

## SUPPLEMENTAL DATA

Molecular markers potentially used for the identification of metastatic disease, since they are more often expressed in malignant appendiceal neuroendocrine neoplasms (metastatic) compared with not metastatic (Modlin, et al. 2006)

MAGE-D2: melanoma-associated antigen D2	Adhesion gene
NAP1L1: nucleosome assembly protein 1-like 1	Apoptotic marker
MTA1: metastasis-associated Protein 1	Oestrogen-antagonistic breast cancer malignancy gene

Case reports or case series with functional syndromes in patients with appendiceal NENs.

<b>Authors, Date</b>	<b>Functional syndrome</b>	<b>Case reports/series</b>
(Markgraf and Dunn 1964)	Carcinoid syndrome	1
(Prunty 1965)	Cushing's syndrome	1
(Miller, et al. 1971)	Cushing's syndrome	1
(Johnston and Waisman 1971)	Cushing's syndrome	1
(Goldfine and Balthazar 1979)	Carcinoid syndrome	1
(Bhagat and Patoria 1981)	Carcinoid syndrome	1
(Sjoblom, et al. 1987)	Carcinoid syndrome	1
(Sjoblom 1988)	Carcinoid syndrome	1/28
(Urbanczyk and Tomaszewska 1994)	Insulinoma	1
(Dobnig, et al. 1996)	Cushing's syndrome	1
(Grossman, et al. 2006)	Cushing's syndrome	1
(Liu, et al. 2010)	Carcinoid syndrome	4/51
(Perakakis, et al. 2011)	Cushing's syndrome	1
(Beddy and Larson 2011)	Cushing's syndrome	1
(Grozinsky-Glasberg, et al. 2013)	Carcinoid syndrome	2/28

Novel pathological markers recently used to identify the tissue of origin of metastatic foci and/or the malignant potential of gastrointestinal-neuroendocrine neoplasms

Secretoneurin	33 amino-acid peptide; detected more frequently (94%) than Chromogranin A in aNENs	(Prommegger, et al. 1998)
<i>CDX2</i> (caudal type homeobox 2)	histological marker for aNENs, duodenal and siNENs: involved in the process of intestinal cell proliferation, differentiation, adhesion and apoptosis → considered specific for enterocytes	(Desouki, et al. 2013; Lin, et al. 2007; Saqi, et al. 2005; Srivastava and Hornick 2009)
<i>Catestatin</i>	neuropeptide derived from Chromogranin A (93% of aNENs)	(Prommegger, et al. 2004)
<i>beta-catenin</i>	neuropeptide (71% of aNENs)	(Barshack, et al. 2002)
<i>Calbindin-D28k</i>	neuroendocrine marker	(Katsetos, et al. 1994).

aNENs: appendiceal neuroendocrine neoplasms

A list of published reports of appendiceal neuroendocrine neoplasms with rare metastatic sites

Breast	(Vergier, et al. 1991)
Mesenteric invasion, peritoneal seeding, terminal ileal ischemia and features of the carcinoid syndrome	(Johnston and Waisman 1971)
Pelvic metastatic foci	(Robbins and Sunshine 2000)
Intra-cardiac	(Patel, et al. 2009)

Co-morbidities documented in small series or case reports of patients with aNENs.

Secondary gastro-intestinal malignancies	Synchronous or metachronous NEN	10%-18.2%	(Fucs, et al. 2005)
	colorectal carcinomas		(Bucher, et al. 2004; Connor, et al. 1998; Modlin, et al. 2003; Modlin and Sandor 1997)
Inflammatory bowel disease	Crohn's disease	4/111 (3.6%) with CD and aNENs	(West, et al. 2007)
		1000 patients with CD, 3/441 (0.68% among appendicectomies; 0.3% among CD) patients had aNENs, all females	(Freeman 2003)
	Ulcerative colitis	2 patients reported	(Le Marc'hadour, et al. 1994)
	Crohn's disease		
	Crohn's disease	Case report	(Kosakowski, et al. 1986)
Crohn's disease	Case report (child)	(Janin, et al. 1981)	
von Recklinghausen disease, Familial adenomatous polyposis, Hereditary non-polyposis colorectal cancer	Case reports	(Hendi, et al. 2005; Kulkarni, et al. 2011; Miquel, et al. 2004)	
Immunosuppressed patients with renal transplants	2 patients reported	(Basic-Jukic, et al. 2010)	
Obese patients undergoing bariatric procedures	7/477 (1.4%) post appendicectomy had aNENs	(Crea, et al. 2011)	

