

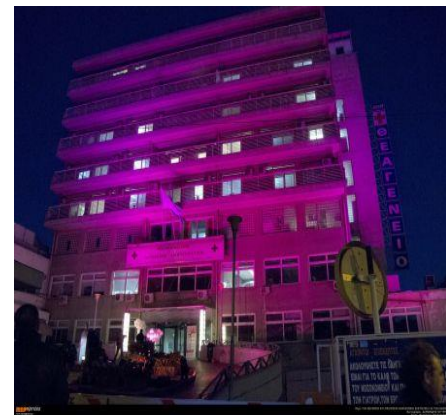


ΠΑΘΗΣΕΙΣ ΤΟΥ ΠΕΡΙΤΟΝΑΙΟΥ: ΤΙ ΠΡΕΠΕΙ ΝΑ ΓΝΩΡΙΖΕΙ Ο ΚΛΙΝΙΚΟΣ ΓΑΣΤΡΕΝΤΕΡΟΛΟΓΟΣ

Ψευδομύξωμα του Περιτοναίου



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Γαστρεντερολόγος
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Θεσσαλονίκης



Δήλωση Σύγκρουσης Συμφερόντων

Καμία

Ψευδομύξωμα Περιτοναίου: Ένα σπάνιο νόσημα



RARE CANCER DAY

OCTOBER 1, 2019

Appendix Cancer & Pseudomyxoma Peritonei

Appendix Cancer

- Appendix cancer starts with a tumor in the cells inside of appendix
- Many different types of tumors
- Frequently spread inside abdominal cavity
- Depending on tumor type, can lead to condition called **peritoneal carcinomatosis** or **peritoneal surface malignancy**

Pseudomyxoma peritonei (PMP)

- Accumulation of mucinous tumor cells within abdomen/pelvis
- Spreads throughout surrounding surfaces

Incidence, Symptoms, Diagnosis

2 in a million

- **Cancers & tumors of the appendix are extremely rare**
- Average age of onset is 50-55 years
- Affects men and women equally

Symptoms

- Appendix cancer & PMP often misdiagnosed
- Abdominal pain, bloating, hernia, & ovarian cysts in women

Diagnosis

- Appendix cancer & PMP sometimes discovered during unrelated surgery
- CT Scan, MRI, diagnostic laparoscopy, tumor marker blood test

Treatment

Surgery &/or Systemic Chemo

- Dependent on stage and subtype, and whether localized or has spread
- When spread, intravenous chemotherapy and/or surgery

Cytoreductive Surgery (CRS) / Heated Intraperitoneal Chemotherapy (HIPEC)

- Indicated when tumors have spread throughout abdomen; chemo heated and applied directly
- "Mother Of All Surgeries"
- Provides survival in up to 90% of patients with low-grade pathology when properly diagnosed
- When misdiagnosed, patients less likely to benefit from CRS/HIPEC, some never offered it



“Stand Alone Disease”

Specialized Tumor Board

**Surgical
Oncology**

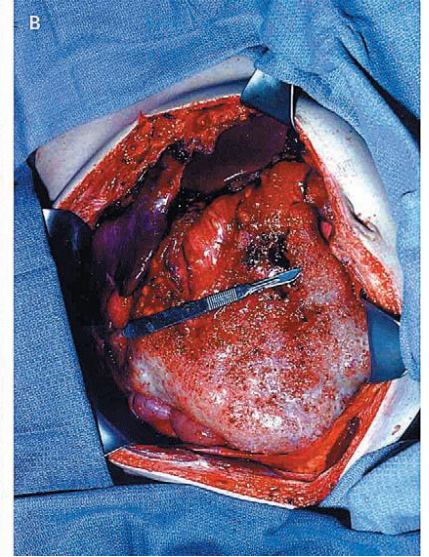
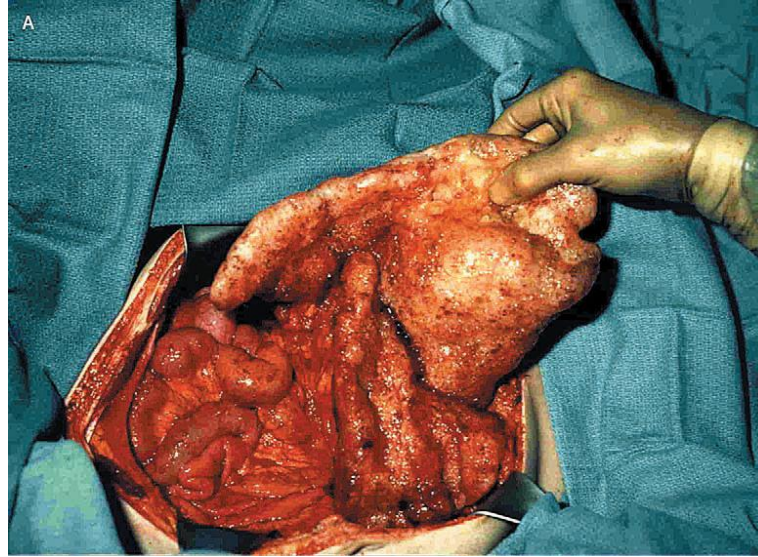
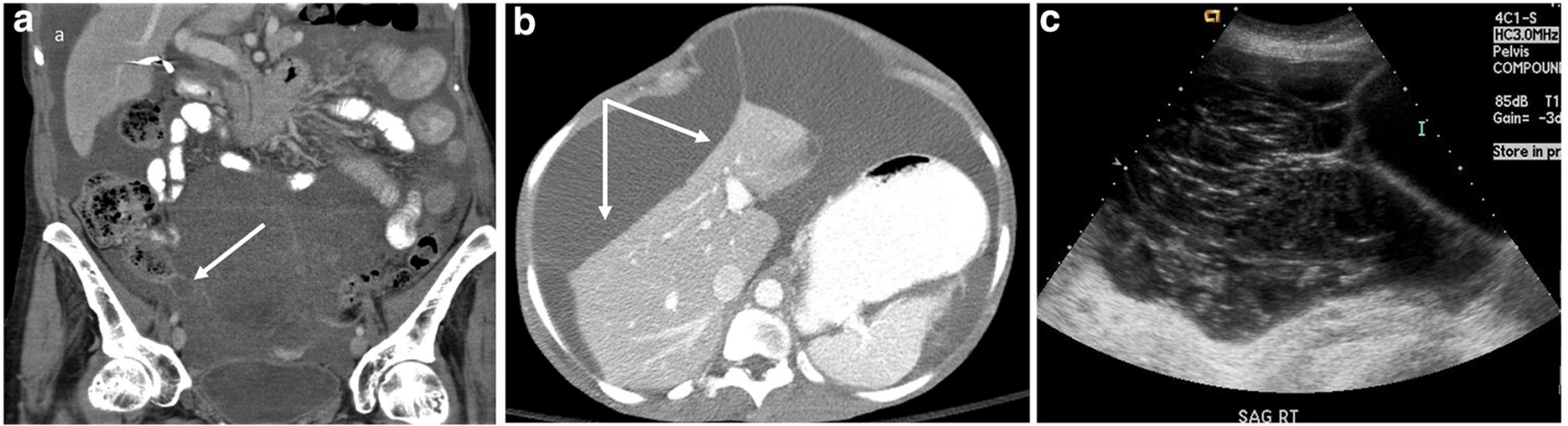
Radiology



Pathology

**Medical
Oncology**

Pseudomyxoma Peritonei Syndrome



Van Hooser, *Abdom Radiol* 2018
Sugarbaker, *Lancet* 2006

Pseudomyxoma Peritonei-PMP

Κλινική Παρουσίαση



	Men (n=105)	Women (n=112)
Appendicitis	36 (34%)	22 (20%)
Increased abdominal girth	28 (27%)	21 (19%)
Ovarian mass	NA	44 (39%)
Hernia	26 (25%)	4 (4%)
Ascites	5 (5%)	4 (4%)
Abdominal pain	5 (5%)	3 (3%)
Other	5 (5%)	14 (13%)

NA=not applicable

Table 2: Frequency of symptoms and signs of pseudomyxoma peritonei syndrome¹⁰

Sugarbaker, Lancet 2006
Esquivel, Br J Surgery 2000

Pseudomyxoma Peritonei-PMP

Επιδημιολογία

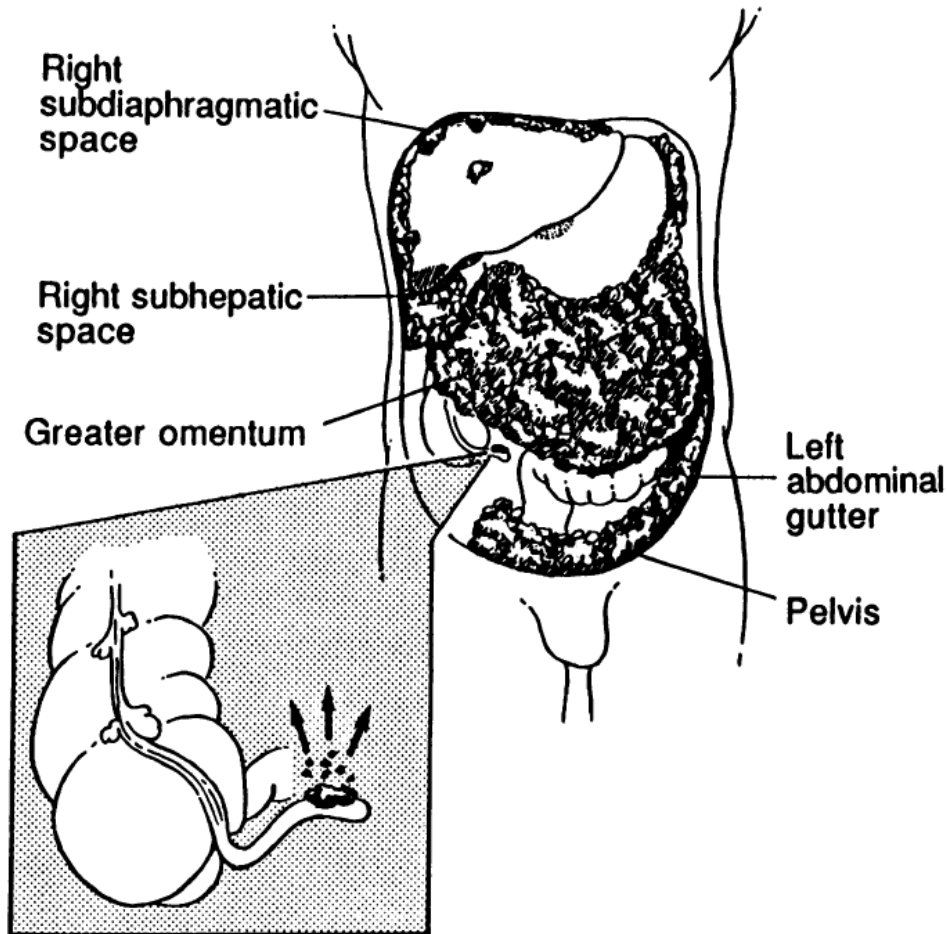
- Ενδοπεριτοναϊκοί βλεννώδεις όγκοι, Βλεννώδης Ασκίτης
- **Ρήξη Βλεννώδους Νεοπλάσματος Σκωληκοειδούς**
- Επίπτωση 1 (2/3) στο εκατομμύριο
- 4^η-6^η δεκαετία
- Borderline Malignant/Locoregional Disease
- Προχωρημένη Νόσος:
 - Εντερική Απόφραξη, Αποφρακτική Ουροπάθεια
 - Επηρεασμένη Ποιότητα Ζωής

Επιθηλιακά Νεοπλάσματα Σκωληκοειδούς

Ογκολογική Ιδιαιτερότητα

Νεοπλάσματα Σκωληκοειδούς	≠	Νεοπλάσματα Παχέος Εντέρου
Επίπτωση: σπάνια (1500 σε Η.Π.Α.)		Επίπτωση: συχνή (150,000 σε Η.Π.Α.)
Βλεννώδη: 85%		Βλεννώδη: 15%
Επιθετική Ιστολογία: 10%		Επιθετική Ιστολογία: 95%
Μεταστάσεις σε Λεμφαδένες: 2%		Μεταστάσεις σε Λεμφαδένες: 50%
Μεταστάσεις σε Ήπαρ: 2%		Μεταστάσεις σε Ήπαρ: 20%
5ετής Επιβίωση: 30%		5ετής Επιβίωση: 70%
(συμβατικό χειρουργείο)		(συμβατικό χειρουργείο)
Χημειοθεραπεία;		Χημειοθεραπεία: ν

