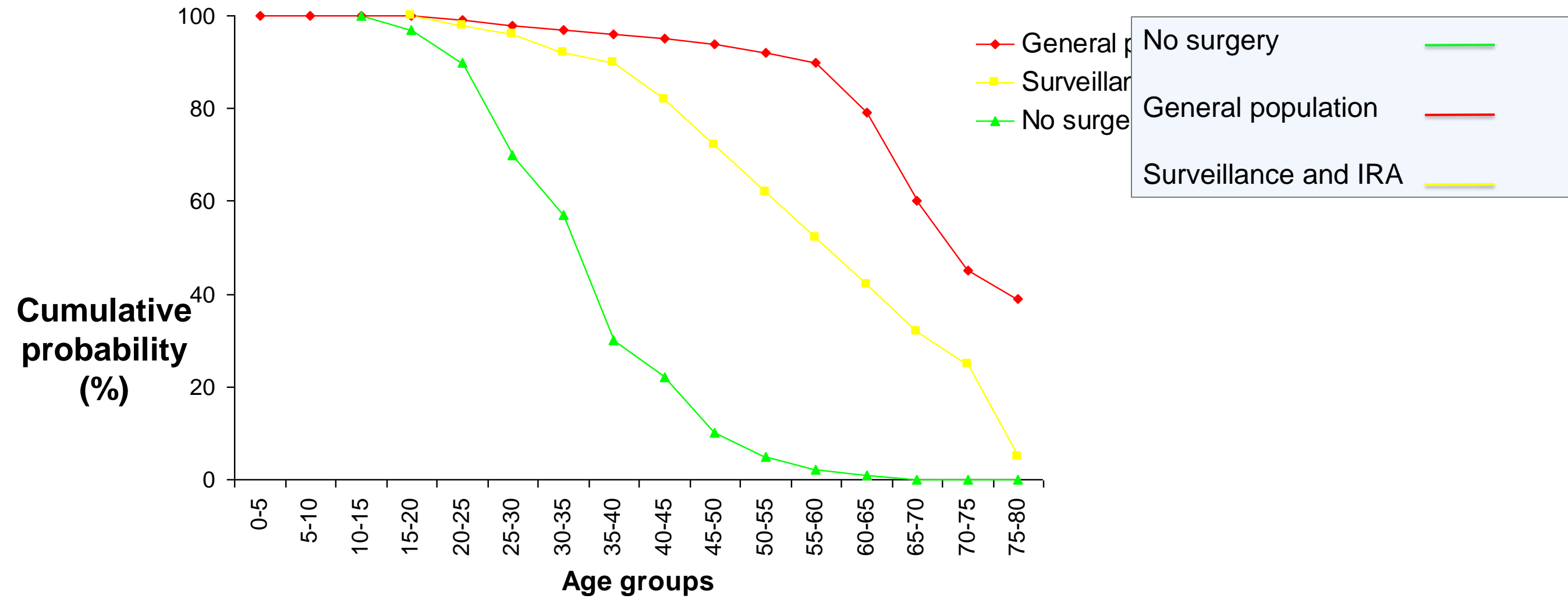
Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline *APC* mutation

N J H Sturt, M C Gallagher, P Bassett, C R Philp, K F Neale, I P M Tomlinson, A R J Silver, R K S Phillips

Gut 2004;**53**:1832–1836. doi: 10.1136/gut.2004.042705



Survival in classical FAP



Nugent et al, *Dis Colon Rectum* 1993

Treatment Options

| Treatment | Pros | Cons | Estimated response rate and time |
|---|---|--|---|
| NSAIDs/anti-estrogens (ER inhibition) 300mg sulindac | Pills, few side effects ? Adjuvant therapy after surgery, etc. Can give in combination. | Rarely produce responses | Max RR 15-20% 8-12 months Better to stabilize disease |
| Imatinib (PDGFR inhibition) | Pills | More side effects but usually mild | RR <20% but >50% stabilization rate - median stabilization ~ 1 year, patients eventually progress |
| Sorafenib (TK inhibitor, anti-VEGF) | Pills | More side effects Less effective in FAP patients | 25% PR rate, also good for stabilization |
| Interferon- α | Injections | Limited data | Small studies, stabilization ~ 3 years, ? Of IFN up-regulating precursor cells |
| Cytotoxic chemotherapy: Doxil (monotherapy) | Well tolerated even in sick patients, dose flexible | Long duration of therapy (several months) | 36% responses - some took up to 4 years - med stabilization time 14 mos |
| MTX/Vinblastine or vinorelbine | Less toxic than D/D, but still induces neutropenia | Very long duration (1 year) and weekly treatments | PR-CR in up to 60% of patients |
| Doxorubicin/dacarbazine | Fastest treatment with fastest response | Long-term risk of side effects, generally avoided in benign dz | 100% PR or CR rate, can facilitate surgical resection - usually 4-6 cycles (3-4 mos) |
| Gamma secretase inhibitors | Effective in FAP patients, less toxicity than chemo | Phase II trial | We shall see - very promising in phase I |

Long-term outcome of SERM treatment

Familial Cancer
DOI 10.1007/s10689-015-9830-z



ORIGINAL ARTICLE

Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients

Daniel Robert Quast¹ · Ralph Schneider² · Emanuel Burdzik³ · Steffen Hoppe⁴ · Gabriela Möslein²

Our preferred treatment and strategy

Table 1 SERM dosing

| | Dose/day Week 1 (mg) | Dose/day Week 2 (mg) | Dose/day Week 3 (mg) | Dose/day Week 4 (target dose) (mg) |
|------------|-------------------------|-------------------------|-------------------------|--|
| Tamoxifen | 30 | 60 | 90 | 120 |
| Raloxifene | 60 | 120 | 180 | 240 |
| Toremifene | 30 | 60 | 90 | 120 |

