

Friday, November 3, 2006

TOPIC: WELL-DIFFERENTIATED MIDGUT ENDOCRINE TUMORS INCLUDING THE APPENDIX

- 9:00 - 12:35 p.m. **Appendiceal tumors**
Chair: U. Plöckinger, Berlin, Germany
- 9:00 - 9:20 a.m. **Case presentation: appendiceal tumors**
U. Plöckinger, Berlin, Germany
- 9:25 - 10:35 a.m. **Working Group Sessions**
Pathology and Genetics
Group leader: A. Couvelard, Clichy, France
Medicine and Clinical Pathology
Group leader: R. Salazar, Barcelona, Spain
Surgery
Group leader: M. Falconi, Verona, Italy
Imaging
Group leader: A. Sundin, Uppsala, Sweden
- 10:35 - 11:05 a.m. **COFFEE BREAK**
- 11:05 - 12:35 p.m. **General assembly**
Presentation of statements by the session chairs & general discussion
U. Plöckinger, Berlin, Germany

 Pathology and Genetics  Medicine and Clinical Pathology  Surgery  Imaging

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Endocrine tumors of the Appendix

Epidemiology

The incidence rates of appendiceal endocrine tumours account for 0.075 new cases per 100,000 population per year [3–7]. 19% of all gastrointestinal endocrine tumours have been reported to be localised in the appendix. They more often present in the 4th and 5th decade of life and are more common in females.

Clinicopathological staging [15]

- 1 Well-differentiated endocrine tumour (carcinoid), benign behaviour, non-functioning, confined to appendiceal wall, ≤ 2 cm non-angioinvasive
 - 1.1.1 Serotonin-producing tumour
 - 1.1.2 Enteroglucagon-producing tumour
- 1.2 Well-differentiated endocrine tumour (carcinoid), uncertain behaviour, non-functioning, confined to subserosa, > 2 cm in size, or angioinvasive
 - 1.2.1 Serotonin-producing tumour
 - 1.2.2 Enteroglucagon-producing tumour
- 2 Well-differentiated endocrine carcinoma (malignant carcinoid), low-grade malignant, invading the mesoappendix or beyond, and/or with metastases
 - 2.1 Serotonin-producing endocrine tumour with or without carcinoid syndrome
 - 2.2 Enteroglucagon-producing tumour
- 3 Mixed exocrine-endocrine carcinoma
 - 3.1 Low-grade, malignant, goblet cell carcinoid

 Q: Do you agree with the above statements concerning epidemiology and clinical settings?

Incidence 2-3/1000000/year

Clinicopathological staging: < 1cm/1-2cm/ >2cm due to higher rate of metastasis

Low-grade malignancy of goblet cell carcinoids to be discussed with pathol:

Pathology: Separate GCC from pure/classical AC -> extra chapter

Serotonin/enteroglucagon-differentiation of no clinical value

Serosal involvement of no clinical value

Insert in pathological classification a remark underlining the synonymous nature of the terms, adenocarcinoid, goblet cell tumors, mucinous adenocarcinoid.

Q2: In your experience and according to the literature, is there a gender, age and race preferential distribution?

Gender preference for women (male/female 1:2) in young age

No race preference

Q3: In your experience and according to the literature, what is the incidence of functioning tumors?

<1%

Q4: Is the subtyping of endocrine cell (EC vs L) tumors useful for patient management?

Not useful

Q5: In your experience and according to the literature, what is the incidence of goblet-cell carcinoid?

0,5/1000000/year (SEER), <5% of all appendiceal Tms (ref. to be added)

Comment: SEER-data base reports higher incidence of GCC in relation to AC but considers only “malignant” appendiceal tumors

Q6: In your experience and according to the literature, is the goblet-cell carcinoid associated with hormonal hyperfunction?

No

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Prognosis/Survival

Most patients with appendiceal carcinoids have a favourable prognosis. Carcinoids of <2 cm in size, confined to the appendiceal wall and not angio-invasive are completely cured by appendectomy [12–14]. Invasion of the mesoappendix, a size of >2 cm and angio-invasion carry an uncertain malignant potential as do tumours at the base of the appendix with involvement of the surgical margin or of the caecum [15]. Five-year survival of patients with an appendiceal carcinoid is 95% for localized disease, 85% for those with regional disease and 34% for those with distant metastases [12–14]. Goblet cell carcinoids are more aggressive tumours, but they are not as malignant as adenocarcinomas of the appendix. They are characterised by a predominant submucosal growth and are composed of signet ring-like cells and an endocrine component.