Pseudomyxoma Peritonei: The Redistribution Phenomenon



Pseudomyxoma Peritonei Θεραπεία

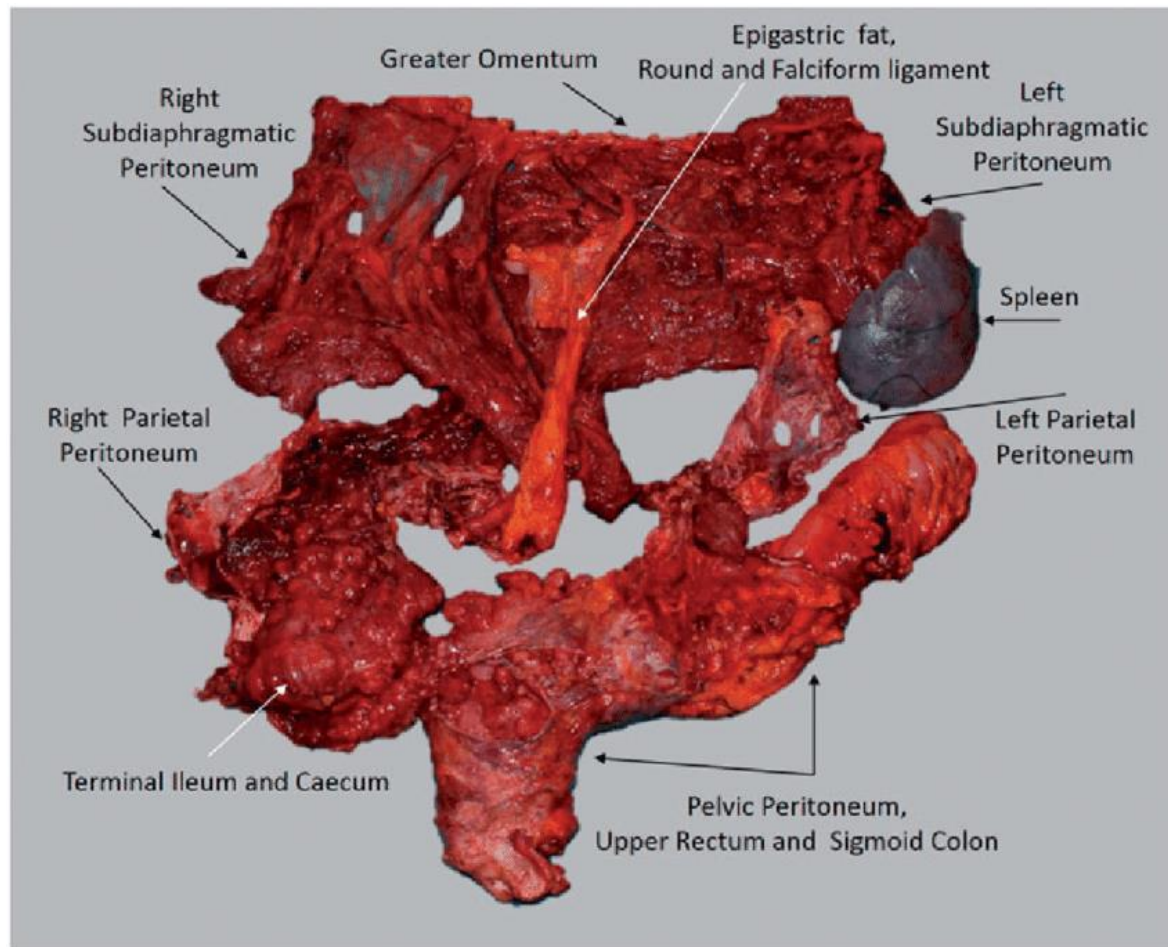
Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)



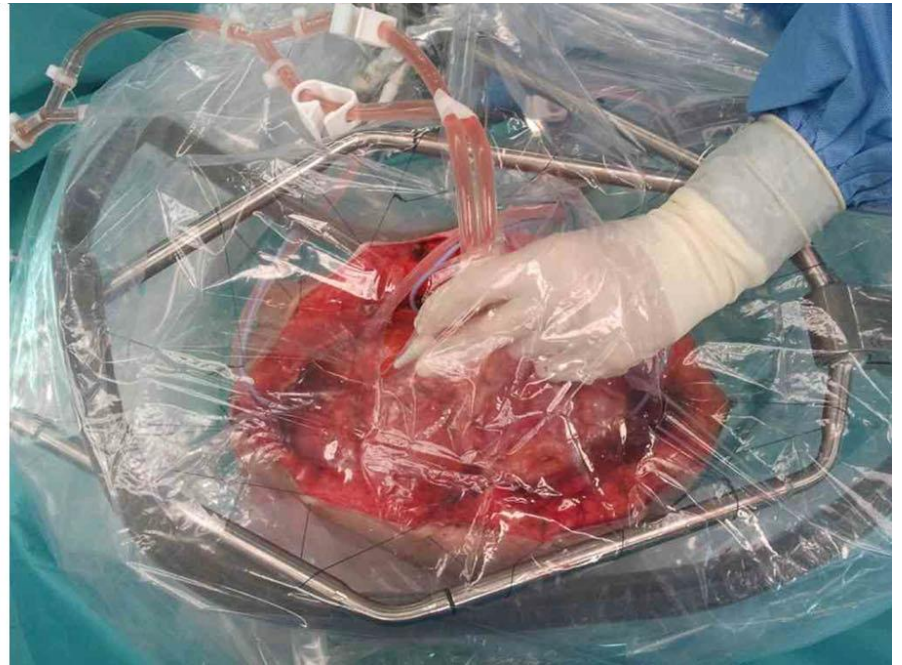
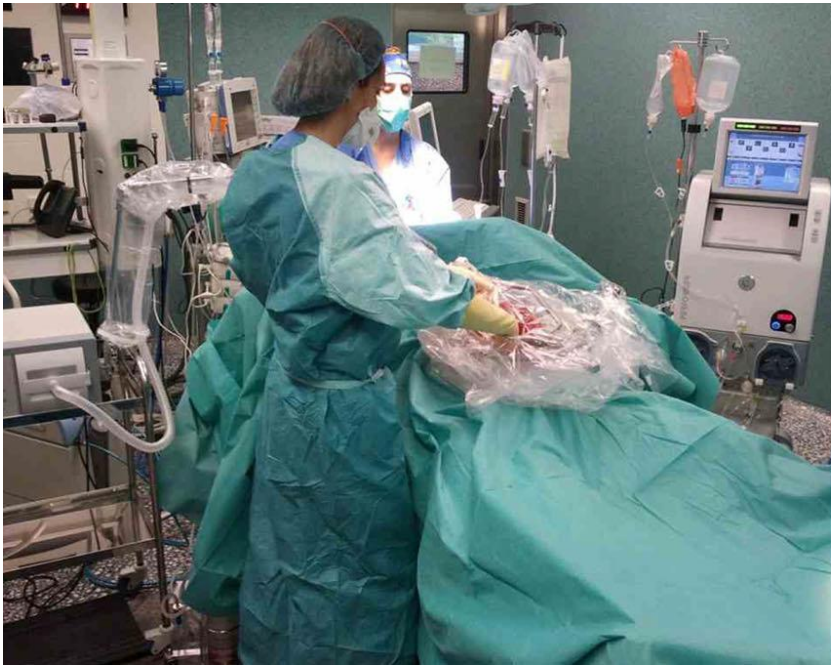
“HIPEC”

CRS+HIPEC

The Mother of All Surgeries!

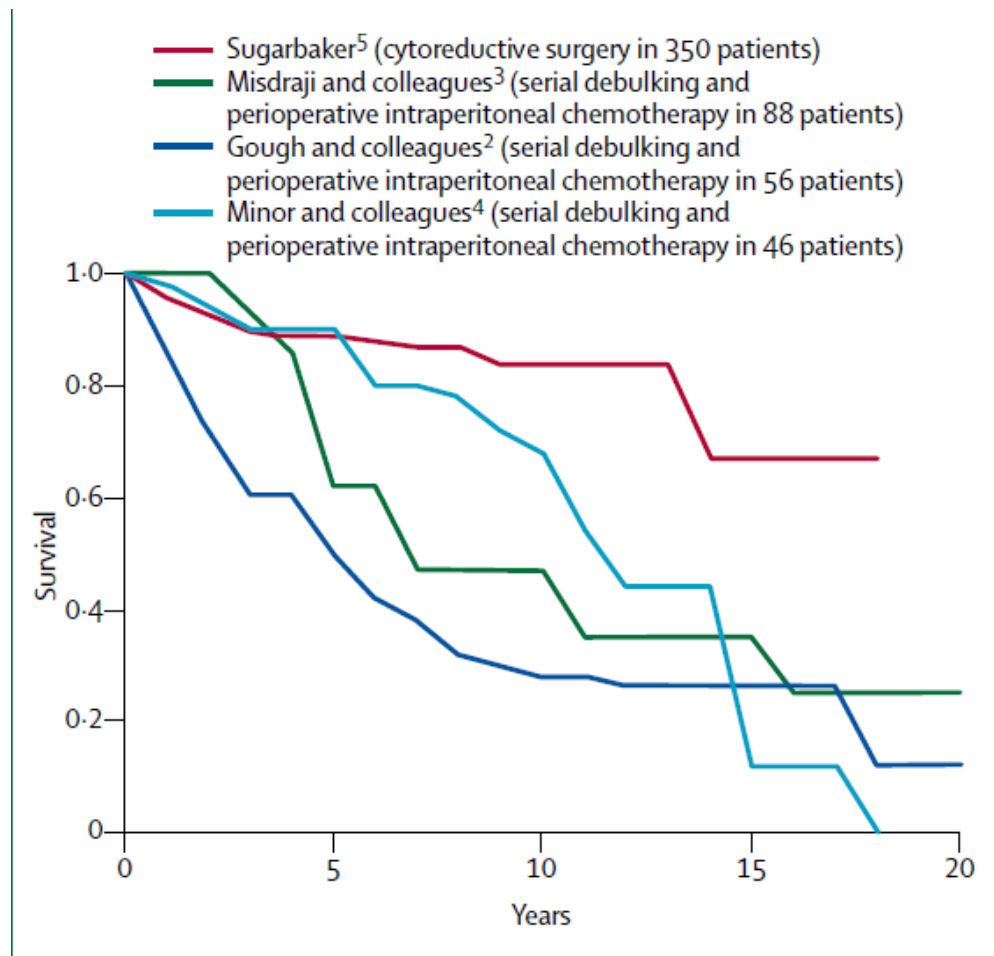


HIPEC: Coliseum Modality



Pseudomyxoma Peritonei-Surgery

Debulking, Cyto-reductive, Perioperative Intraperitoneal Chemotherapy



CRS+HIPEC: Αποτελεσματικότητα

15year Survival: 59%

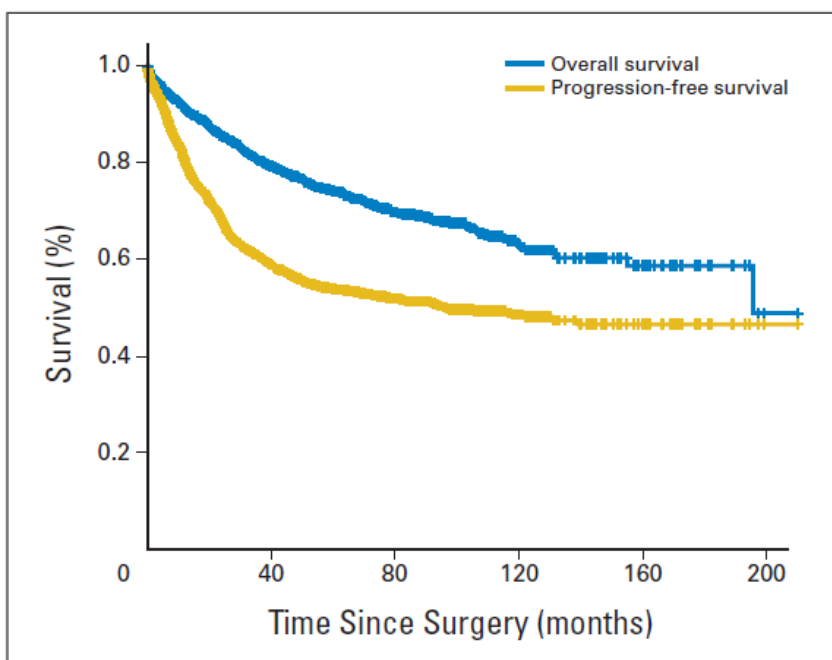


Fig 1. Overall survival and progression-free survival rates of 2,298 patients with appendiceal pseudomyxoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