CD: Crohn's disease; NEN: neuroendocrine neoplasm; aNENs: appendiceal NENs

TNM staging for aNEN proposed by ENETS (Pape, et al. 2012; Sobin LH 2009) and UICC/AJCC (Rindi, et al. 2007)

ENETS		UICC/AJCC	
<i>T primary tumour</i>		<i>T primary tumour</i>	
Tx	Primary tumour cannot be assessed	<i>Same as ENETS staging</i>	
T0	No evidence of primary tumour	<i>Same as ENETS staging</i>	
T1	Tumour $\leq$ 1cm invades muscularis propria and submucosa		
T1a		Tumour $\leq$ 1 cm in greatest dimension	
T1b		Tumour $>$ 1 cm but $\leq$ 2 cm in greatest dimension	
T2	Tumour $\leq$ 2 cm invades muscularis propria, submucosa and/or minimally ( $<$ 3 mm) invading subserosa/mesoappendix	Tumour $>$ 2 cm but $\leq$ 4 cm or with extension to the caecum	
T3	Tumour $>$ 2 cm and/or extensive ( $>$ 3 mm) invasion of subserosa/ mesoappendix	Tumour $>$ 4 cm with extension to the ileum	
T4	Tumour invades peritoneum or other organs	Tumour perforates peritoneum and invades other adjacent organs or structures, e.g. abdominal wall and skeletal muscle	
<i>N – regional lymph nodes</i>		<i>N – regional lymph nodes</i>	
Nx	Cannot be assessed	<i>Same as ENETS staging</i>	
N0	No regional lymph nodes metastasis	<i>Same as ENETS staging</i>	
N1	Regional lymph node metastasis	<i>Same as ENETS staging</i>	
<i>M – distant metastasis</i>		<i>M – distant metastasis</i>	
Mx	Cannot be assessed	<i>Same as ENETS staging</i>	
M0	No distant metastasis	<i>Same as ENETS staging</i>	
M1	Distant metastasis	<i>Same as ENETS staging</i>	
<i>Disease stage according ENETS</i>		<i>Disease stage according UICC/AJCC</i>	
0	Tis N0 M0		
I	T1 N0 M0	I	T1 N0 M0
IIa	T2 N0 M0	II	T2-3 N0 M0
IIb	T3 N0 M0	III	T4 N0 M0
IIIa	T4 N0 M0		Any T N1 M0
IIIb	Any T N1 M0	IV	Any T Any N M1
IV	Any T Any N M1		

#### ENETS grading system for GI-NENs including aNEN

Grade	Mitotic count (mitoses/10 HPF)*	Ki-67 index (%)**
G1	$<$ 2	$\leq$ 2
G2	2-20	3-20
G3	$>$ 20	$>$ 20

ANEN: Appendiceal Neuroendocrine Neoplasms; ENETS: European Neuroendocrine Tumour Society, GI-NENs: Gastrointestinal Neuroendocrine Neoplasms, \* 10 HPF: high power field = 2mm<sup>2</sup>, at least 40 fields (at 40x magnification) evaluated in areas of highest mitotic density, \*\*MIB1 antibody: % of 2,000 tumour cells in areas of highest nuclear labelling

5-year survival rates for aNENs as reported in different series taken from the literature