Q7: Is your experience consistent with the above?

Pts. with size of 1-2cm have a risk of <1% (case reports), discrepancy: decreased 5-year-survival rate (possibly older pts.)

Infiltration of mesoappendiceal invasion may carry risk of metastasis but there is conflicting data on these data.

Discuss with pathol/surgery: role / determination of angioinvasion in small AC -> no data existing: Size and mesoappendiceal invasion matters (Moertel et al), no data exist on the relevance of angioinvasion

Q8: What is your experience as to the “stage” of the disease and proliferative (Ki67) index?

No data

Q9: In your experience and according to the literature, is the goblet-cell carcinoid associated with a more aggressive course?

Yes. Advanced GCC are likely as aggressive as adenocarcinoma.

Clinical presentation

Appendiceal carcinoids are mostly detected incidentally during appendectomy. By obstructing the lumen they can produce appendicitis.

Q10: Is your experience consistent with the above?

Yes

Q11: What is the most frequent presentation symptom?

Most frequently found on appendectomy without acute appendicitis

Q12: What proportion of patients, if any, present the “typical carcinoid syndrome”?

<1%

Diagnostic procedures

1. Imaging NA

Q13: Which procedure(s) is/are required for a **minimal** diagnostic approach?

Additional investigation **after incidental diagnosis**: depends on size

< 1cm nothing

1-2cm: not sufficient data to make a clear-cut decision, most participants thought nothing needs to be done, but discussion with the patient is needed CT-scan of abdomen + pelvis or MRI (**controversial**), with other pathological features of infiltration (as a comment)

>2cm CT-scan of abdomen + pelvis or MRI/ Octreoscan

Q14: Which procedure should be initially performed?

CT-scan of abdomen + pelvis

Q15: Is EUS required? When is it recommended? What about CT/MRI and SRS?

Carcinoids:

Operated patients, tumor <1 cm, regardless of location in the appendix: No further imaging.

1-2 cm tumors: If low-risk: see above. If high-risk: see below. Suggested high-risk: Ki >25% (?), or location base, or vascular involvement, or mesoappendiceal involvement.

Operated patients, tumors ≥2 cm, all locations in the appendix: If available: CT-SPECT (CT diagnostic, contrast enhanced, multiphase, SPECT OctreoScan) or CT-PET (PET: Ga-68 somatostatin analogue), in case of negative SPECT or PET CT limited to abdomen.

If no hybrid camera available: CT Abdomen (including pelvis) as above plus octreoscan.

All patients: Colonoscopy or if available colon CT (with neutral enema) for synchronous tumors?

Goblet cell carcinoid tumors: As “normal” carcinoid tumors >2 cm, but include a chest CT.

Q16: Please suggest your imaging/procedure flow-chart for appendiceal tumors.

See Q15

2. Biochemical diagnosis

Chromogranin A, 5-HIAA in 24-hour urine (see lower jejunum-ileum tumors).

Comments

Chromogranin A, a regulator of secretory granule biogenesis, serves as a sensitive but non-specific tumour marker in non-functioning and in functioning endocrine midgut tumours. Excessively elevated levels (> 1,000 pg/ml) indicate an unfavourable prognosis [24]. 5-HIAA is an excretory product of serotonin. It serves as a sensitive tumour marker for diagnosis and follow-up in patients with carcinoid syndrome and should be estimated in two 24-hour urine collections. In patients with carcinoid syndrome treated with long-acting somatostatin analogues, a decrease in chromogranin A and urinary 5-HIAA mirror relief of symptoms as flushing and diarrhoea. Available assays for the estimation of chromogranin A may differ due to different antibody specificities [25]. This should be kept in mind if levels originating from different laboratories are compared. There is a slight increase in circulating chromogranin A in patients taking proton pump inhibitors and a marked increase in patients with type-A gastritis [26]. Falsely elevated 5-HIAA urine levels can be caused by foods such as avocado, pineapple, banana, kiwi, melon, plum, walnuts and by drugs such as acetaminophenol, coumarin, reserpine, nicotine, caffeine, melphalan, paracetamol, phenacetin, phenobarbital. Falsely low levels can be caused by ethanol, aspirin, MAO inhibitors, ranitidine and others. Serotonin should not be used as a marker for endocrine tumours due to difficulties in reliable measurement [24].