CCR0: complete

CCR2: 2.5 mm-2.5 cm

CCR1: <2.5 mm

CCR3: >2,5 cm

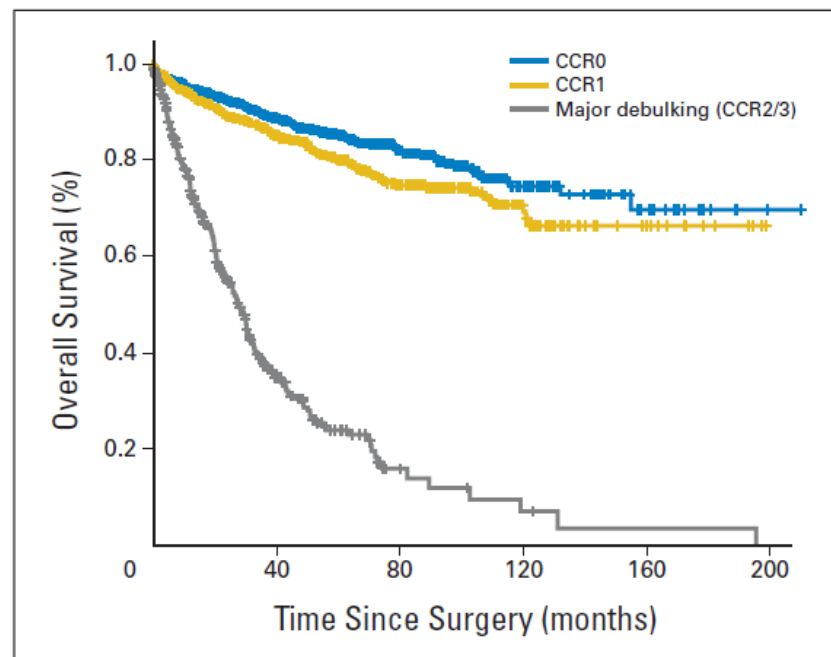
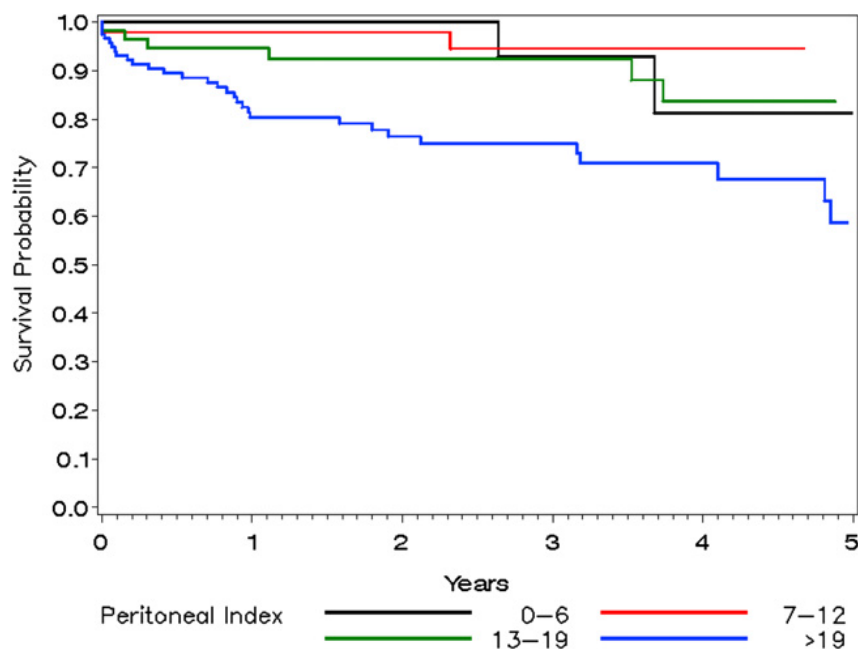


Fig 2. Prognostic impact of completeness of cytoreduction (CCR) in surgery on overall survival ($P < .001$).

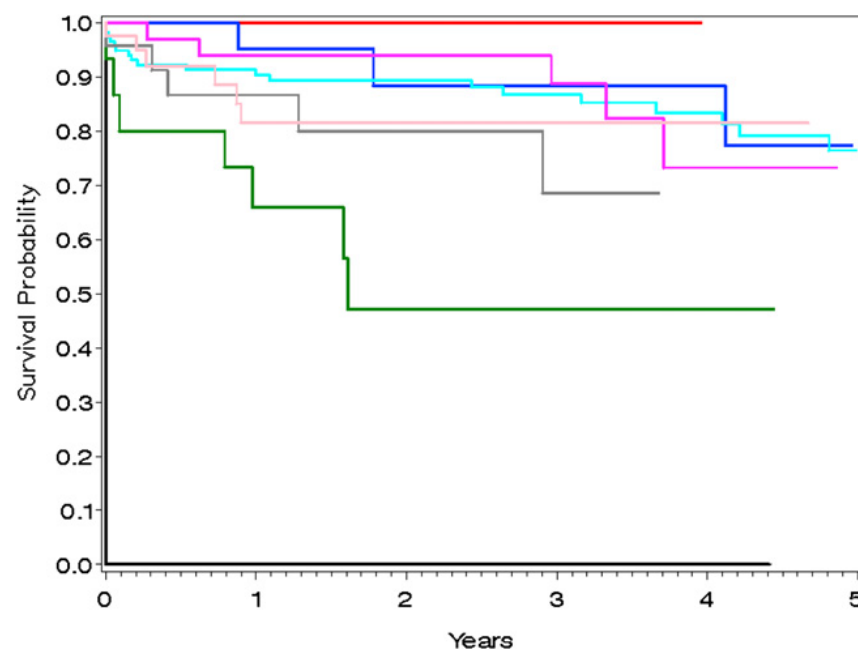
Mortality: 2%, Complications: 24%

CRS+HIPEC: SOC?

Survival and Peritoneal Index

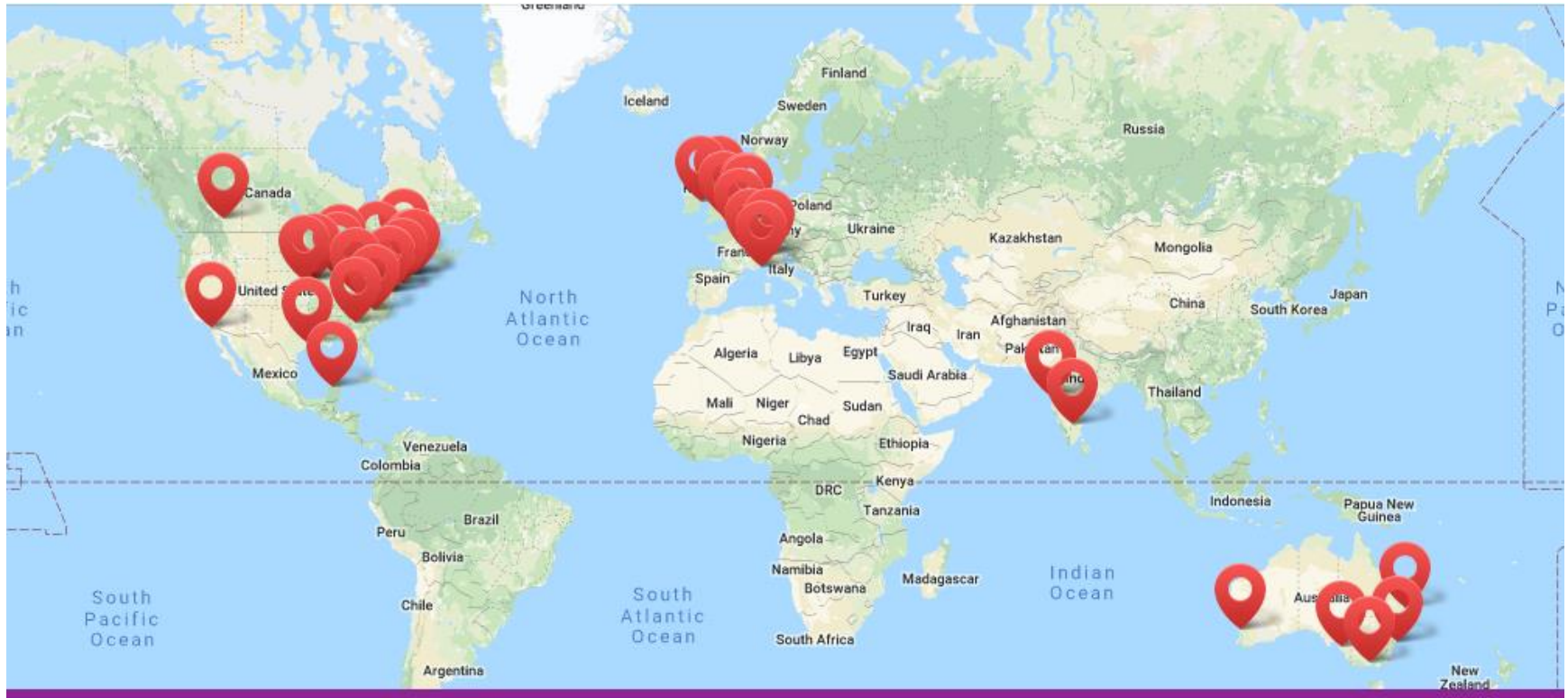


Survival and Surgical Center



Mortality: 4.4%, Morbidity: 40%

Ψευδομύξωμα Περιτοναίου και Χειρουργείο: Εξειδικευμένα Κέντρα Αναφοράς



www.pseudomyxomasurvivor.org

From Appendiceal Lesions to PMP

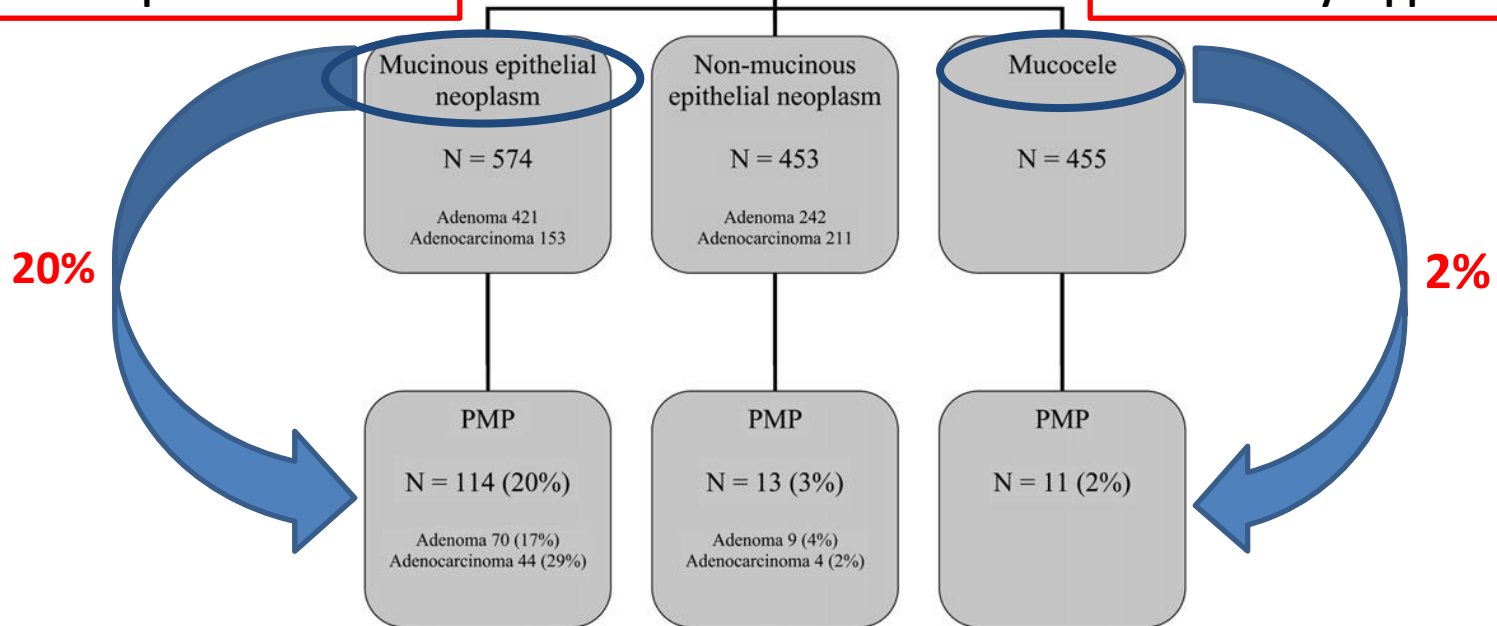
**Netherlands 1995-2005
PALGA Database
167,744 appendectomies**