<b>Origin</b>	<b>STUDY PERIOD</b>	<b>Size of Population studied</b>	<b>5-year survival rate (%)</b>
Sweden (Ahlberg, et al. 1980)	1969-1970	22 aNENs in patients <30 years old	100
Finland (Sjoblom 1988)	1968-1986	28 aNENs	96
New Zealand (Shaw and Canal 1989)	1976-1987	56 aNENs	95
Tuscany Tumour Registry (Crocetti 1997)	1985-1991	7 aNENs	100
SEER DATA/ ERG/ TNCS (Modlin and Sandor 1997; Sandor and Modlin 1998)	1950-1991 (SEER) 1973-1991 (ERG) 1950-69 (TNCS) 1969-71)	1570 aNENs	
		410 (SEER)	85.9
		Localised	94
		Regional invasion	84.6
		Distant metastases	33.7
Netherlands Survival Data (Quaedvlieg, et al. 2001)	1980-1997	198 aNENs	95
		186 Localised	96
		8 Regional	100
		2 Distant	0
		2 Unknown	55
SEER DATA (McCusker, et al. 2002)	1983-1997	1061 appendiceal malignancies: 324 malignant aNENs	>90%
SEER DATA (Modlin et al. 2003)	1973-1991	13,715 NENs:1679 aNENs	83±1.9
	1992-1999		71±5.9
	1973-1991	localised	92.3
	1992-1999		80.8
	1973-1991	regional	81.3
	1992-1999		88.1
	1973-1991	distant	30.6
	1992-1999		9.6
	1973-1991	unstaged	62.5
	1992-1999		66.7
Switzerland (Bucher et al. 2004)	1991-2003	21 aNENs with laparoscopic resection	100
		21 aNENs with open resection	94
Padua (pediatric) (Dall'Igna, et al. 2005)	1986-2001	14 aNENs	100
SEER DATA (McGory, et al. 2005)	1973-2001	435 aNENs	83
		localised	94
		Regional	83
		Distant	31
SEER DATA (Landry, et al. 2008)	1977-2004	900 NE malignancies®	90
		Stage I	100
		Stage II	100
		Stage III	78
		Stage IV	32
Genova (Fornaro, et al. 2007)	1990-2000	7 aNENs	100

German (Benedix, et al. 2010)	2000-2004	31341 malignancies: 196 appendiceal: 48 aNENs®	83.1
		Localised	92.2
		Regional	80
		Distant	50
		sized <1 cm	100
		sized 1-1,9 cm	80
		sized ≥ 2 cm	50
SEER DATA (Groth, et al. 2011)	1988-2005	576 aNENs	
		131 unknown size	98 vs.92 <sup>△</sup> *
		61 sized <1 cm	100 vs.100 <sup>△</sup> *
		46 sized 1-1,9 cm	100 vs.96 <sup>△</sup> *
		34 sized ≥ 2 cm	95 vs. 91 <sup>△</sup> *
		131 unknown size	89 vs.84 <sup>△</sup>
		61 sized <1 cm	100 vs.89 <sup>△</sup>
		46 sized 1-1,9 cm	87 vs.76 <sup>△</sup>
34 sized ≥ 2 cm	88 vs. 80 <sup>△</sup>		
SEER DATA (Mullen and Savarese 2011)	1988-2003	4 aNENs ≤ 1 cm with (+)ve LNs	100*
		16 aNENs > 1 cm but ≤ 2 cm with (+)ve LNs	92*
		24 aNENs > 2 cm with (+)ve LNs	91*
SEER DATA (Turaga, et al. 2012)	1973-2007	5655 appendiceal malignancies: 625 malignant aNENs	93 <sup>†</sup>
US National Cancer Database (Hsu, et al. 2013)	1998-2007	2,812 NE malignancies: 902 malignant aNENs	86.3
		Colectomy: 519 aNENs	88.3
SEER DATA (Murray, et al. 2014)	1994-2010	31 aNENs ≤1 cm	100
SEER DATA (Shaib, et al. 2015) <sup>△</sup>	1973-2011	1021 aNENs	NR
		Localised	NR
		Regional	NR
		Distant	32 (95% CI, 13- NR)#

\*: 10-year survival; \*\*: 7-year survival; † NE malignancies: Neuroendocrine neoplasms of the appendix include malignant carcinoid tumour, goblet cell carcinoid (GCCs), composite goblet cell carcinoid-adenocarcinoma; <sup>△</sup>AE: appendectomy only vs. RHC: right hemicolectomy; †: cancer specific survival; ®: including GCCs; <sup>△</sup> in the specific study median overall survival was calculated in months; #: months; aNENs: appendiceal neuroendocrine neoplasms; CI: confidence interval; ERG: End Results Group; NR: not reached; TNCS: Third National Cancer Survey;