Q17: What are the recommended biochemical tests in patients with appendiceal tumors?

Differentiate between AC (appendix carcinoid)/GCC (goblet cell carcinoid)

In metastatic disease: AC: CgA, GCC: CEA, CA-19-9, CA-125

Q18: Which circulating markers should be tested for?

AC: CgA

GCC: no CgA

Q19: When should biochemical tests be performed?

In metastatic setting

Q20: Is germline DNA testing recommended?

No

If so, which genes?

No

Which method?

No

Q21: Is somatic (tumor) DNA testing recommended?

No

If so, which genes?

No

Which method?

No

Q22: Is genetic counseling recommended?

No

Q23: Would you recommend collecting a consensus statement for genetic testing?

N.A.

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3. Histopathology

Hematoxylin-eosin, Chromogranin, Synaptophysin, Ki-67 (see lower jejunum-ileum tumors).

Comments

Most endocrine tumours of the appendix are serotonin-positive, a minority are glucagon-like peptide and PP/PYY-producing tumours. Goblet cell tumours are characterised by a predominant submucosal growth. The mucosa is characteristically spared. Tumours are composed of small, rounded nests of signet ring-like cells resembling intestinal goblet cells expressing CEA. The endocrine component reacts with antibodies against serotonin, chromogranin A, enteroglucagon, somatostatin, and PP. High Ki-67 and mitotic counts serve as a parameter for poor prognosis. In

the absence of defined limits, Ki-67 >10% and mitotic counts ≥10/HPF may be used as indicative of aggressive endocrine carcinoma.

Q24: Is histology required?

Yes

Q25: What are the minimal ancillary tests required?

CgA, synaptophysin

add PAS-AB if “Goblet cell carcinoid” (mixed exocrine and endocrine carcinoma) suspected.

Q26: Should the mitotic index be assessed?

Yes

If so, which method?

See See VA06 TNM1 paper.

Q27: Is the Ki-67 index necessary?

Yes

If so, which method?

See See VA06 TNM1 paper.

Q28: Is IHC required for tumor cell subtyping and, if so, when?

No, only for differential diagnosis.

Q29: Would you recommend IHC staining for p53?

No

Q30: Would you recommend IHC staining for SSR2A receptor?

On demand

Q31-Q31-Q31-Q31: Do we need a tumor grading system?

All groups: Yes

Surgery group: Yes

We need a general agreement for Ki67 limits for each tumor entity (<2%; 2-x%; >x%) (x: 10%; 15%; 20%; 25%)

Q32-Q31-Q32-Q32: Do we need a TNM classification? Please see the proposal for appendiceal tumors and make your comments.

All groups: Yes

Imaging group: Yes, but check tumor sizes (Q 16 according to data provided by Dr. Plockinger)

Surgery group: Yes

T1 differentiated into T1a (<1cm); T1b (1-2cm).

Does the distance to the base of the appendix should be included?

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Surgical therapy

Appendiceal carcinoids can be cured by appendectomy if the tumour is located at the tip of the appendix *and* the tumour diameter is <1 cm. Right hemicolectomy is indicated if any of the following is present: tumour diameter >2 cm; angio- or neural invasion; location of the tumour at the base of the appendix; histopathological classification of the tumour as goblet cell carcinoid or mixed endocrine-exocrine (compound) tumour; a tumour between 1 and 2 cm in size *with* meso-appendiceal involvement and/or positive margins [6–8].

Q33: Which type of surgical resection would you recommend?

We support this statement (we question, whether localisation is an independent factor)

Reintervention should be performed if there are positive or unclear margins. Timing of hemicolectomy is recommended within three months and can safely be performed by a laparoscopic approach.