Appendiceal lesion
N = 1482

**Netherlands 1995-2005
PMP Database
267 patients**

**Appendiceal Neoplasms: 0.9%
Mucinous Neoplasms : 0.3%**

**Incidence: 2/million
Primary: Appendix 82%**

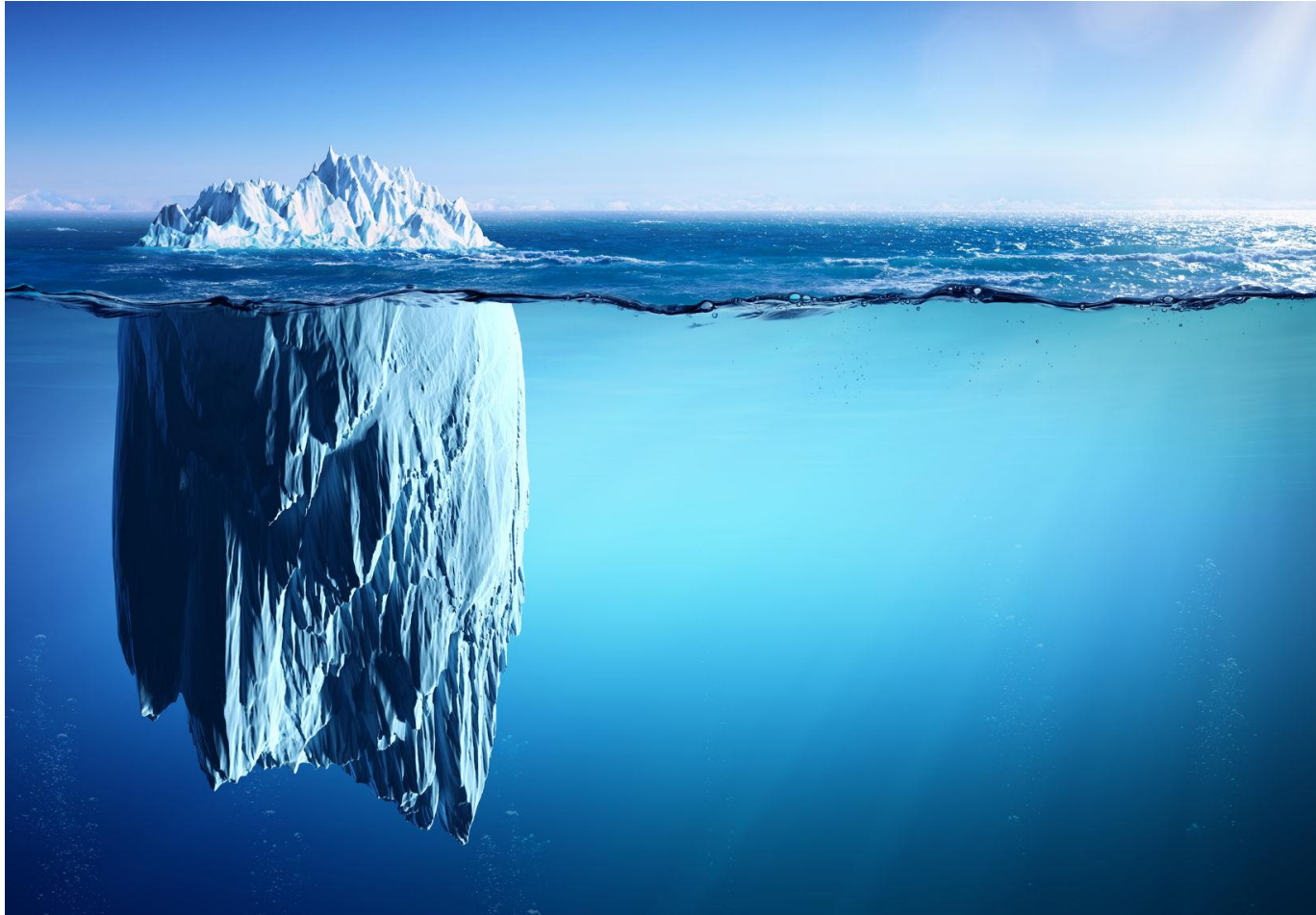


Colonic Neoplasm: 13%

Median Time to PMP: 2 years

Smeenk, EJSO 2008

Pseudomyxoma Peritonei



Appendiceal Mucocele

Aggressive Surgical Approach



Appendiceal Mucocele

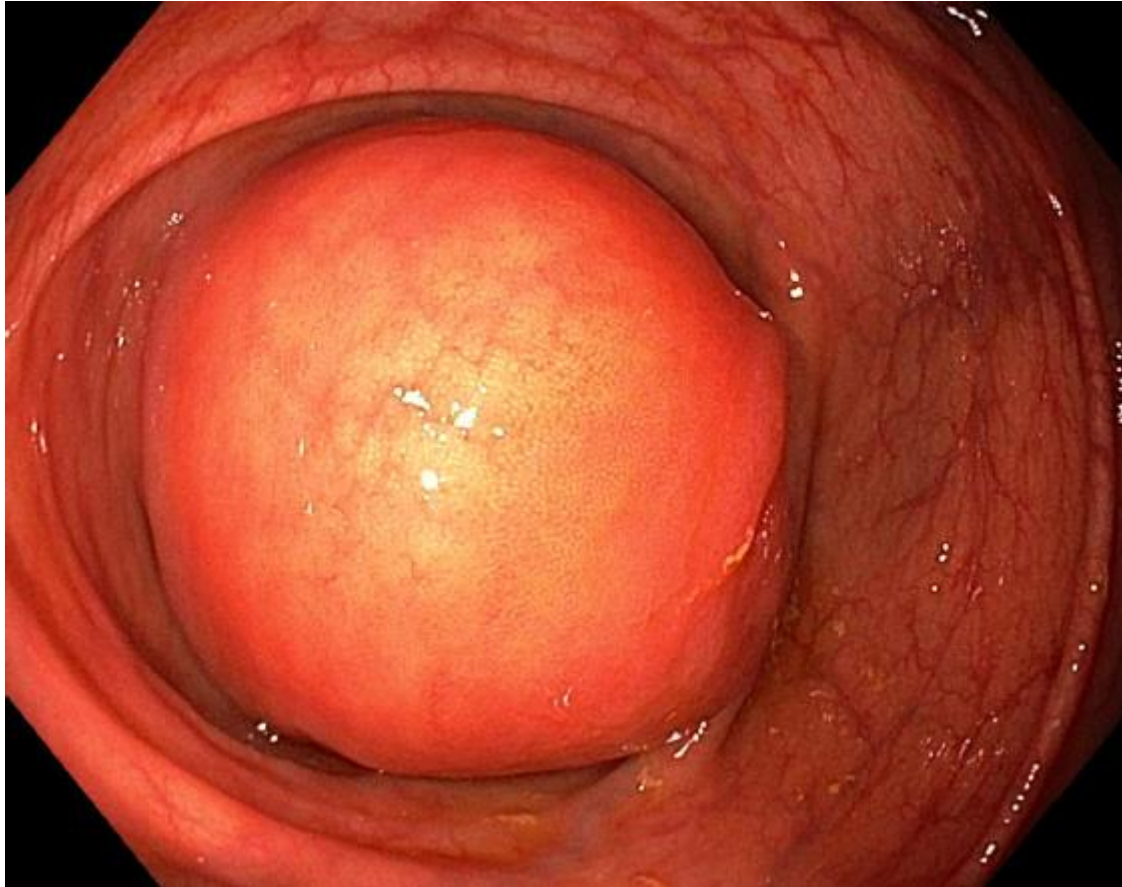
Κολονοσκοπική Διάγνωση Βλεννοκήλης

TABLE 1. Data obtained for 7 patients with colonoscopically diagnosed mucocoele of the appendix

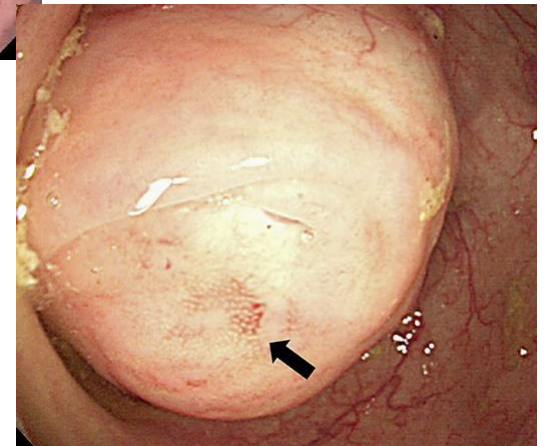
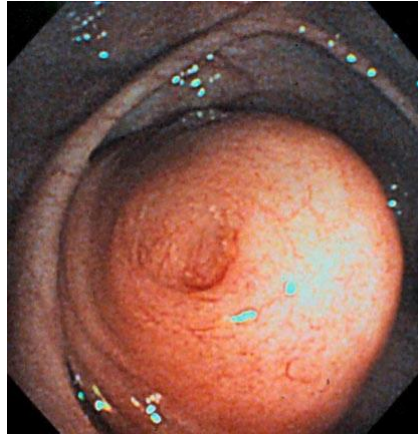
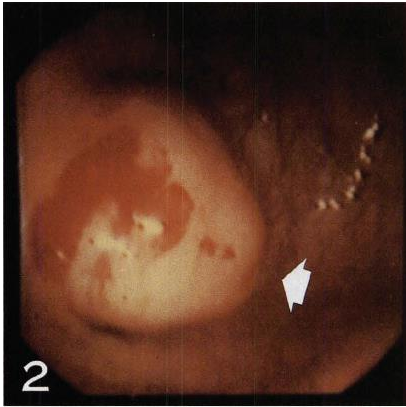
	1	2	3	4	5	6	7
Age, y	38	39	52	57	70	49	60
Gender	M	F	F	F	F	F	F
Symptoms	Low pain; hematochezia	RLQ pain; hematochezia	—	—	RLQ pain	Diarrhea; epigastric pain	RLQ pain
Barium enema	Cecal filling defect	Cecal filling defect	—	—	Cecal filling defect	—	—
Colonoscopy; indication	Symptoms; BE findings	Symptoms; BE findings	UC; surveillance	Screening	Symptoms; BE findings	Symptoms	Symptoms
Colonoscopy findings	Submucosal cecal lesion at appendiceal orifice	Glassy, rounded, protruding mass from appendiceal orifice	Submucosal cecal lesion at appendiceal orifice	Submucosal cecal lesion at appendiceal orifice	Submucosal cecal lesion at appendiceal orifice	Submucosal cecal lesion at appendiceal orifice	Submucosal cecal lesion at appendiceal orifice
CT report	—	—	—	Normal	—	Mucocoele; appendix	Mucocoele; appendix
Surgery	+	+	+	+	+	+	+
Complications	—	—	—	—	—	—	Wound; abscess
Pathology	Mucinous; cystadenoma	Mucinous; cystadenoma	Mucinous; cystadenoma	Mucinous; cystadenoma	Mucinous; cystadenoma	Mucinous; cystadenoma	Mucinous; cystadenoma

RLQ, Right lower quadrant; BE, barium enema; UC, ulcerative colitis.