+ 300 mg sulindac

Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients

Our Response Rate of 85%

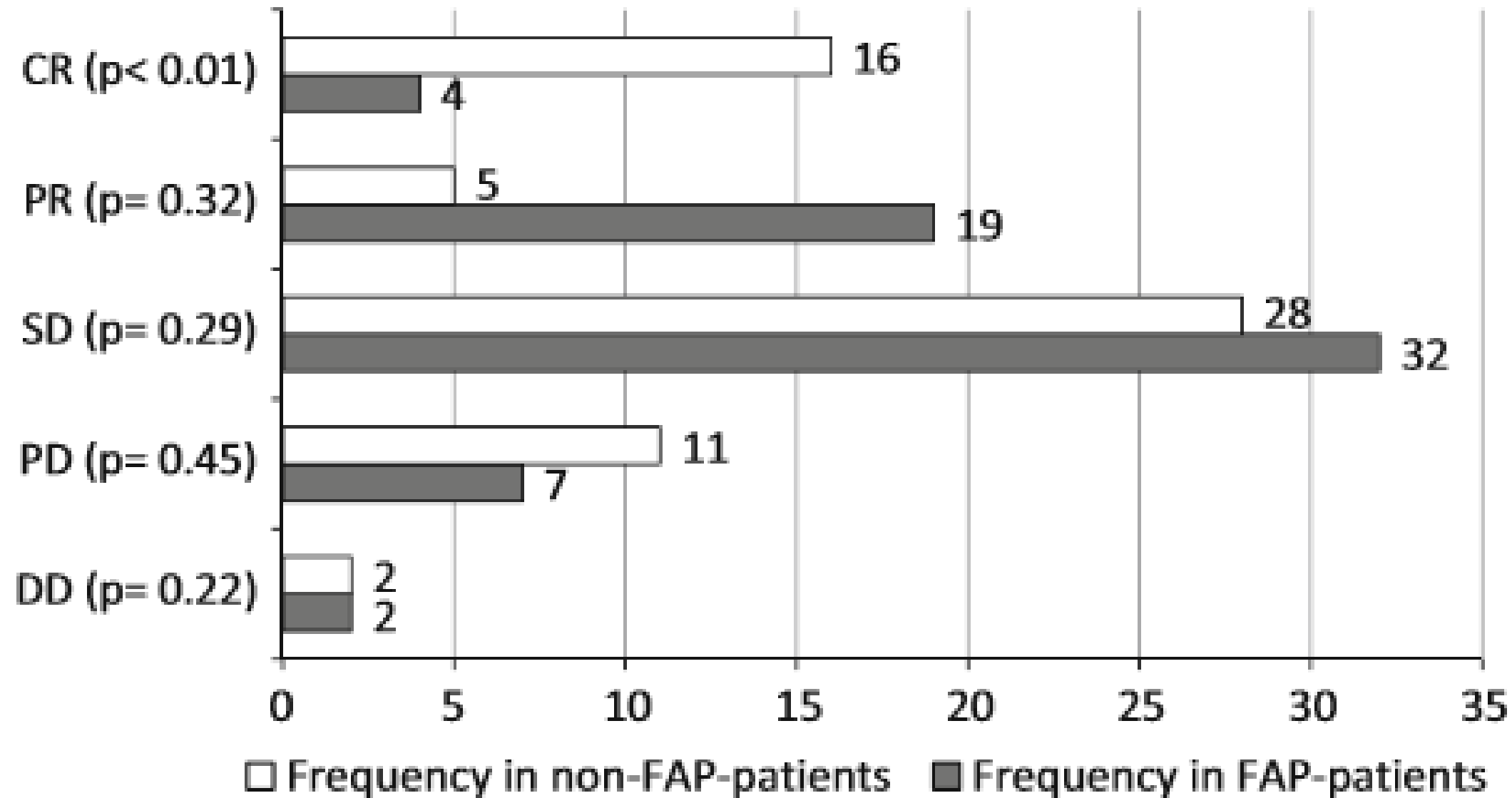


Fig. 1 Outcome considering genetic status. *CR* complete remission, *PR* partial regression, *SD* stable disease, *PD* progressive disease, *DD* desmoid related death

Desmoid Tumor in FAP: Site of predilection



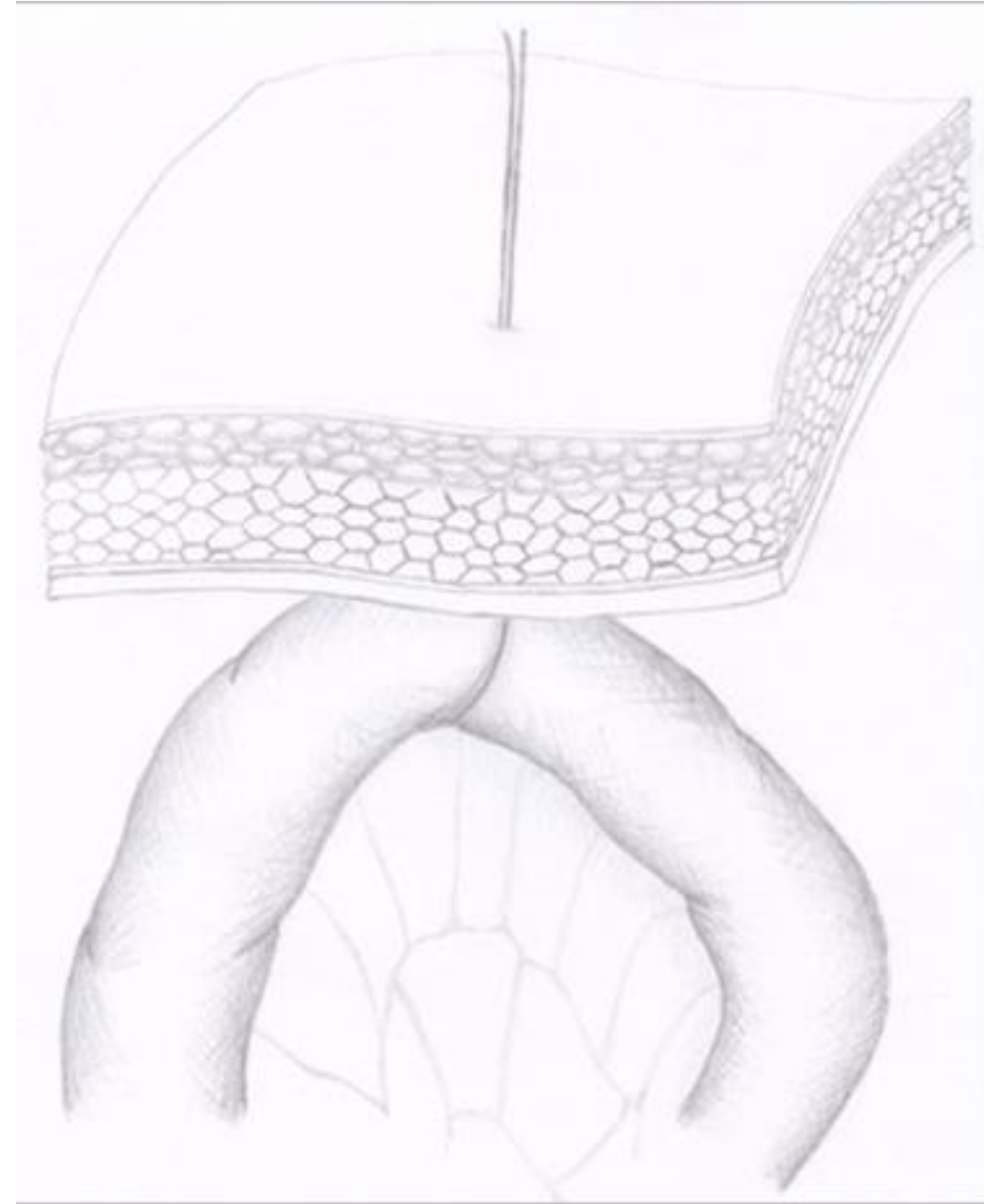
Desmoid Tumor in FAP: Site of predilection



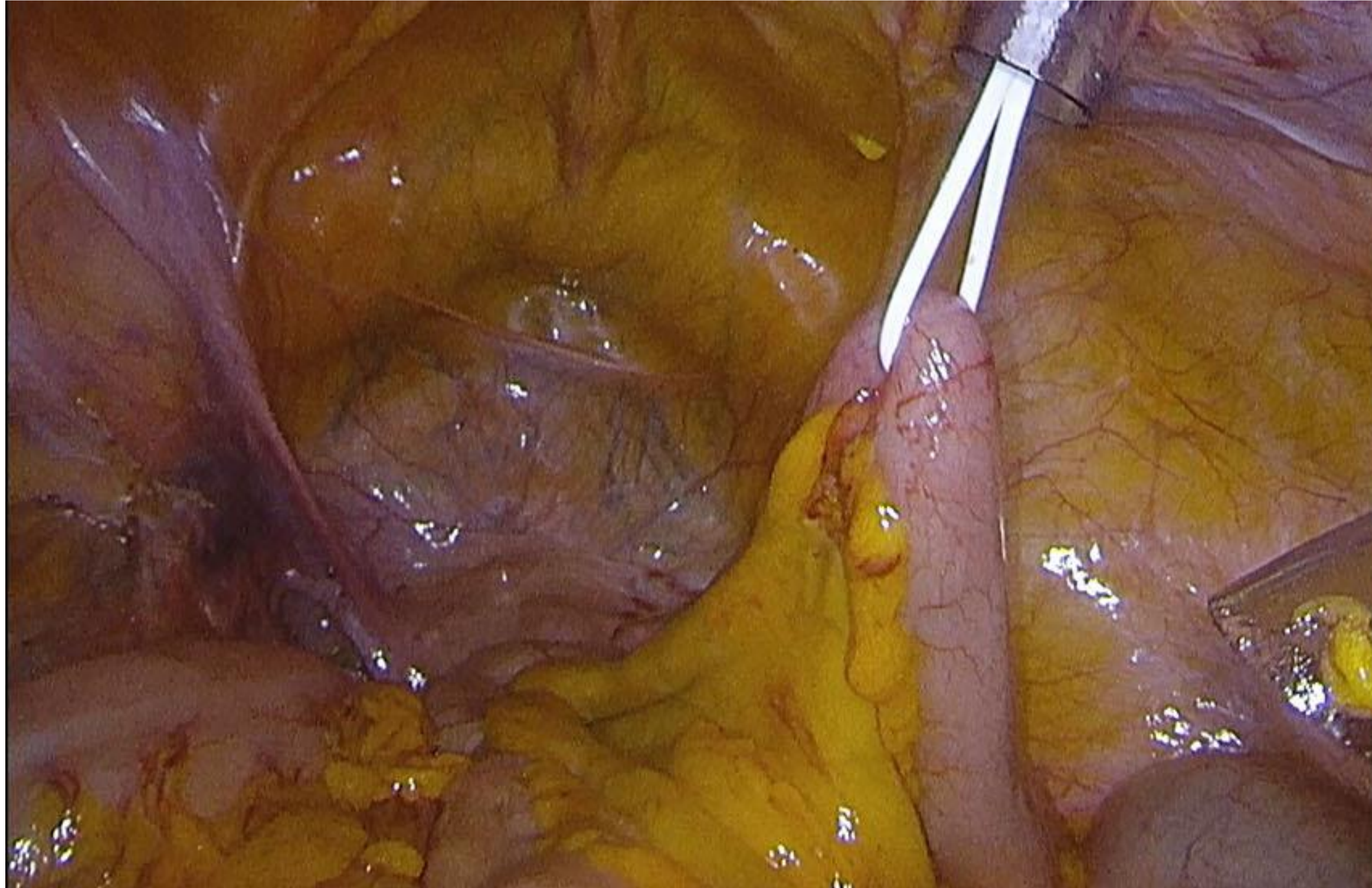
Attempt to avoid desmoids: Virtual ileostomy