## REFERENCES

- Ahlberg J, Bergstrand O, Holmstrom B, Ullman J & Wallberg P 1980 Carcinoids of the colon and rectum in patients aged 30 and younger. *Acta Chir Scand Suppl* **500** 33-35.
- Barshack I, Goldberg I, Chowers Y, Horowitz A & Kopolovic J 2002 Different beta-catenin immunoexpression in carcinoid tumors of the appendix in comparison to other gastrointestinal carcinoid tumors. *Pathol Res Pract* **198** 531-536.
- Basic-Jukic N, Furic-Cunko V, Coric M, Bubic-Filipi LJ, Kastelan Z, Pasini J & Kes P 2010 Appendiceal carcinoid and mucinous cystadenoma in renal transplant recipients: case reports. *Transplant Proc* **42** 1704-1707.
- Beddy D & Larson D 2011 Cushing's syndrome cured by resection of an appendiceal carcinoid tumor. *Int J Colorectal Dis* **26** 949-950.
- Benedix F, Reimer A, Gastinger I, Mroczkowski P, Lippert H, Kube R & Study Group Colon/Rectum Carcinoma Primary T 2010 Primary appendiceal carcinoma--epidemiology, surgery and survival: results of a German multi-center study. *Eur J Surg Oncol* **36** 763-771.
- Bhagat KP & Patoria NK 1981 Functioning carcinoid of the appendix. *J Indian Med Assoc* **76** 213-214.
- Bucher P, Mathe Z, Demirag A & Morel P 2004 Appendix tumors in the era of laparoscopic appendectomy. *Surg Endosc* **18** 1063-1066.
- Connor SJ, Hanna GB & Frizelle FA 1998 Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* **41** 75-80.
- Crea N, Pata G, Di Betta E, Titi A & Mittempergher F 2011 High incidence of appendix carcinoid tumors among candidates for bariatric surgery: diagnostic and therapeutic implications. *Obes Surg* **21** 151-156.
- Crocetti E 1997 Gastrointestinal carcinoid tumours. A population-based study. *Ital J Gastroenterol Hepatol* **29** 135-137.
- Dall'Igna P, Ferrari A, Luzzatto C, Bisogno G, Casanova M, Alaggio R, Terenziani M & Cecchetto G 2005 Carcinoid tumor of the appendix in childhood: the experience of two Italian institutions. *J Pediatr Gastroenterol Nutr* **40** 216-219.
- Desouki MM, Liyod J, Xu H, Cao D, Barner R & Zhao C 2013 CDX2 may be a useful marker to distinguish primary ovarian carcinoid from gastrointestinal metastatic carcinoids to the ovary. *Hum Pathol* **44** 2536-2541.
- Dobnig H, Stepan V, Leb G, Wolf G, Buchfelder M & Krejs GJ 1996 Recovery from severe osteoporosis following cure from ectopic ACTH syndrome caused by an appendix carcinoid. *J Intern Med* **239** 365-369.
- Fornaro R, Frascio M, Sticchi C, De Salvo L, Stabilini C, Mandolfino F, Ricci B & Gianetta E 2007 Appendectomy or right hemicolectomy in the treatment of appendiceal carcinoid tumors? *Tumori* **93** 587-590.
- Freeman HJ 2003 Appendiceal carcinoids in Crohn's disease. *Can J Gastroenterol* **17** 43-46.
- Fucs M, Romero FR, Germanos de Castro M, de Carvalho Fernandes R, Camara-Lopes LH & Cardenuto Perez MD 2005 Testicular metastasis 10 years after resection of appendiceal carcinoid. *Urology* **65** 591.
- Goldfine SL & Balthazar EJ 1979 Malignant carcinoid of the appendix: case report with radiographic and angiographic demonstration. *Am J Gastroenterol* **71** 627-632.
- Grossman AB, Kelly P, Rockall A, Bhattacharya S, McNicol A & Barwick T 2006 Cushing's syndrome caused by an occult source: difficulties in diagnosis and management. *Nat Clin Pract Endocrinol Metab* **2** 642-647.
- Groth SS, Virnig BA, Al-Refaie WB, Jarosek SL, Jensen EH & Tuttle TM 2011 Appendiceal carcinoid tumors: Predictors of lymph node metastasis and the impact of right hemicolectomy on survival. *J Surg Oncol* **103** 39-45.
- Grozinsky-Glasberg S, Alexandraki KI, Barak D, Doviner V, Reissman P, Kaltsas GA & Gross DJ 2013 Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. *Neuroendocrinology* **98** 31-37.