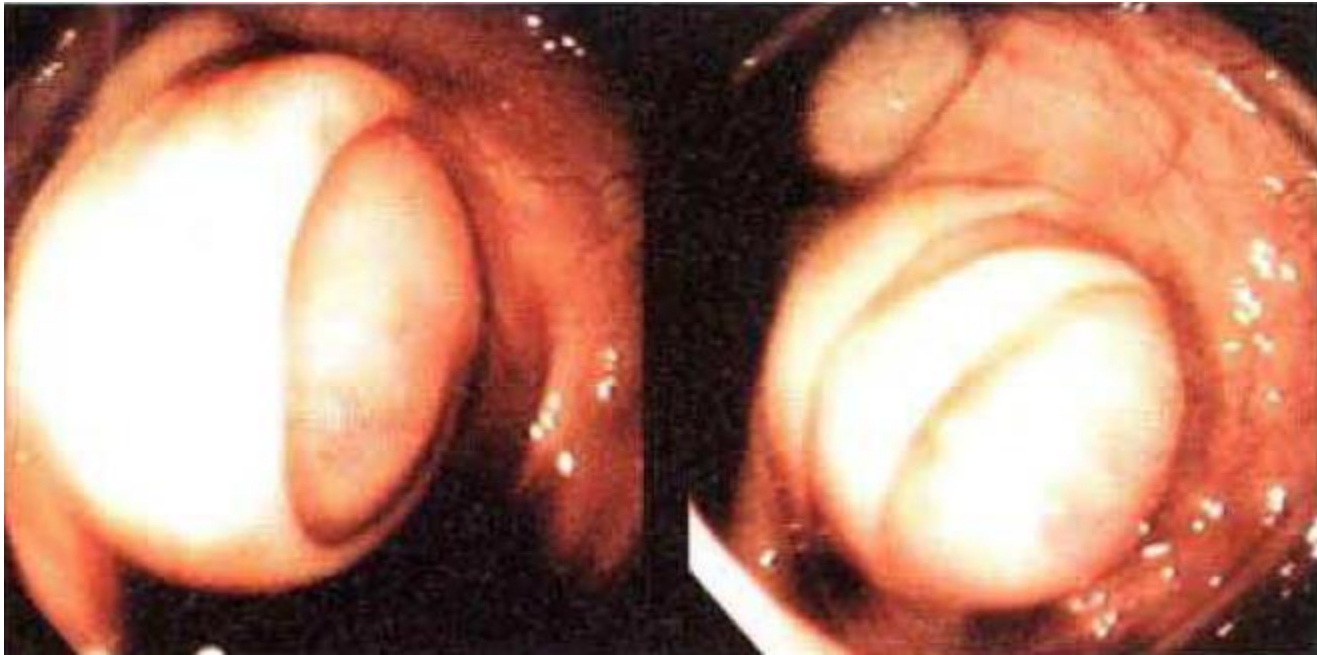
Η κλασική Ενδοσκοπική Εικόνα



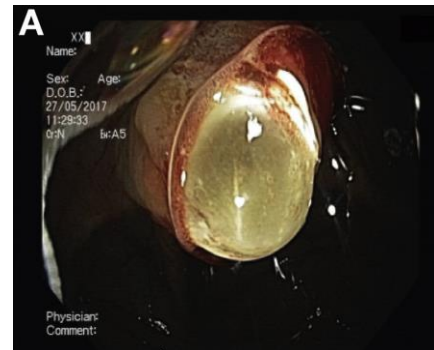
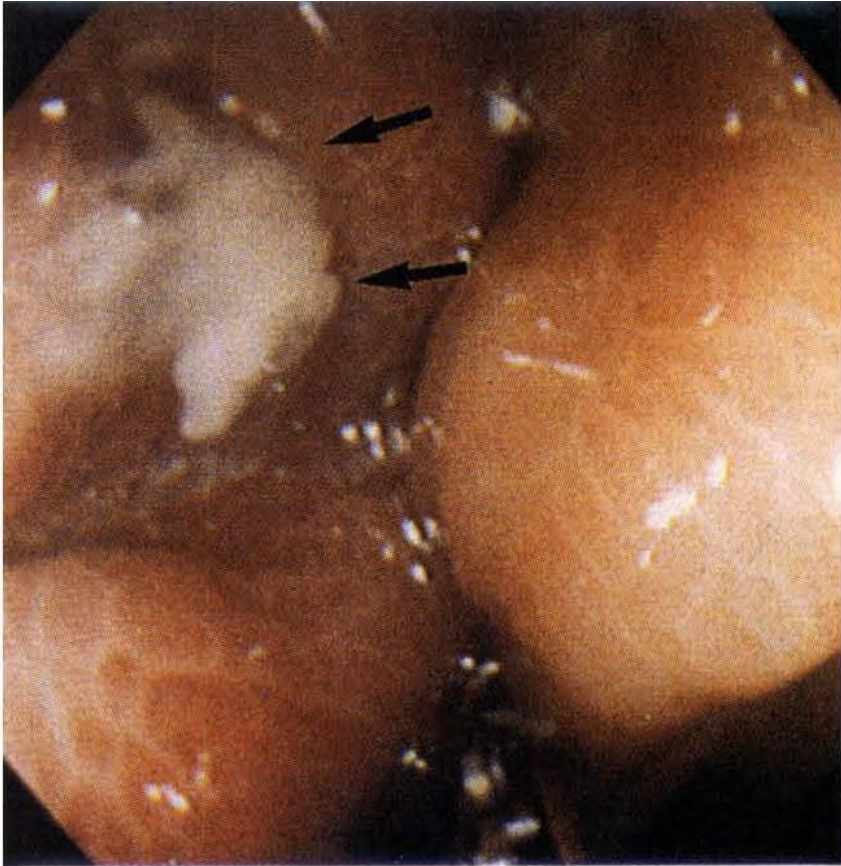
The Volcano Sign



The Trapped Balloon sign

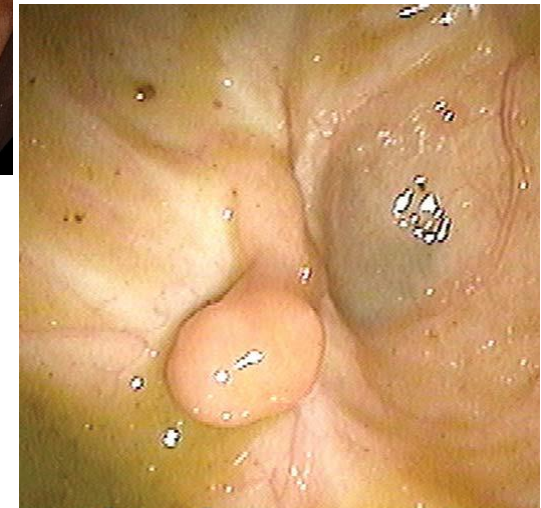
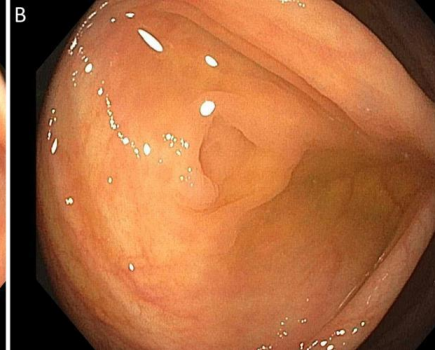
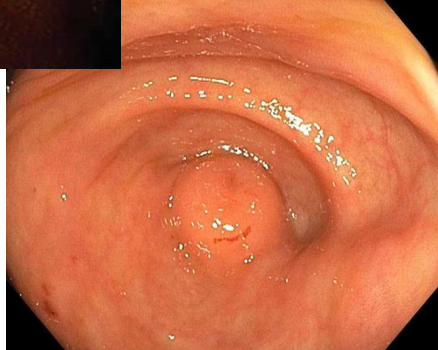


Έξοδος Βλέννης



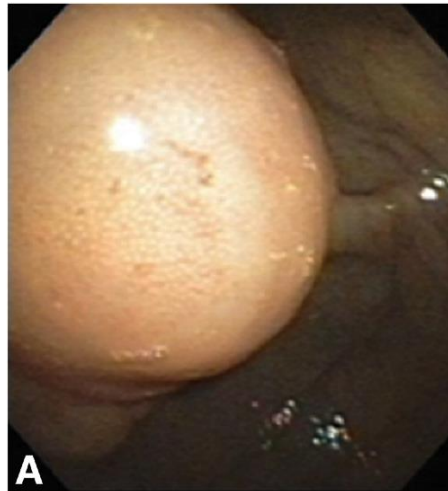
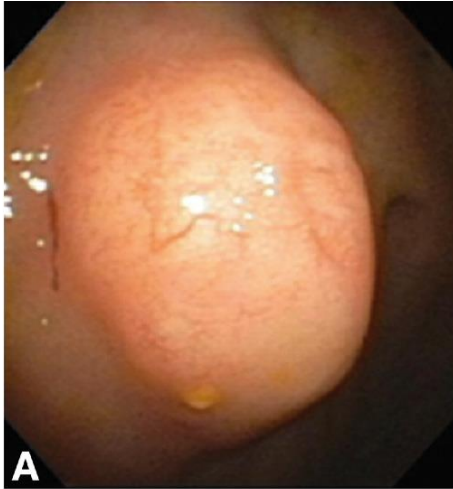
Nakagawa, Gastrointest Endosc 1994

Inverted Appendiceal Stump



Prout, AJR 2006

Endoscopic Ultrasonography?