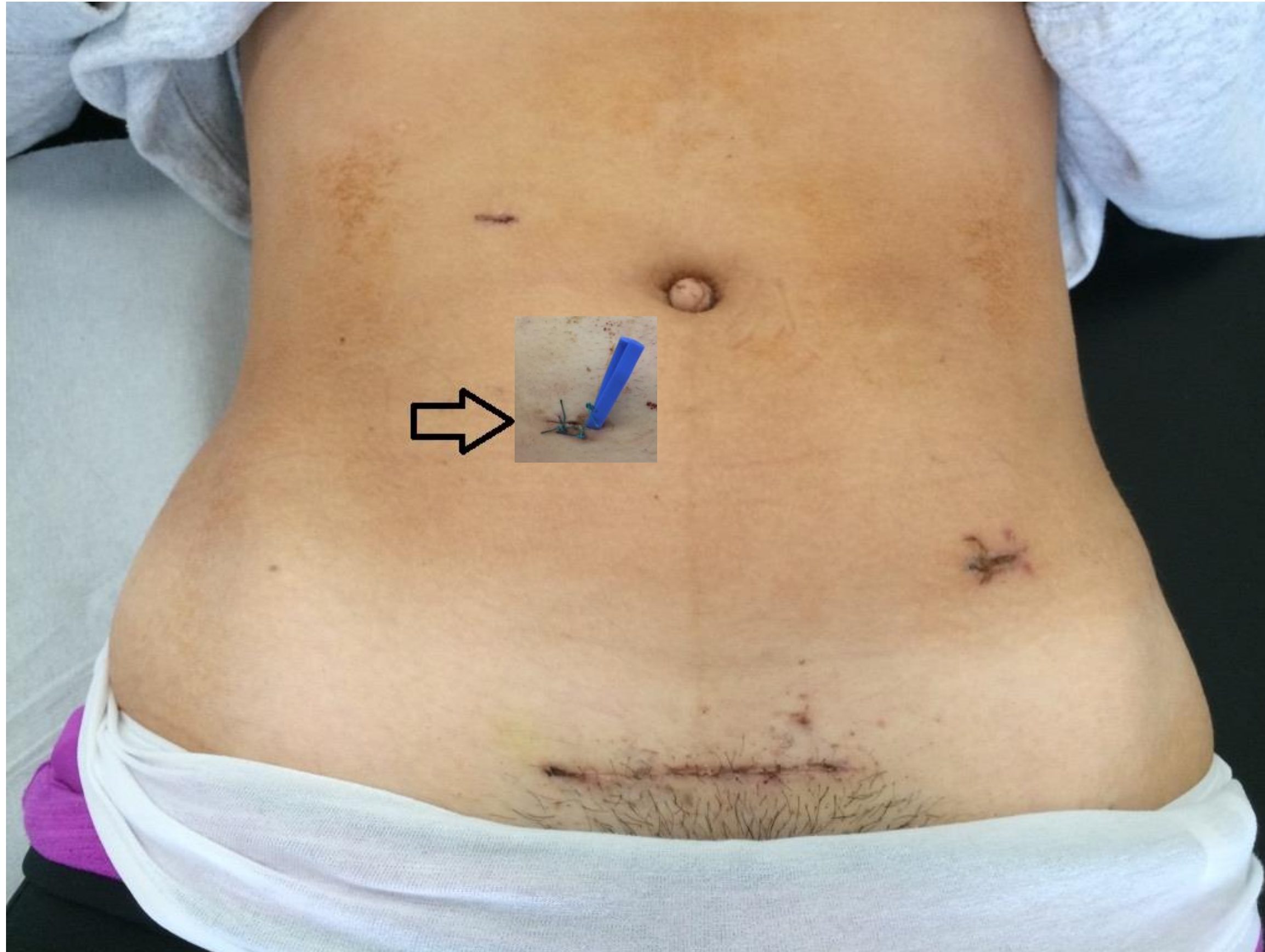
Virtual Ileostomy



Virtual Ileostomy



Attempt to avoid desmoids: Virtual ileostomy

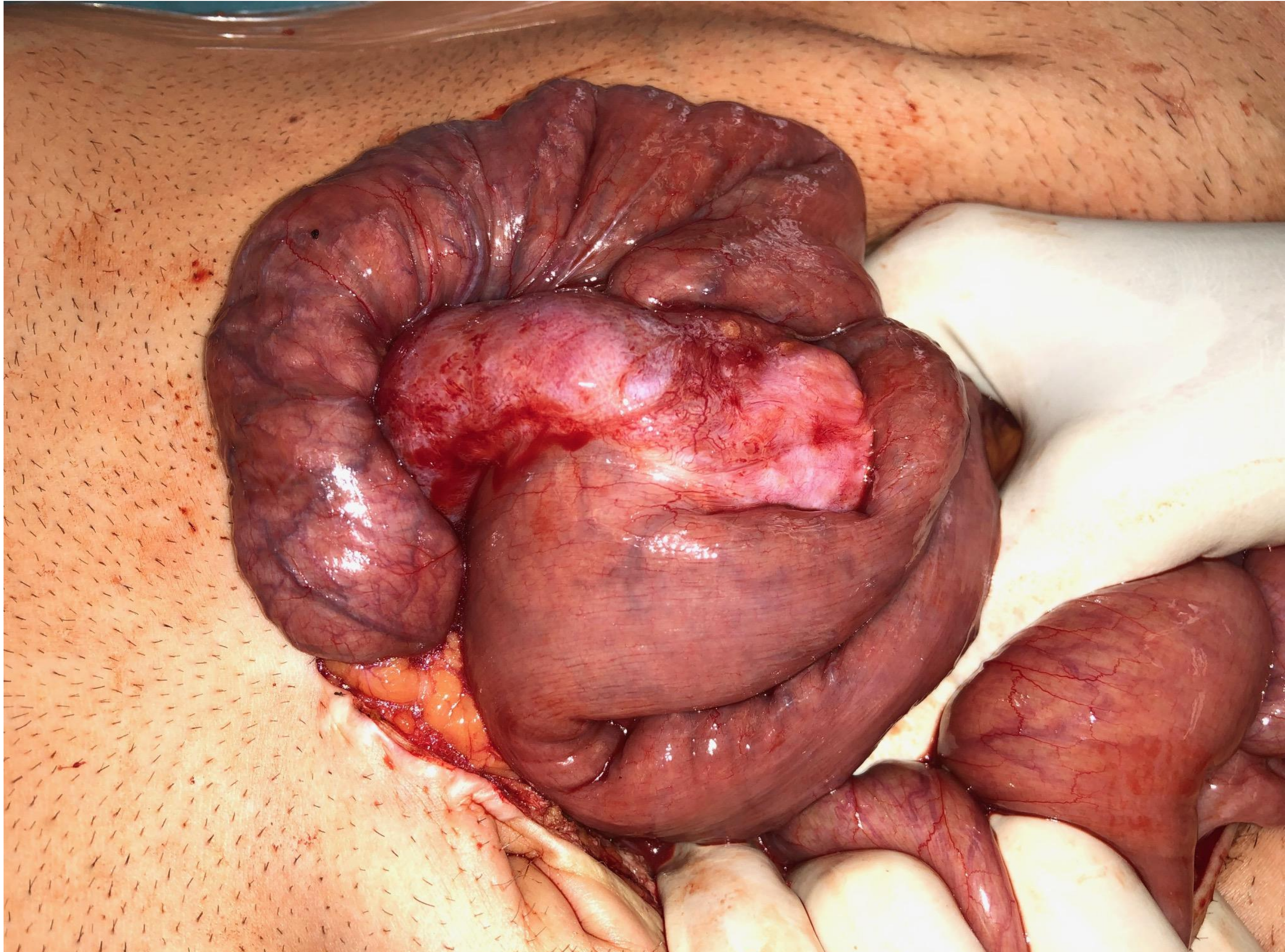