Hendi JM, Horton KM & Fishman EK 2005 Somatostatinoma of the ampulla and appendical carcinoid in a patient with von Recklinghausen disease. *J Comput Assist Tomogr* **29** 418-419.

Hsu C, Rashid A, Xing Y, Chiang YJ, Chagpar RB, Fournier KF, Chang GJ, You YN, Feig BW & Cormier JN 2013 Varying malignant potential of appendiceal neuroendocrine tumors: importance of histologic subtype. *J Surg Oncol* **107** 136-143.

Janin Y, Schwartz D, Becker JM & Valderama E 1981 Crohn's disease and carcinoid tumor of the appendix in a child. *Z Kinderchir* **32** 376-379.

Johnston WH & Waisman J 1971 Carcinoid tumor of the vermiform appendix with cushing's syndrome. Ultrastructural study of a case. *Cancer* **27** 681-686.

Katsetos CD, Jami MM, Krishna L, Jackson R, Patchefsky AS & Cooper HS 1994 Novel immunohistochemical localization of 28,000 molecular-weight (Mr) calcium binding protein (calbindin-D28k) in enterochromaffin cells of the human appendix and neuroendocrine tumors (carcinoids and small-cell carcinomas) of the midgut and foregut. *Arch Pathol Lab Med* **118** 633-639.

Kosakowski C, Thompson JE, Jr. & Feinberg MJ 1986 Coexistence of primary Crohn's disease and carcinoid tumor isolated to the appendix. A case report. *Acta Chir Scand* **152** 233-236.

Kulkarni KP, Desai S, Chiu B & Sergi C 2011 Familial adenomatous polyposis with concurrent metastatic appendiceal carcinoid and ovarian cystadenoma. *Pediatr Blood Cancer* **57** 702-703.

Landry CS, Woodall C, Scoggins CR, McMasters KM & Martin RC, 2nd 2008 Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. *Arch Surg* **143** 664-670; discussion 670.

Le Marc'hadour F, Bost F, Peoc'h M, Roux JJ, Pasquier D & Pasquier B 1994 Carcinoid tumour complicating inflammatory bowel disease. A study of two cases with review of the literature. *Pathol Res Pract* **190** 1185-1192; discussion 1193-1200.

Lin X, Saad RS, Luckasevic TM, Silverman JF & Liu Y 2007 Diagnostic value of CDX-2 and TTF-1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. *Appl Immunohistochem Mol Morphol* **15** 407-414.

Liu E, Telem DA, Hwang J, Warner RR, Dikman A & Divino CM 2010 The clinical utility of Ki-67 in assessing tumor biology and aggressiveness in patients with appendiceal carcinoids. *J Surg Oncol* **102** 338-341.

Markgraf WH & Dunn TM 1964 Appendiceal Carcinoid with Carcinoid Syndrome. *Am J Surg* **107** 730-732.

McCusker ME, Cote TR, Clegg LX & Sobin LH 2002 Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer* **94** 3307-3312.

McGory ML, Maggard MA, Kang H, O'Connell JB & Ko CY 2005 Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum* **48** 2264-2271.

Miller T, Bernstein J & Van Herle A 1971 Cushing's syndrome cured resection of appendiceal carcinoid. *Arch Surg* **103** 770-773.

Miquel C, Sabourin JC, Elias D, Grandjouan S, Viguier J, Ducreux M, Duvillard P & Praz F 2004 An appendix carcinoid tumor in a patient with hereditary nonpolyposis colorectal cancer. *Hum Pathol* **35** 1564-1567.

Modlin IM, Kidd M, Latich I, Zikusoka MN, Eick GN, Mane SM & Camp RL 2006 Genetic differentiation of appendiceal tumor malignancy: a guide for the perplexed. *Ann Surg* **244** 52-60.

Modlin IM, Lye KD & Kidd M 2003 A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* **97** 934-959.

Modlin IM & Sandor A 1997 An analysis of 8305 cases of carcinoid tumors. *Cancer* **79** 813-829.

Mullen JT & Savarese DM 2011 Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol* **104** 41-44.