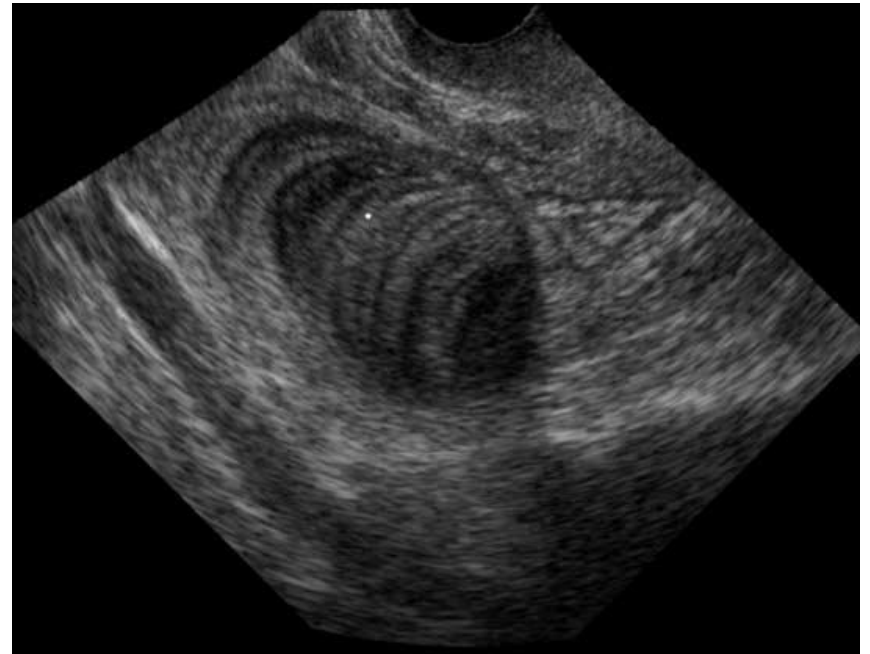


Lymphoma

Mucinous Cystadenoma

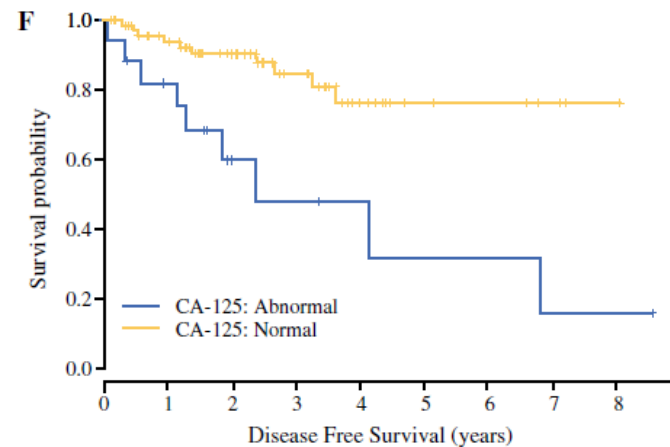
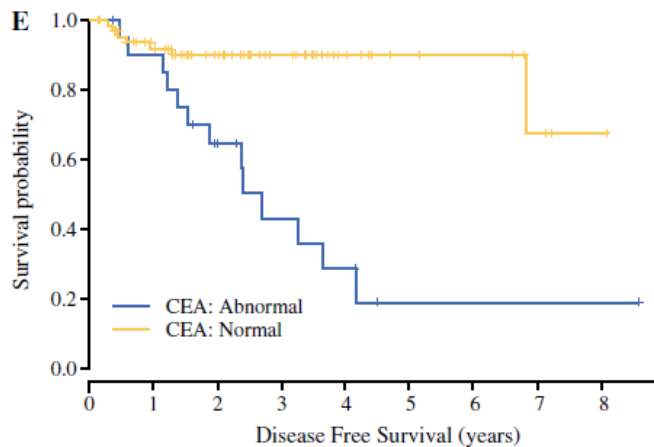
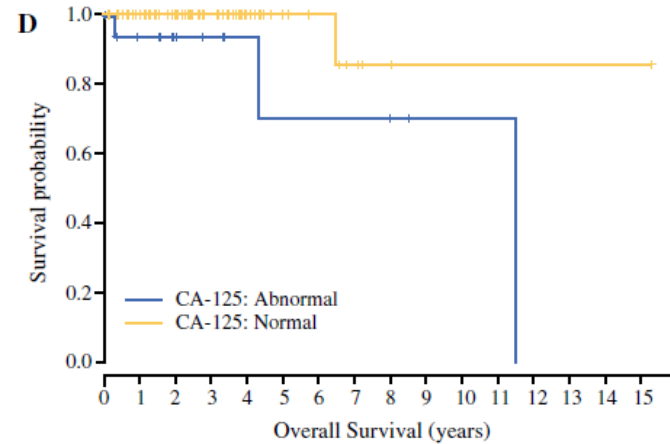
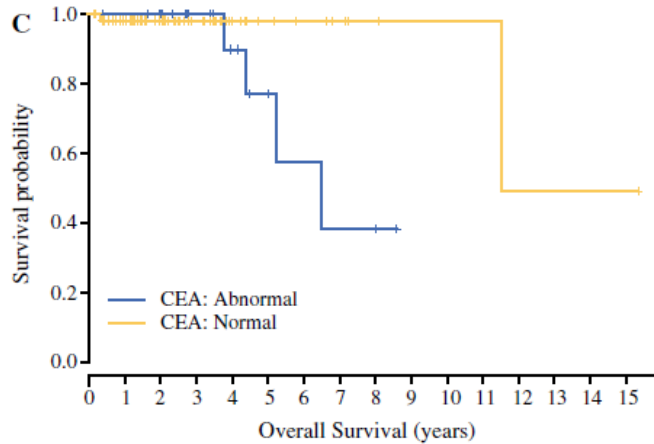
GIST

Υπερηχογράφημα Onion Skin Sign



*Caspi, J Ultrasound Med 2004
Leschinskyi, Abdom Radiol 2018*

Καρκινικοί Δείκτες: CEA, CA 19-9, CA 125



Βλεννώδη Νεοπλάσματα Σκωληκοειδούς: Ορολογία και Σύγχυση

McDonald and Woodruff (5) (1940)	Carr et al. (10) (1995)	Misdraji et al. (7) (2003)	Pai et al. (6) (2009)	World Health Organization (2010)	Carr et al. (8) Modified Delphi Consensus (2016)
-Benign mucocoele -Cystadenocarcinoma	-Mucocoele -Hyperplastic polyp -Adenoma -Cystadenoma -Carcinoma -Cystadenocarcinoma -Mucinous tumors of uncertain malignant potential	-Low-grade appendiceal mucinous neoplasm -Mucinous adenocarcinoma -Discordant	-Mucinous adenoma -Low-grade mucinous neoplasm, low risk of recurrence -Low-grade mucinous neoplasm, high risk of recurrence -Mucinous adenocarcinoma	-Adenoma -Low-grade appendiceal mucinous neoplasm -Mucinous adenocarcinoma	-Adenoma -Serrated polyp -Low-grade appendiceal mucinous neoplasm -High-grade appendiceal mucinous neoplasm -Mucinous adenocarcinoma -Poorly differentiated (mucinous) adenocarcinoma with signet ring -(Mucinous) Signet ring cell carcinoma -Adenocarcinoma

Adenomas, Serrated Polyps, LAMN, HAMN, Mucinous Adenocarcinoma, Signet Ring Cells

Lesion	Terminology
Adenoma, confined to mucosa, muscularis mucosae intact	Tubular, tubulovillous or villous adenoma with low or high grade dysplasia (as per colorectal adenoma classification)
Tumour with serrated features confined to mucosa, muscularis mucosae intact	Serrated Polyp with or without dysplasia
Mucinous neoplasm with low-grade cytologic atypia ^a	Low grade appendiceal mucinous neoplasm (LAMN)
Mucinous neoplasm with architectural features of a LAMN and no infiltrative invasion but with high grade cytologic atypia	High grade appendiceal mucinous neoplasm (HAMN)
Mucinous neoplasm with infiltrative invasion ^b	Mucinous adenocarcinoma (well, moderately, or poorly differentiated)
Neoplasm with signet ring cells ≤ 50 %	Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
Neoplasm with signet ring cells >50 %	(mucinous) signet ring cell carcinoma
Nonmucinous adenocarcinoma resembling colorectal adenocarcinoma	Adenocarcinoma (well, moderately, or poorly differentiated)

^aLAMNs are associated with any of the following: Loss of the muscularis mucosae. Fibrosis of the submucosa. “Pushing invasion”. Dissection of acellular mucin in the wall. Undulating or flattened epithelial growth. Rupture of the appendix. Mucin and/or cells outside the appendix. Pushing invasion has a broad front of cells which expands into the surrounding tissue without destructive features. ^bFeatures of Infiltrative invasion include: Tumour budding and/or small irregular glands, typically within a desmoplastic stroma.

*Carr, Am J Pathol 2016
Carr, Histopathology 2017
WHO 5th Edition 2019*

Ο Ρόλος του Παθολογοανατόμου

- ❖ *Discordance 18% (57/323), 7% (22/57) from LAMN to hyperplastic changes...*

Basingstoke, UK

Amin, J Clin Pathol 2019

- ❖ *Discordance in Terminology 28%, Grading 50%, flawed chemotherapy 6+6%...*

Pittsburg, USA

Choudry, Ann Surg Oncol 2019

- ❖ *43 (38) Appendiceal Consults, 19 down grades, 5 Upgrades...*

7 Academic Centers, USA

Arnold, Modern Pathol 2019

Central Pathology Review from Referral Center Expert Pathologist

CT και Οξεία Σκωληκοειδίτιδα: Βλεννοκήλη;

TABLE 2: Percentage of Patients with Each CT Finding and Significance in Differentiating Acute Appendicitis With and Without Mucocele

CT Finding	Normal Appendix	Appendicitis without Mucocele	Appendicitis with Mucocele	p^a	
				Reader 1	Reader 2
Cystic dilatation	0 (0/57)	6.9 (4/58)	66.7 (16/24)	0.0066	< 0.0001
Mural calcification	0 (0/57)	0 (0/57)	25 (6/24)	0.0846	0.0049
Mural enhancement	8.6 (5/58)	92.6 (50/54)	66.7 (16/24)	0.0020	1.0000
Appendicolith	0 (0/58)	22.8 (13/57)	0 (0/24)	0.1529	0.0850
Intraperitoneal fluid	6.9 (4/58)	34.5 (20/58)	33.3 (8/24)	1.0000	1.0000
Lymphadenopathy	17.2 (10/58)	75.9 (44/58)	54.2 (13/24)	0.1654	0.3069
Small bowel mural thickening	1.7 (1/58)	23.6 (13/55)	20.8 (5/24)	1.0000	1.0000
Periappendiceal fat stranding	3.5 (2/58)	86.2 (50/58)	83.3 (20/24)	0.4410	1.0000
Extraluminal gas	0 (0/58)	5.2 (3/58)	17.4 (4/23)	0.5670	0.1781
Intraluminal gas	56.9 (33/58)	26.3 (15/57)	8.3 (2/24)	0.2332	0.3984
Arrowhead sign	1.7 (1/58)	52.6 (30/57)	41.7 (10/24)	1.0000	0.3246
Target sign	0 (0/58)	37.5 (21/56)	20.8 (5/24)	1.0000	0.0855
Abscess	0 (0/58)	15.5 (9/58)	16.7 (4/24)	1.0000	1.0000
Focal mass	0 (0/58)	1.8 (1/57)	8.3 (2/24)	1.0000	0.2002
Irregular wall contour	0 (0/58)	29.8 (17/57)	25.0 (6/24)	0.4507	0.7211

Note—Values in parentheses are raw numbers. Magnitude and variation of the denominators reflect missing data and the fact that data were provided by each of two readers (denominator = 2 × number of subjects – number missing).

^aFisher's exact test.

CT Diameter > 1.3 cm: Sensitivity 71.4%, Specificity 94.6% (Bennett, AJR 2009)

US Diameter > 1.5 cm: Sensitivity 83.0%, Specificity 92.0% (Lien, Am J Emerg Med 2006)

Βλεννοκήλη: Νεοπλασματική;

Focal Distal Dilatation+

Diameter >2 cm, No Periappendiceal Fat Stranding, Mural Calcifications

TABLE 3: Morphologic Findings, by Underlying Histopathologic Diagnosis

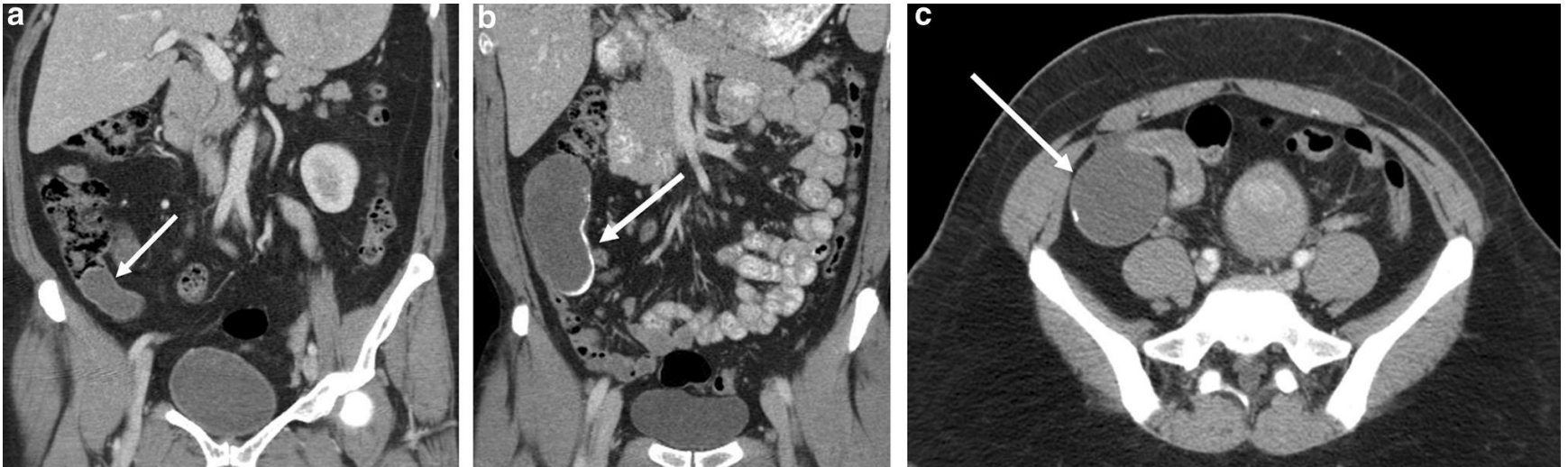
Morphologic Finding	Histopathologic Diagnosis, No. (%) of Cases		<i>p</i>
	Nonneoplastic Mucocele (<i>n</i> = 15) ^a	Neoplastic Mucocele (<i>n</i> = 34) ^b	
Mural calcification	1 (6.7)	16 (47.1)	0.006
Internal septations	2 (13.3)	5 (14.7)	0.899
Periappendiceal fat stranding	10 (66.7)	8 (23.5)	0.004
Free intraperitoneal fluid	4 (26.7)	7 (20.6)	0.638
Wall irregularity	2 (13.3)	8 (23.5)	0.414
Pseudomyxoma peritonei	0 (0.0)	1 (2.9)	0.502
Soft-tissue thickening	2 (13.3)	6 (17.6)	0.707

^aIncludes simple mucocele and mucosal hyperplasia.