Take home message



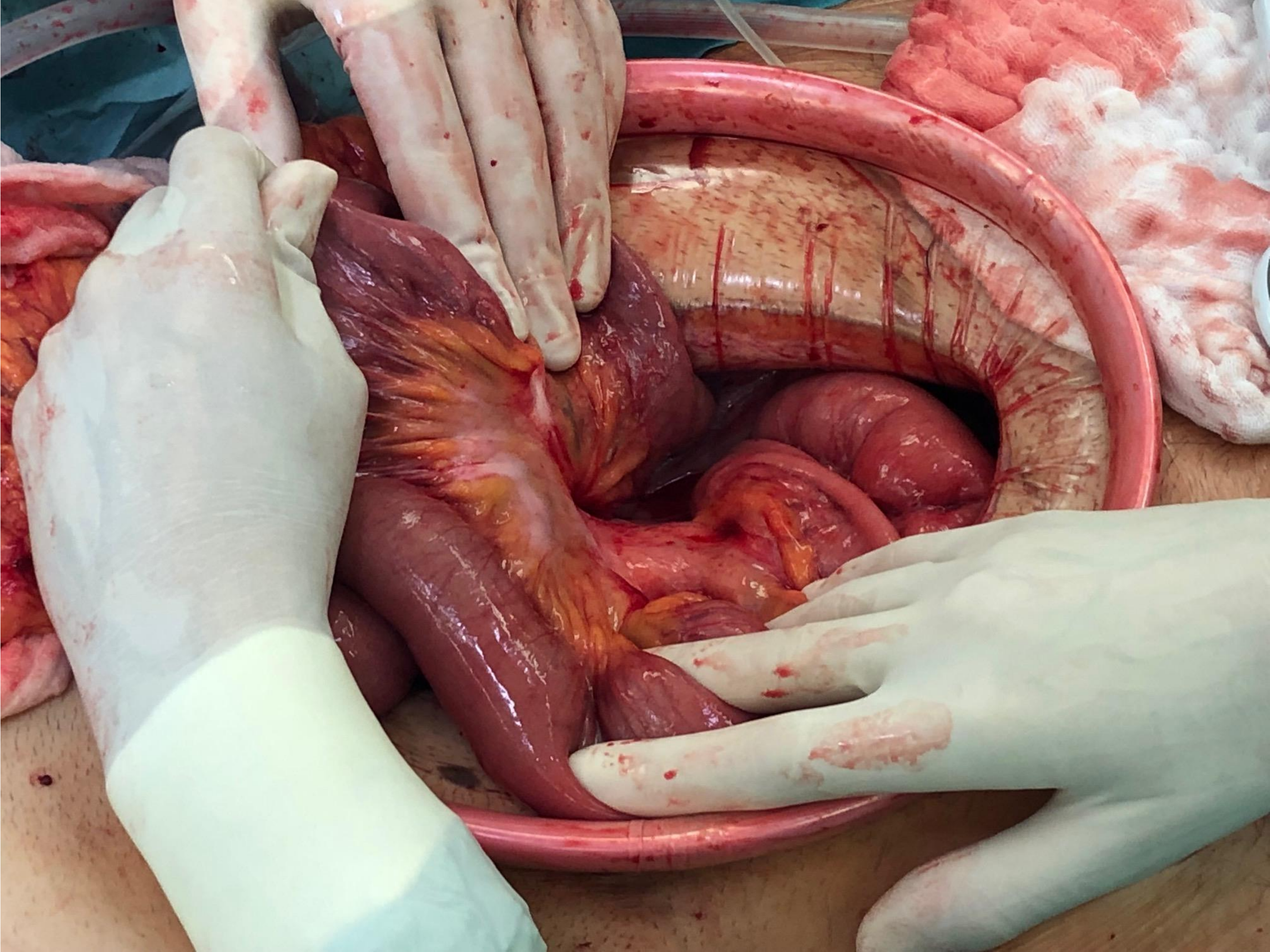
Prevent them in
FAP....

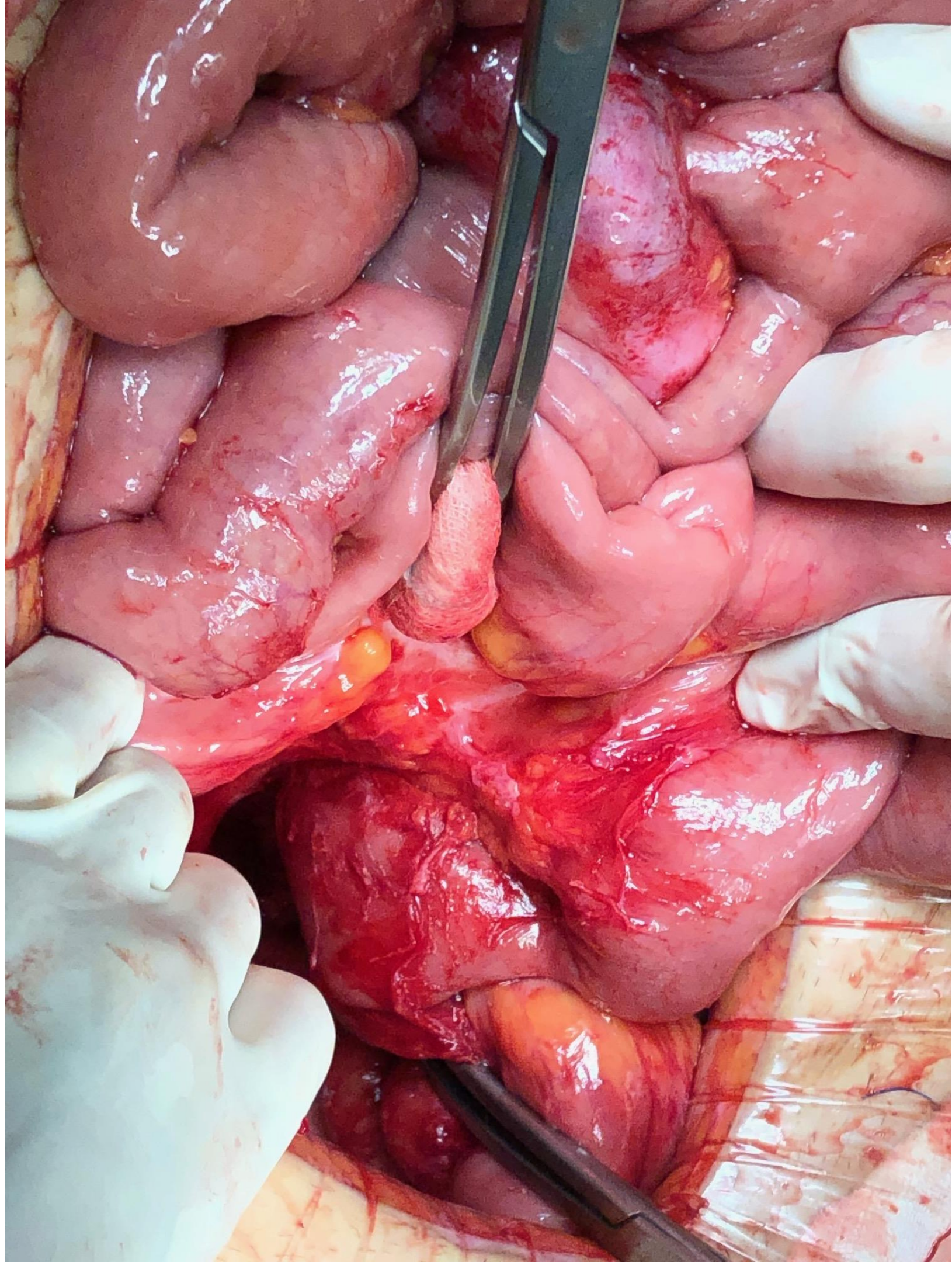
If they occur,
be
conservative!