Q34: For advanced appendiceal tumors, does the same surgical strategy apply as for colonic-rectal tumors?

Yes, but even more aggressive for local and regional problems, particularly in goblet cell tumors.

Single institution experience exists that some patients (GCC) with peritoneal carcinomatosis may benefit from vast resection procedures (Sugarbaker) and intraperitoneal chemotherapy.

Q35: If present, when is the treatment of liver metastases recommended?

We follow the standard procedures (guidelines for intestinal NEC) but have no experience with it, since it seems to be extremely rare. Should goblet cell tumor metastases be treated differently, such as colorectal adenocarcinomas (lack of data) ?

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Medical therapy

1. Biotherapy (see lower jejunum-ileum tumors section).

1.1 Somatostatin analogues

1.2 Interferon

2. Systemic Chemotherapy

3. Somatostatin Receptor Radionuclide Therapy

Q36: Is any medical therapy recommended in patients with appendiceal tumors?

Not in surgically resected

Same approach as in midgut tumors as in metastatic disease in pure AC.

In GCC treat as adenocarcinomas.

Q37: Which cases require medical therapy?

See Q36

Q38: Is SOM analog therapy recommended? If so, when and how?

AC: see midgut section

Q39: Is interferon therapy recommended? If so, when and how?

AC: see midgut section

Q40: When is chemotherapy recommended?

Not in pure AC, but in GCC

Q41: Which cytotoxic agents and protocols are recommended?

GCC: no data exist, option: treat as CRC , adjuvant CTx can be an option

Q42: Can chemotherapy be proposed in an adjuvant setting?

No clinical data

In GCC in analogy to CRC, particularly in perforated GCC (high risk situation)

Q43-Q43: Can PRRT be recommended? If so, when and which type?

Medical group: no data; if metastatic and Octreoscan positive PRRT is an option (still investigational)

Imaging group: Yes, if tumors are somatostatin receptor positive (OctreoScan), and inoperable or metastatic

Q44-Q44: What is the scheduled follow-up for patients after curative surgical treatment?

If curative treatment of appendiceal carcinoids of less than 1cm tumors or NOM0 after hemicolectomy only one CgA and 5-HIAA in between 6-12 months postoperatively. In all other patients with carcinoid tumors clinical, biochemical and imaging control after six months and then yearly.

Gastrointestinal follow-up is recommended because of the high coincidence (7-48%) of gastrointestinal neoplasms in these patients.

For GCC follow-up should fulfill the guidelines for colorectal adenocarcinomas.

Q45-Q45: What are the minimal examinations required and for how long?

See above (Q44)! Except for patients with curative treatment of appendiceal carcinoids of less than 1cm tumors or N0M0 after hemicolectomy the follow-up should be lifelong.

**Proposal for a
TNM classification and disease staging for
NET of the appendix**

TNM

T-primary tumor

TX primary tumor cannot be assessed

T0 no evidence of primary tumor

T1 tumor <1cm invading submucosa and muscularis propria

T2 tumor ≤2cm invading submucosa, muscularis propria and/or minimally (up to 3mm) invading subserosa/mesoappendix

T3 tumor >2cm and/or extensive (more than 3mm) invasion of subserosa/mesoappendix

T4 tumor invades peritoneum/other organs

N-regional lymph nodes

NX regional lymph nodes cannot be assessed

N0 no regional lymph node metastasis

N1 regional lymph node metastasis

M-distant metastasis

MX distant metastasis cannot be assessed

M0 no distant metastases

M1* distant metastasis

*M1 specific sites defined according to Sobin LH, Wittekind C (ed) (2002) TNM Classification of malignant tumours. Wiley-Liss, New York-Toronto; mod. from Klöppel G, unpublished.

STAGE

Disease Stages				
Stage I	T1	N0	M0	
Stage IIA	T2	N0	M0	
Stage IIB	T3	N0	M0	
Stage IIIA	T4	N0	M0	
Stage IIIB	any T	N1	M0	
Stage IV	any T	any N	M1	

Mod from: Sobin LH, Wittekind C (ed) (2002) TNM Classification of malignant tumours. Wiley-Liss, New York-Toronto.