^bIncludes mucinous cystadenoma, mucinous neoplasm of uncertain malignant potential, mucinous neoplasm of low malignant potential, and mucinous cystadenocarcinoma.

Computed Tomography

Multidetector, Multiplanar, Coronal

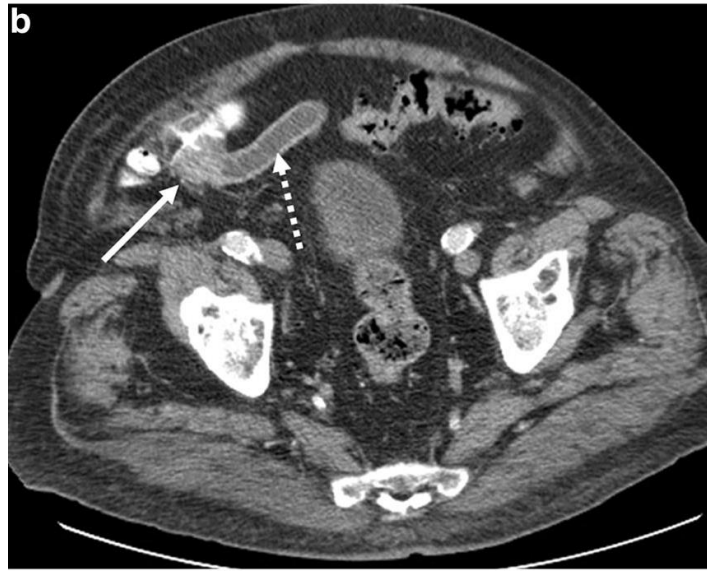


**Low Attenuating Cystic Round/Tubular Lesion with Enhancing Wall
Wall Calcifications, No Periappendiceal Inflammation/Abscess**

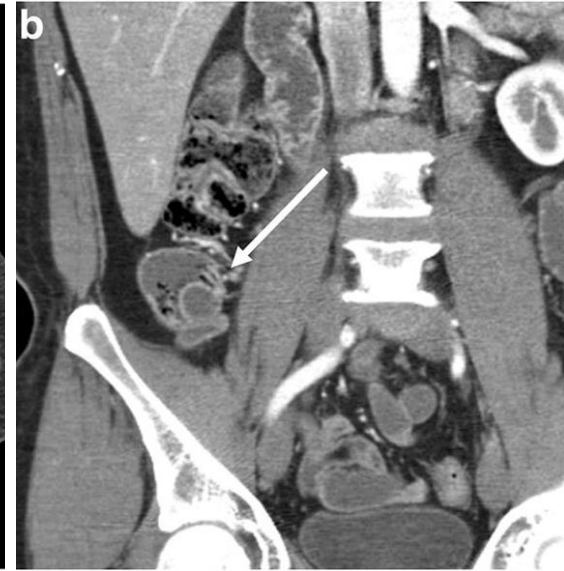
Mimics-CT



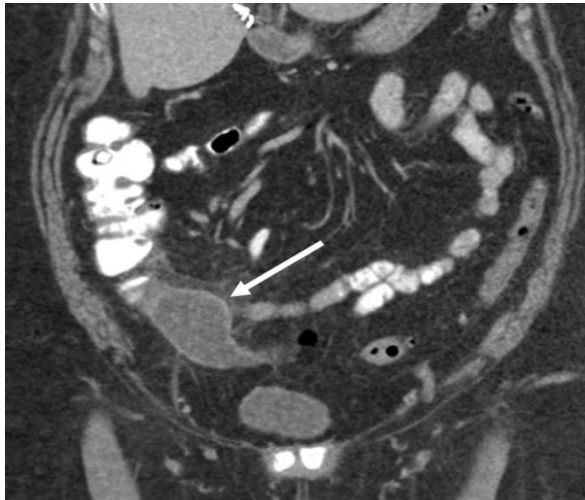
Appendicitis



Cecal Adenocarcinoma

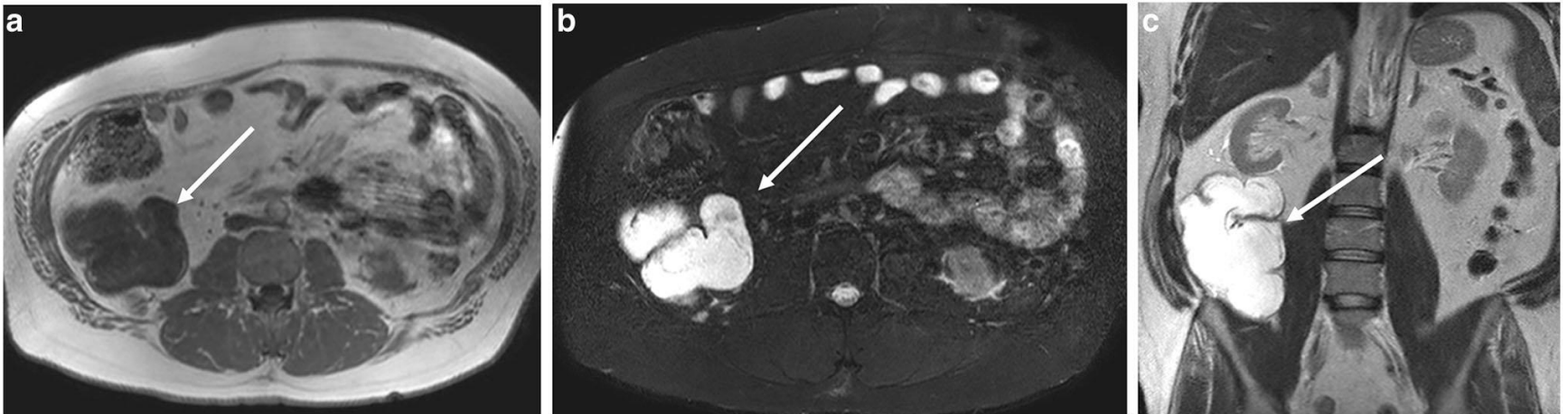


Lymphoid Hyperplasia



Magnetic Resonance Imaging

Extraluminal Mucin, Ovarian vs Appendiceal Origin, Surveillance



Λαπαροσκοπική Σκωληκοειδεκτομή: κίνδυνος ρήξης

Table 5 Univariate and multivariate analysis for rupture of mucocoele

Variable	Univariate analysis	
	OR (95% CI)	<i>P</i>
Age > 60 years	0.917 (0.124–6.788)	1.000
Male	3.900 (0.391–38.915)	0.322
BMI > 24	0.380 (0.038–3.788)	0.622
ASA ≥ 3	3.074 (0.289–32.733)	0.361
WBC > $1.0 \times 10^4/\mu\text{L}$	12.333 (1.211–125.632)	0.032
Diameter > 2 cm	1.381 (0.138–13.850)	1.000
Operator of professor	0.333 (0.044–2.503)	0.277
Laparoscopic surgery	0.643 (0.087–4.770)	0.647

OR odd ratio, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *WBC* white blood cell count

Κίνδυνος εμφάνισης Σκωληκοειδικής Νεοπλασίας σε ασθενείς με Περισκωληκοειδικό Απόστημα που αντιμετωπίστηκαν συντηρητικά

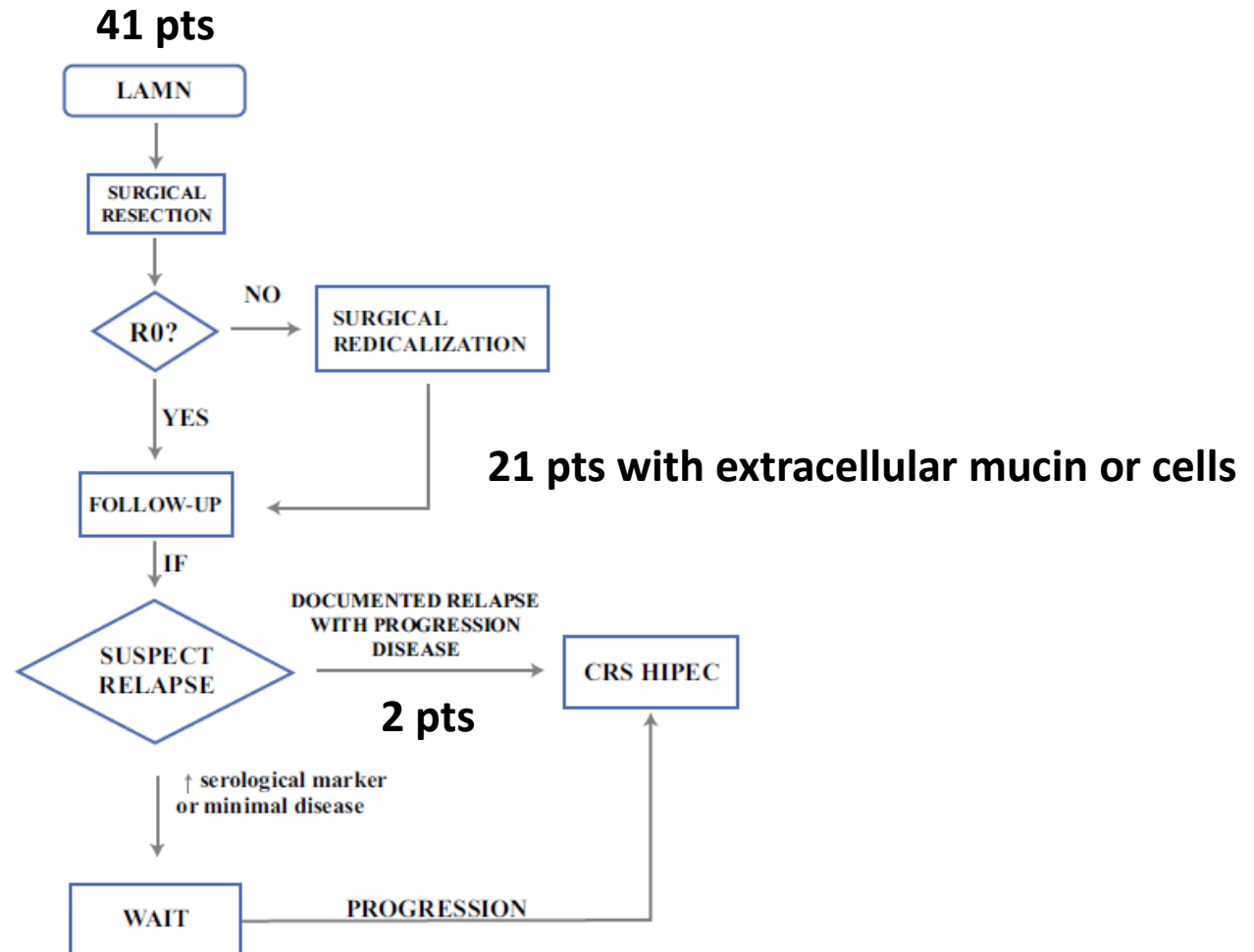
Table 4. Neoplasms Found in the Study Population

Patient Sex/Age, y	Reason for Intervention	Time to Intervention, d	Intervention	Histological Findings	Time to Secondary Intervention, d	Secondary Intervention
F/56	Allocated intervention	90	Appendectomy	LAMN and pseudomyxoma peritonei	156	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
M/47	Allocated intervention	120	Appendectomy	LAMN	NA	Surveillance
M/59	Allocated intervention	134	Appendectomy	Sessile serrated adenoma	NA	Surveillance
M/59	Recurrent symptoms	329	Ileocecal resection	Adenocarcinoma of the appendix	378	Right hemicolectomy
M/59	Recurrent symptoms	18	Appendectomy	LAMN	98	Ileocecal resection
M/61	Recurrent symptoms	330	Appendectomy	Mucinous cystadenoma	NA	Surveillance
M/55	Recurrent symptoms	189	Appendectomy	Goblet cell carcinoid	252	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
F/58	MRI tumor suspicion	199	Appendectomy	Sessile serrated adenoma	NA	Surveillance
F/53	CT tumor suspicion	171	Chemotherapy	Cecal adenocarcinoma and sessile serrated appendiceal adenoma	332	Right hemicolectomy (palliative)
M/61	Recommended	429	Appendectomy	LAMN	NA	Surveillance
F/41	Recommended	142	Appendectomy	LAMN	NA	Surveillance

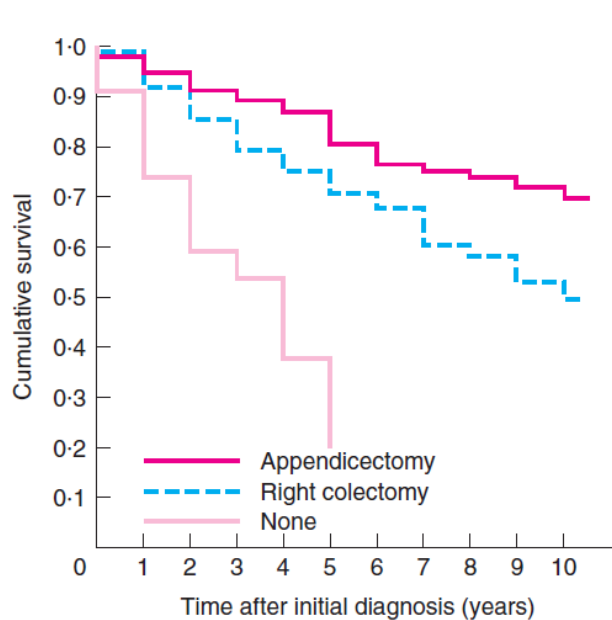
Κίνδυνος Νεοπλασματος 20% > 40 έτη

Acuta RCT, Mallinen, JAMA Surg 2019

Low Grade Appendiceal Mucinous Neoplasia: Watch and Wait?