1.8.2024





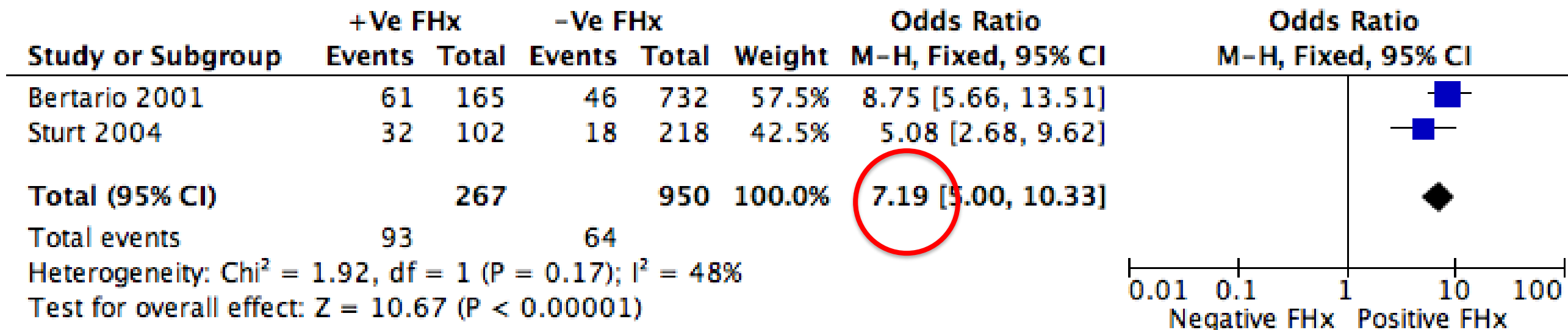


COLON CANCER

Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline *APC* mutation

N J H Sturt, M C Gallagher, P Bassett, C R Philp, K F Neale, I P M Tomlinson, A R J Silver, R K S Phillips

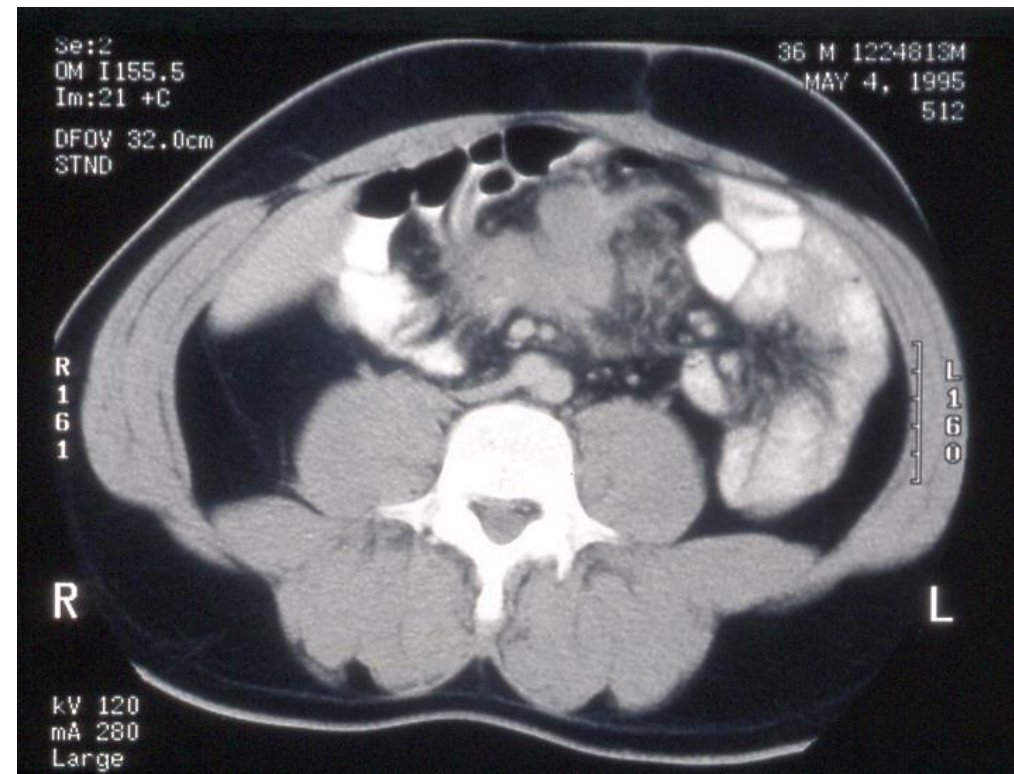
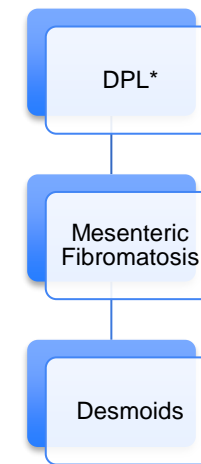
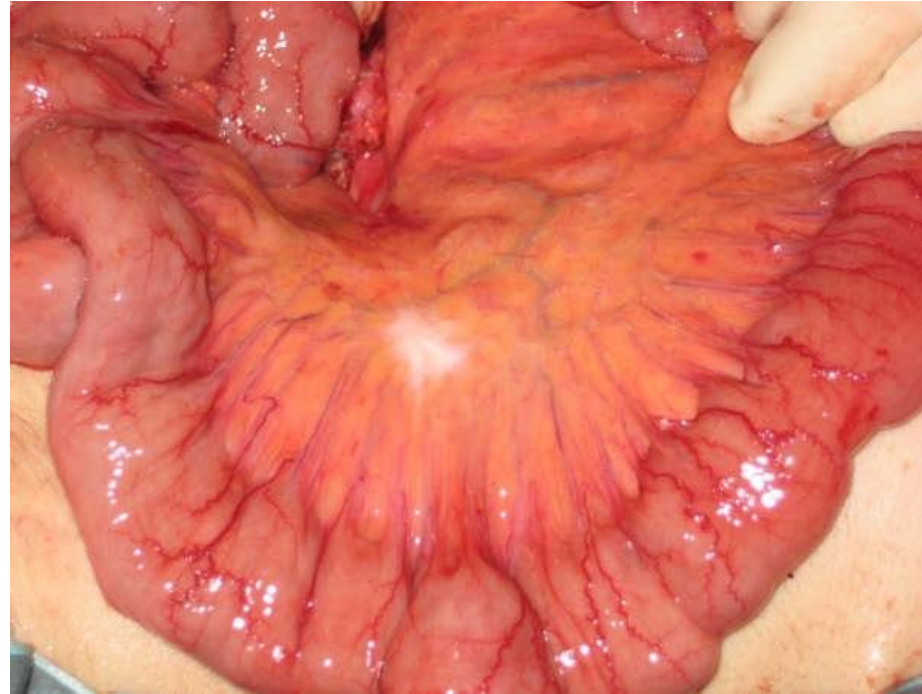
Gut 2004;**53**:1832–1836. doi: 10.1136/gut.2004.042705