Murray SE, Lloyd RV, Sippel RS, Chen H & Oltmann SC 2014 Postoperative surveillance of small appendiceal carcinoid tumors. *Am J Surg* **207** 342-345; discussion 345.

Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, Arnold R, Denecke T, Plockinger U, Salazar R, et al. 2012 ENETS Consensus Guidelines for the management of patients with neuroendocrine

neoplasms from the jejunum-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology* **95** 135-156.

Patel S, Heetun M, Gurjar SV & Szakacs S 2009 A rare case of intra-cardiac metastasis from an appendiceal carcinoid tumour without liver metastases. *Int J Colorectal Dis* **24** 993-994.

Perakakis N, Laubner K, Keck T, Steffl D, Lausch M, Meyer PT, Burger D, Csanadi A & Seufert J 2011 Ectopic ACTH-syndrome due to a neuroendocrine tumour of the appendix. *Exp Clin Endocrinol Diabetes* **119** 525-529.

Prommegger R, Ensinger C, Adlassnig C, Vaingankar S, Mahata SK, Marksteiner J & Margreiter R 2004 Catestatin--a novel neuropeptide in carcinoid tumors of the appendix. *Anticancer Res* **24** 311-316.

Prommegger R, Obrist P, Ensinger C, Schwelberger HG, Wolf C, Fischer-Colbrie R, Mikuz G & Bodner E 1998 Secretoneurin in carcinoids of the appendix-immunohistochemical comparison with chromogranins A,B and secretogranin II. *Anticancer Res* **18** 3999-4002.

Prunty FT 1965 Successful Treatment of Cushing's Syndrome Secondary to an Argentaffinoma by Bilateral Adrenalectomy. *Proc R Soc Med* **58** 573-575.

Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijnen ML & Taal BG 2001 Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* **12** 1295-1300.

Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, et al. 2007 TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* **451** 757-762.

Robbins ML & Sunshine TJ 2000 Metastatic carcinoid diagnosed at laparoscopic excision of pelvic endometriosis. *J Am Assoc Gynecol Laparosc* **7** 251-253.

Sandor A & Modlin IM 1998 A retrospective analysis of 1570 appendiceal carcinoids. *Am J Gastroenterol* **93** 422-428.

Saqi A, Alexis D, Remotti F & Bhagat G 2005 Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from pulmonary carcinoids. *Am J Clin Pathol* **123** 394-404.

Shaib W, Krishna K, Kim S, Goodman M, Rock J, Chen Z, Brutcher E, Staley CI, Maithel SK, Abdel-Missih S, et al. 2015 Appendiceal Neuroendocrine, Goblet and Signet-Ring Cell Tumors: A Spectrum of Diseases with Different Patterns of Presentation and Outcome. *Cancer Res Treat*.

Shaw JH & Canal A 1989 Carcinoid tumours in Auckland, New Zealand. *Aust N Z J Surg* **59** 229-233.

Sjoblom SM 1988 Clinical presentation and prognosis of gastrointestinal carcinoid tumours. *Scand J Gastroenterol* **23** 779-787.

Sjoblom SM, Hockerstedt K & Jarvinen H 1987 Hepatic dearterialization in the treatment of carcinoid syndrome. *Acta Chir Scand* **153** 523-529.

Sobin LH GM, Wittekind C 2009 *TNM Classification of Malignant Tumours*. Chichester: Wiley & Blackwell.

Srivastava A & Hornick JL 2009 Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors. *Am J Surg Pathol* **33** 626-632.

Turaga KK, Pappas SG & Gamblin T 2012 Importance of histologic subtype in the staging of appendiceal tumors. *Ann Surg Oncol* **19** 1379-1385.

Urbanczyk K & Tomaszewska R 1994 Cytological pattern of multihormonal carcinoid of the appendix with metastasis to the liver corresponding a clinical insulinoma. *Pol J Pathol* **45** 225-229.

Vergier B, Trojani M, de Mascarel I, Coindre JM & Le Treut A 1991 Metastases to the breast: differential diagnosis from primary breast carcinoma. *J Surg Oncol* **48** 112-116.

West NE, Wise PE, Herline AJ, Muldoon RL, Chopp WV & Schwartz DA 2007 Carcinoid tumors are 15 times more common in patients with Crohn's disease. *Inflamm Bowel Dis* **13** 1129-1134.