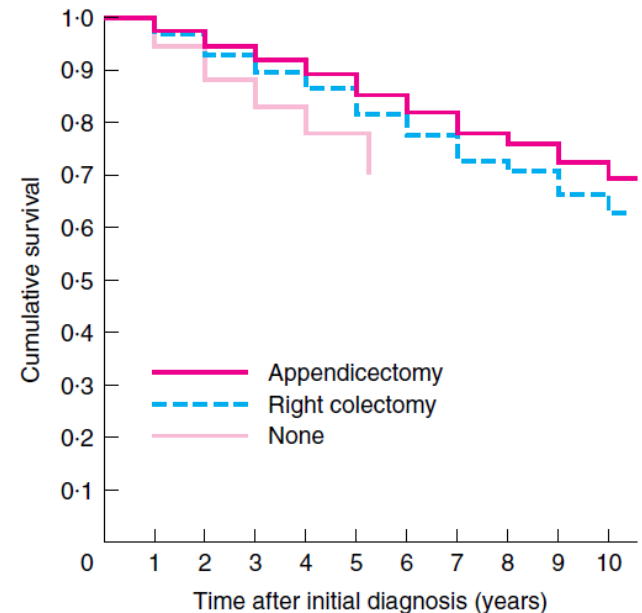
Δεξιά Ημικολεκτομή δεν αυξάνει την επιβίωση ασθενών με βλεννώδες καρκίνωμα σκωληκοειδούς και περιτοναϊκή διασπορά



No. at risk											
Appendicectomy	198	190	184	155	132	112	88	72	64	53	40
Right colectomy	280	271	247	214	184	160	129	112	91	75	53
None	23	21	17	12	10	7					

Fig. 1 Analysis of survival by surgical procedure. $P < 0.001$ (log rank test)

- ❖ Θετικοί επιχώριοι Λεμφαδένες;
- ❖ Καθαρισμός Πρωτοπαθούς εστίας;
- ❖ Μη βλεννώδης ιστολογία;



No. at risk											
Appendicectomy	198	190	184	155	132	112	88	72	64	53	40
Right colectomy	280	271	247	214	184	160	129	112	91	75	53
None	23	21	17	12	10	7					

Fig. 2 Adjusted analysis of survival by surgical procedure. $P = 0.258$ (Cox proportional hazards model)

...In conclusion, we recommend cautious use of the term “mucocele of the appendix”...All mucocèles should be considered and managed as pathologic entities that may harbour a mucinous appendiceal neoplasm...spontaneous or iatrogenic rupture must be avoided...

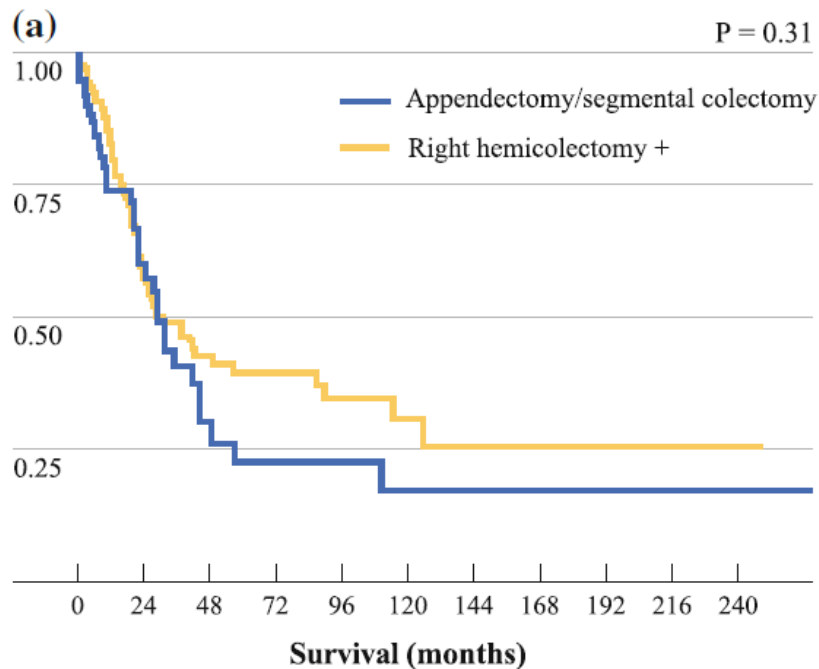
What is a ‘mucocele’ of the appendix and how are these lesions best managed? Beware the wolf in sheep’s clothing

Shinichiro Sakata and Brendan J. Moran

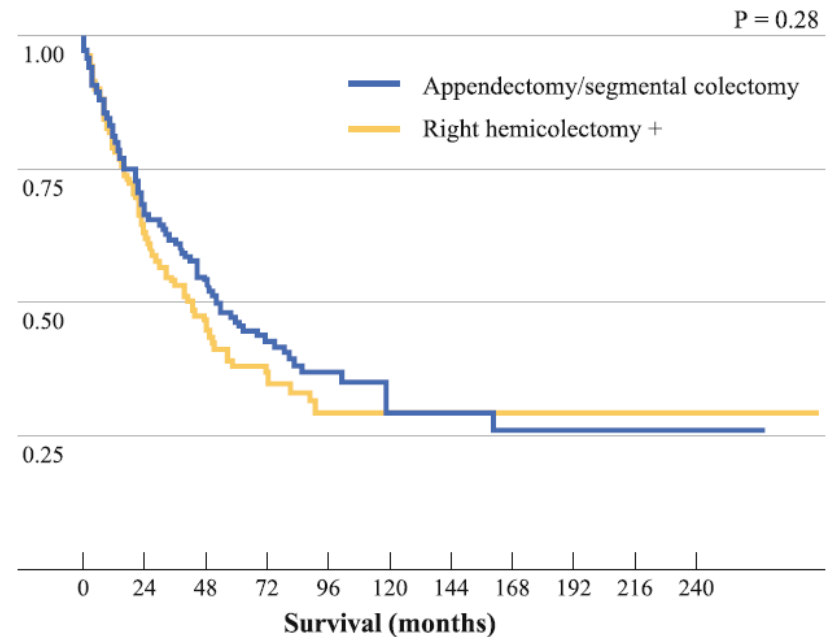
Peritoneal Malignancy Institute, Basingstoke and North Hampshire Hospital, Hampshire
Hospitals National Health Service Foundation Trust, Basingstoke, Hampshire, United
Kingdom

Δεξιά Ημικολεκτομή για Βλεννώδες Αδενοκαρκίνωμα Σκωληκοειδούς: Είναι απαραίτητη;

Node Positive Disease



Metastatic Disease



Mucocele Therapeutic Algorithm

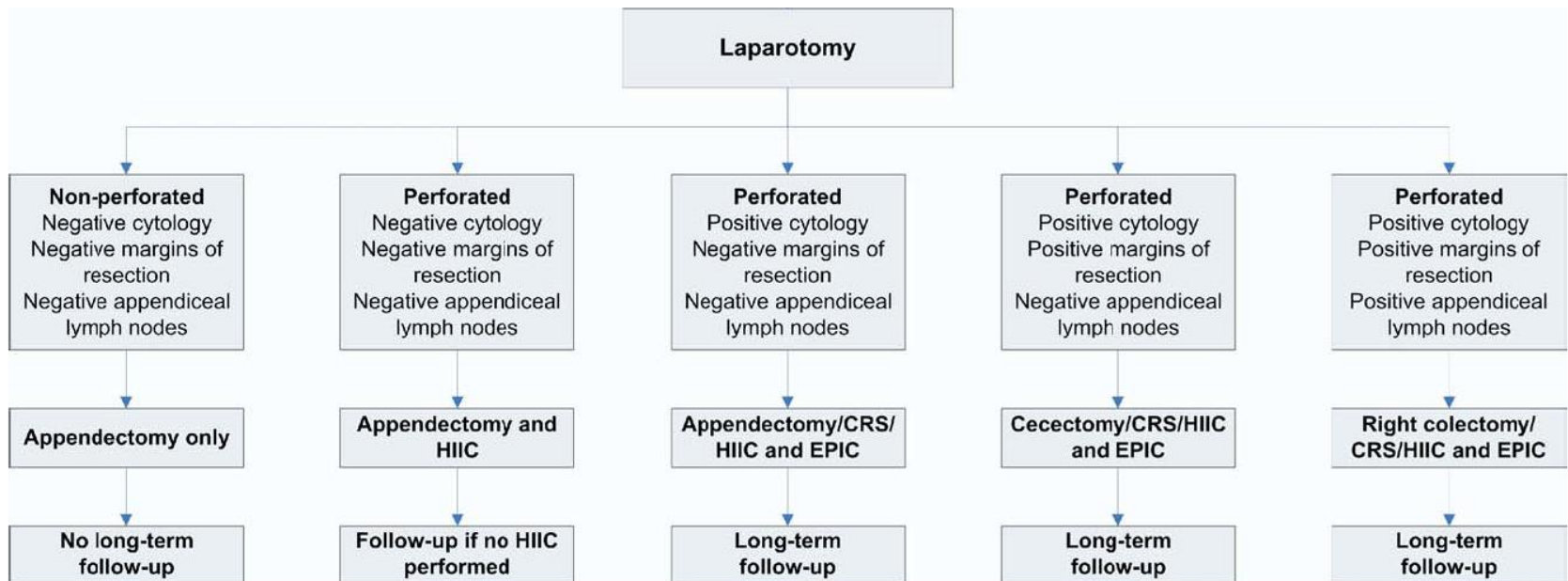


Figure 1. Clinical pathway for treatment of mucocele of the appendix. CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; HIIC, heated intraoperative intraperitoneal chemotherapy.

Συμπεράσματα

Διάγνωση

- ✓ Ενδοσκόπηση, Αξονική Τομογραφία, Δείκτες, όχι βιοψίες

Θεραπεία

- ✓ Ριζική Σκωληκοειδεκτομή (λαπαροσκοπική;)
- ✓ Εκτίμηση παρασκευάσματος από εξειδικευμένο παθολογοανατόμο/MDT

Παρακολούθηση σε:

- ✓ LAMN, HAMN, G1 MACA, υγιή όρια, μεμονωμένη ακυτταρική βλέννη (T4a)

Συμπληρωματική δεξιά ημικολεκτομή σε:

- ✓ G2-3 MACA

Παραπομπή σε κέντρο CRS+HIPEC σε:

- ✓ Ενδοπεριτοναϊκή βλέννη (M1a), Ενδοπεριτοναϊκά καρκινικά κύτταρα (M1b)

Επιτήρηση

- ✓ Απεικόνιση + δείκτες (διαγνωστική λαπαροσκόπηση;)

Ευχαριστώ