Identification and progression of a desmoid precursor lesion in patients with familial adenomatous polyposis

S. K. CLARK, T. G. P. JOHNSON SMITH*, D. E. KATZ*, R. H. REZNEK† and R. K. S. PHILLIPS

The Polyposis Registry, St Mark's Hospital and *Department of Radiology, Northwick Park Hospital, Harrow and †Academic Department of Radiology, St Bartholomew's Hospital, London, UK
Correspondence to: Mr R. K. S. Phillips, The Polyposis Registry, St Mark's Hospital, Northwick Park, Harrow HA1 3UJ, UK



Stepwise Progression of Familial Adenomatous Polyposis-Associated Desmoid Precursor Lesions Demonstrated by a Novel CT Scoring System

Dis Colon Rectum, April 2005

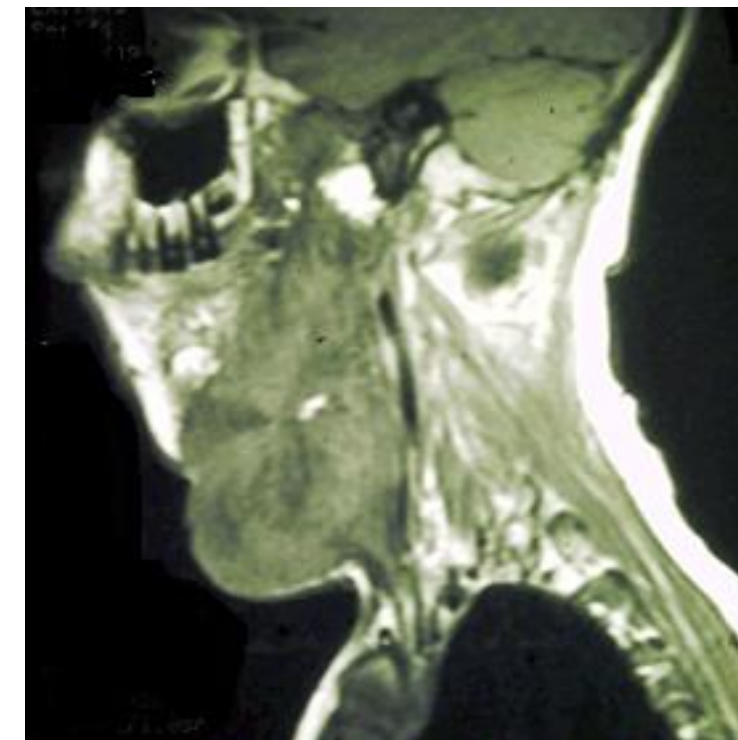
Simon B. Middleton, F.R.C.S. (Gen. Surg.),* Susan K. Clark, F.R.C.S.,*
 Paul Matravers, F.R.C.R.,† David Katz, F.R.C.R.,†
 Rodney Reznick, F.R.C.R.,‡ Robin K. S. Phillips, F.R.C.S.*

CT scan mean 27.5 months after laparotomy

| | DPL | No DPL |
|------------------|---------|---------|
| | 7 | 8 |
| Normal CT | 0 | 4 |
| Desmoid | 3 | 0 |
| Median CT score* | 4 (2-5) | 2 (1-2) |

*p=0.009

- Complications
 - bowel
 - obstruction
 - perforation
 - ureteric obstruction
 - other pressure effects



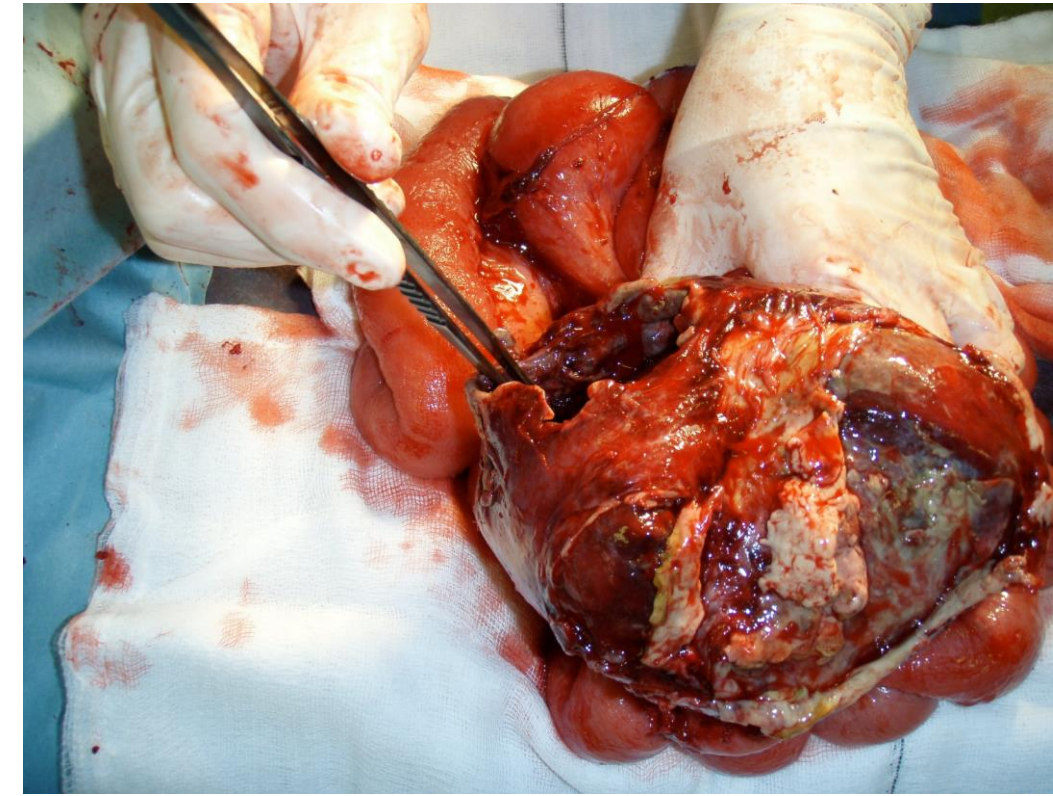


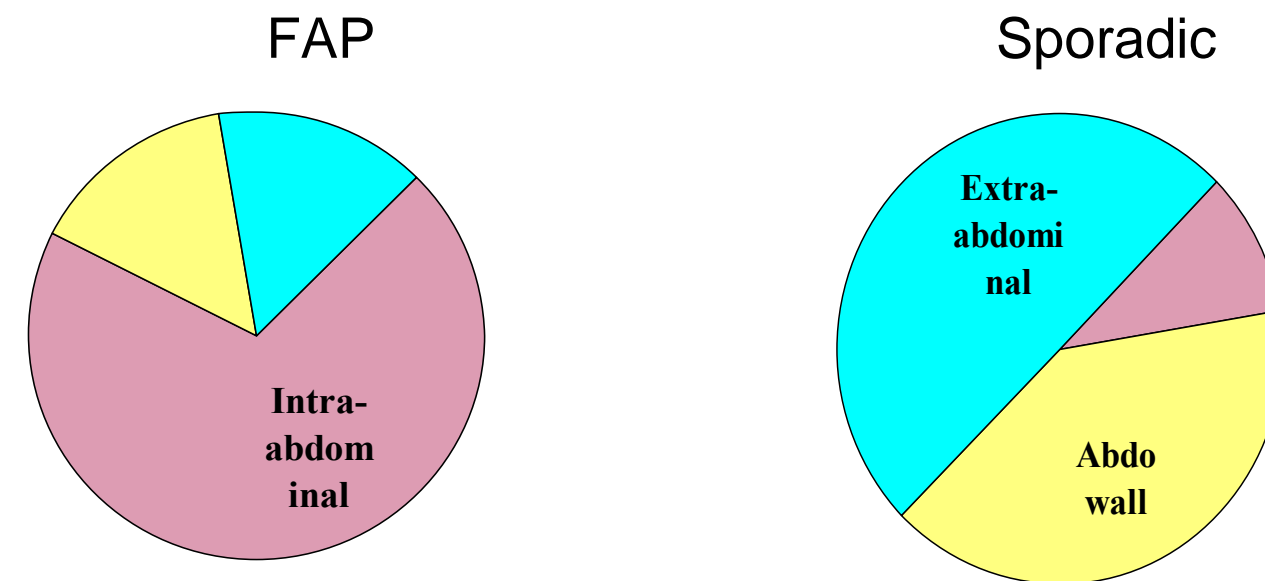
TABLE 2. DT characteristics

| Patients | DT maximum diameter, cm | Clinical presentation | Communication | Microbiology culture from DT | Primary procedure | Secondary procedure |
|----------|-------------------------|------------------------------|------------------------|------------------------------|--------------------|---------------------|
| 1 | >20 | Abdominal pain, PV discharge | Small bowel and uterus | Coliform | Percutaneous drain | Surgery |
| 2 | 17 | Abdominal pain, sepsis | Small bowel | Coliform | Percutaneous drain | - |
| 3 | 15 | Peritonitis | Small bowel | Coliform | Surgery | - |
| 4 | >20 | Abdominal pain, sepsis | Small bowel | <i>E coli</i> and VRE | Percutaneous drain | Surgery |
| 5 | 11 | Abdominal pain, sepsis | Small bowel | Coliform | Percutaneous drain | - |
| 6 | 12 | Abdominal pain, fever | Small bowel | Nil | Nonoperative | - |
| 7 | >20 | Peritonitis | Small bowel | Coliform | Surgery | - |
| 8 | 10 | Peritonitis | Nil | Coliform | Surgery | - |
| 9 | >20 | Abdominal pain, fever | Small bowel | Nil | Nonoperative | - |

DT = desmoid tumor; PV = per vaginam; *E coli* = *Escherichia coli*; VRE = vancomycin-resistant enterococci.

Problems.....

- Sporadic and FAP associated mixed
 - Significant differences
 - biology (*CTNNB1*)
 - anatomical distribution
 - behaviour

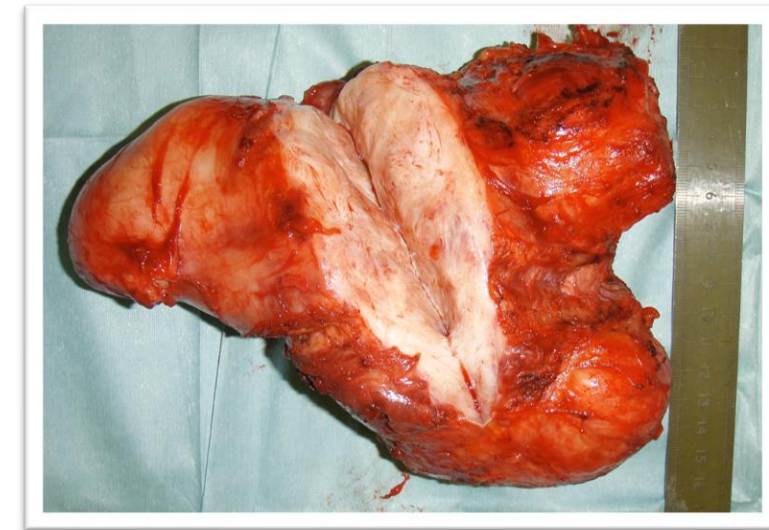
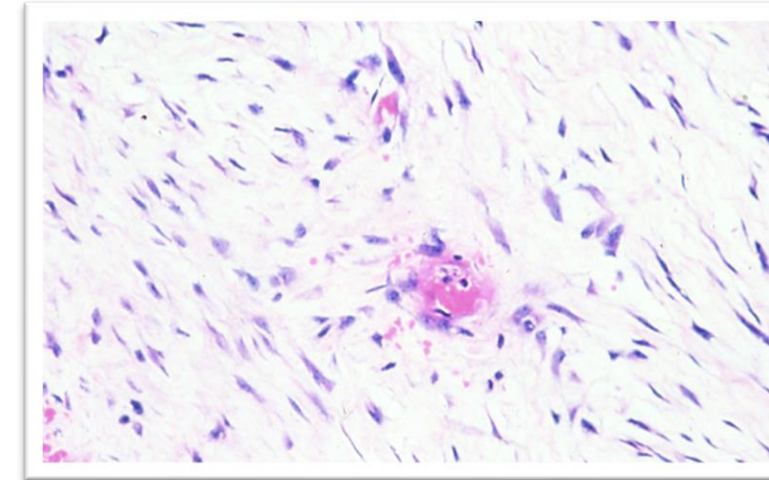


- Fibroblastic tumour / fibromatosis

- myofibroblast origin
- locally invasive / infiltrative
- non-metastasising

- somatic *APC* mutations
 - polyclonal

?



The type of somatic mutation at *APC* in familial adenomatous polyposis is determined by the site of the germline mutation: a new facet to Knudson's 'two-hit' hypothesis

British Journal of Cancer (2000) **82**(4), 827–832

© 2000 Cancer Research Campaign

DOI: 10.1054/bjoc.1999.1007, available online at <http://www.idealibrary.com> on IDEAL®

Desmoids in familial adenomatous polyposis are monoclonal proliferations

Human Molecular Genetics, 2007, Vol. 16, No. 1 78–82

doi:10.1093/hmg/ddl442

Advance Access published on November 29, 2006

APC mutations in FAP-associated desmoid tumours are non-random but not 'just right'

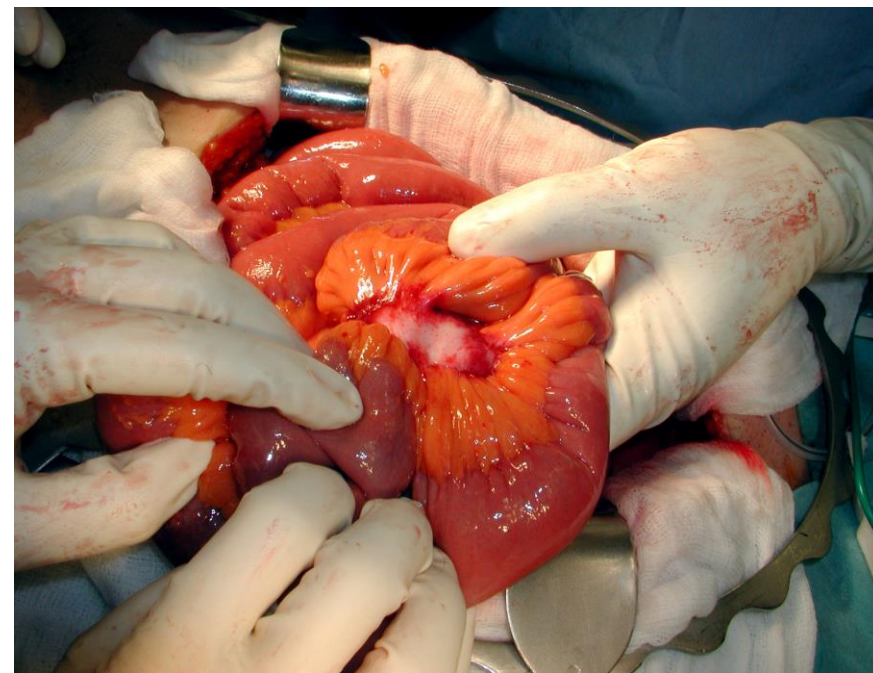
Andrew Latchford^{1,2}, Emmanouil Volikos³, Victoria Johnson², Pauline Rogers²,
Nirosha Suraweera³, Ian Tomlinson^{3,4}, Robin Phillips¹ and Andrew Silver^{3,*}

Desmoids in FAP

Variable behaviour

- 50% stable
- 30% cycles of growth and resolution
- 10% relentless growth
- 10% regress

Church *et al.* Dis Colon Rectum 1995



Jeremiah C. Healy^{1,2}
Rodney H. Reznek²
Susan K. Clark³
Robin K. S. Phillips³
Peter Armstrong²

MR Appearances of Desmoid Tumors in Familial Adenomatous Polyposis

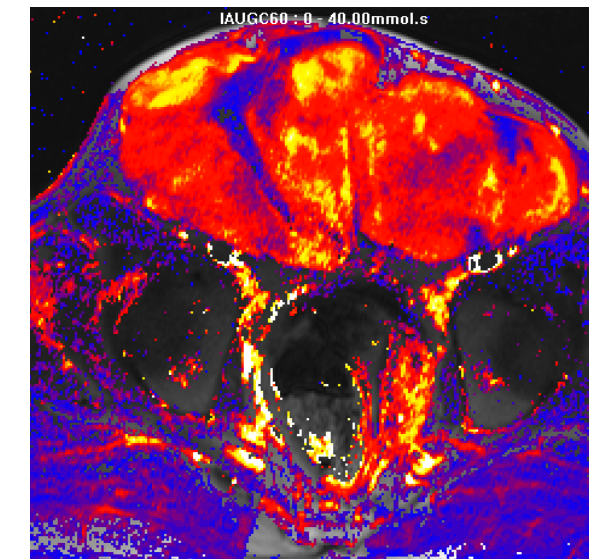
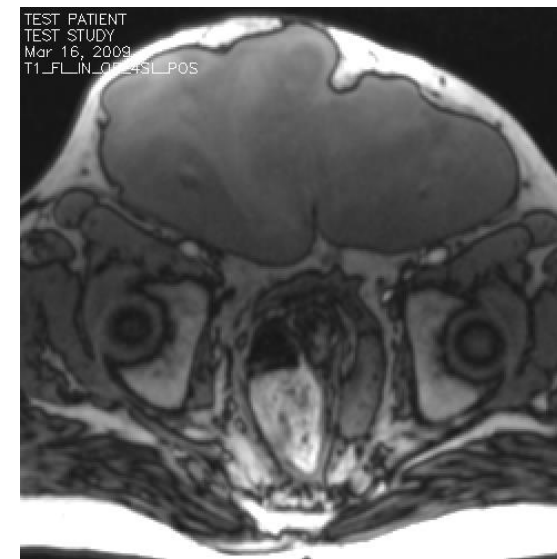
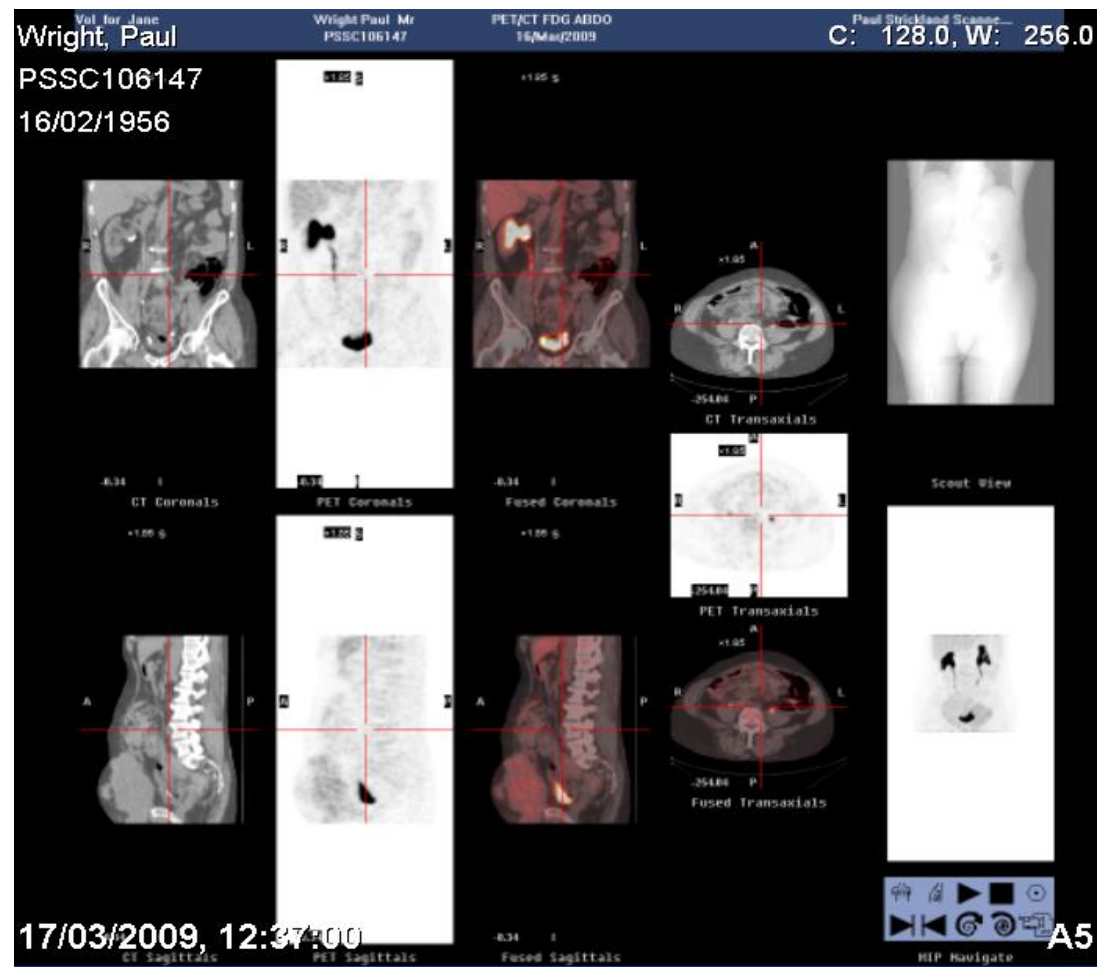
AJR:169, August 1997



ORIGINAL CONTRIBUTION

Can Combined ¹⁸F-FDG-PET and Dynamic Contrast-Enhanced MRI Predict Behavior of Desmoid Tumors in Patients With Familial Adenomatous Polyposis?

S. Bhandari, M.R.C.S.¹ • N. J. Taylor, Ph.D.² • A. Sinha, M.D.¹ • L. Sonoda, F.R.C.R.²
B. Sanghera, Ph.D.² • W. L. Wong, F.R.C.R.² • V. Goh, F.R.C.R.³ • S. K. Clark, F.R.C.S.¹



Desmoid tumours complicating familial adenomatous polyposis

British Journal of Surgery 1999, 86, 1185–1189


S. K. Clark, K. F. Neale, J. C. Landgrebe and R. K. S. Phillips

- 51 abdominal wall desmoids excised
 - no recurrence 59%
 - no perioperative deaths



**WE LEARN FROM FAILURE,
NOT FROM SUCCESS!**

You want to know the
difference between a master
and a beginner?



The master has failed
more times than the
beginner has even tried.

| Somatic mutation | ✓ |
|-------------------------------------|----|
| Description of lesion development | ✓ |
| Usefulness of screening | ✗ |
| Imaging growth prediction – MRI/PET | ✗ |
| Cell culture | ✗ |
| 3D cell culture | ✗ |
| Modifier gene identification | ✗ |
| | |
| Staging | ✓ |
| Risk factors | ✓ |
| Treatment algorithms | ✓✗ |

FAP associated desmoids – important known unknowns

- Why and how do they arise?
 - Modifier gene(s)?
- Why do some progress and others not?
- How can we predict which will progress?
 - Imaging?
 - Something else?
- What is the efficacy of the various treatments?
 - Need large RCTs
- Can we prevent them?
 - Need large RCTs

