

Saturday, November 4, 2006

**TOPIC: POORLY DIFFERENTIATED ENDOCRINE CARCINOMAS OF MIDGUT AND HINDGUT ORIGIN**

**9:00 – 11:00 a.m. Poorly differentiated endocrine carcinomas**

*Chair: H. Ahlman, Gothenborg, Sweden*

9:00 - 9:20 a.m. **Case presentation**

*H. Ahlman, Gothenborg, Sweden*

9:25 - 10:05 a.m. **Working Group Sessions**

**Pathology and Genetics**

*Group leader: A.M. McNicol, Glasgow, United Kingdom*

**Medicine and Clinical Pathology**

*Group leader: P. Ruzsiewicz, Clichy, France*

**Surgery**

*Group leader: B. Niederle, Vienna, Austria*

**Imaging**

*Group leader: J. Rieke, Berlin, Germany*

10:05 – 11:00 a.m. **General assembly**

**Presentation of statements by the session chairs & general discussion**

*H. Ahlman, Gothenborg, Sweden*

 **Pathology and Genetics** **Medicine and Clinical Pathology** **Surgery** **Imaging**

ENETS Guidelines Neuroendocrinology 2004;80:394–424

## Poorly Differentiated Endocrine Carcinomas of Midgut and Hindgut Origin

*Epidemiology and Clinicopathological staging*

**Ileum**

Na: define (not available)

**Colon-rectum**

Na: define (not available)

**Q1:** What is the current knowledge regarding the epidemiology and clinical settings of hindgut and midgut PDECs?

SEER-data: midgut all grades 1,14/1000000 (G3 0,04/G4 0,01 per 1Mio, 4% of all)  
hindgut all grades 1,04/1000000, assumed PDEC: 0,08.(G3 0,06/0,02)

Clinical presentation: same as metastatic CRC

**Q2:** In your experience and according to the literature, what is the average clinicopathological staging of PDECs?

Discuss with pathol

Small cell, intermediate cell, large cell

“well-differentiated” Tms with high Ki67-index

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*Prognosis/Survival*

**Ileum**

Na: define (not available)

**Colon-rectum**

Na (define: not available)

**Q3:** Is there data available concerning prognosis/survival for midgut/hindgut PDECs?

Brenner B et al, JCO, 2004, 22:2730-2739, only few data available, mean survival app. 10 months, 1-year-survival-rate: 46%

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*Diagnostic procedures*

## 1. Tumor imaging

**Ileum**

Na: define (not available).

**Colon-rectum**

*Endoscopy* ...the majority of lesions in the rectum will be diagnosed endoscopically. ...central mucosal depression or ulceration suggests high metastatic potential [2] . *Barium Enema* ...Barium enema may demonstrate colonic tumours where endoscopy is not first performed.

*Endoanal/ Rectal Ultrasound (EUS)* [14–18] is very useful...and...can accurately assess tumour size, depth of invasion and the presence or absence of pararectal lymph node metastases. In conjunction with other investigative techniques and endoscopy this provides important information with respect to choice of therapy. *Ultrasound of Abdomen*. Trans-abdominal ultrasound

has low sensitivity for primary and local disease...*Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)*...These are much more sensitive imaging modalities. Spiral CT is probably the most useful for staging the thorax, abdomen and pelvis, although MRI is probably superior for determining liver metastases [19]. Any lesions with evidence of malignant potential or extension require a pelvic CT/MRI to assess local advancement and involvement of other pelvic structures and resectability. *111-Indium Octreotide Scanning*... the high-grade hindgut lesions are often negative for 111-indium octreotide uptake, and other modalities have to be relied on to detect extra-pelvic disease. *Positron Emission Tomography (PET) Imaging* PET is currently considered experimental but may be of use with labels based on dopa for well-differentiated tumours and FDG for poorly differentiated tumours [21] .

**Q4:** Which procedure(s) is/are required for a **minimal** diagnostic approach in each individual tumor type (midgut, hindgut)?

Depends on location and stage: US with biopsy, then colonoscopy, CTscan (thorax + abdomen)

**Q5:** Which procedure should be initially performed?

See Q4

**Q6:** Is EUS required? When is it recommended?

See Q7.

**Q7:** What is the role of CT, MRI, and SRS? Are there limitations to be considered for PDECs of the midgut and hindgut?

All cases :CT Chest, Abdomen, Pelvis plus SRI. If possible SPECT-CT or PET-CT.

In case of planned curative surgery: MRI liver plus FDG-PET and if rectum is operation site MRI rectum is required.

**Q8:** Is there a role for PET in PDECs? If so, which type?

See Q7.

**Q9:** Please suggest your imaging/procedure flow-chart for PDECs.

See Q7.

2. Biochemical diagnosis

**Ileum**

Na: define (not available).

**Colon-rectum**

Na: define (not available).

**Q10:** What is the minimal biochemical work-up for PDECs?

Limited value: CgA (rarely elevated), NSE (of limited value), stop measuring if initially not elevated

If hormonal symptoms determine the corresponding marker.

**Q11:** When should biochemical tests be performed?

See Q10.

**Q12:** Is germline DNA testing recommended?

No.

Which genes?

No.

Which method?

No.

**Q13:** Is somatic (tumor) DNA testing recommended?

No.

Which genes?

No.

Which method?

No.

**Q14:** When is genetic counseling recommended?

No.

**Q15:** Would you recommend collecting a consensus statement for genetic testing?

N.A.

3. Histopathology

**Ileum**

Na: define (not available)

**Colon-rectum**

Hematoxylin-eosin, Chromogranin, Synaptophysin, Ki-67 (see well-differentiated session).

General: poorly differentiated small cell endocrine carcinomas (WHO group 3) display a solid structure with abundant central necrosis, severe atypia with high mitotic counts and Ki67 index, deep wall invasion often with evident invasion of blood vessels, lymphatics and perineum [3] .

Mucin production may also be observed.

**Q16:** Is histology required?

Yes.

**Q17:** Is cytology recommended and, if so, in which clinical situations?

Yes, if histology not feasible.

**Q18:** What are the minimal ancillary tests to be done to support the histological diagnosis?

PAS-AB, cytokeratin, CgA, synaptophysin and other 2nd line NE markers (NSE, CD56, PGP9.5); positivity of two NE markers for different cell compartments required (consensus).

**Q19:** Should the mitotic index be assessed?

Yes.

If so, which method?

See VA TNM1 paper.

**Q20:** Is the Ki-67 index necessary?

Yes.

If so, which method?

See VA TNM1 paper.

**Q21:** Is IHC required for tumor cell subtyping?

No.

**Q22:** Would you recommend IHC staining for p53?

No.

**Q23:** Would you recommend IHC for SSR2A receptor?

On demand.

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*Surgical therapy (10):*

**Ileum**

Na: define (not available)

**Colon-rectum**

... No particular evidence is available, but it should be advised that any invasive disease (colon) be resected surgically as is practiced with adenocarcinoma...Local resection (rectum) is unlikely to benefit patient survival with metastatic disease, but will provide local symptomatic relief [30]. Loco-regional resection may be argued to control local symptoms and pelvic disease without improving survival [25, 31]. Aggressive surgery has not been shown to improve the survival outcome in this group of patients. Studies are limited and the numbers are invariably small.

**Q24:** When is curative surgery recommended in PDECs?

Preoperative classification is seldomly given but if it is:

Small cell variant: LD – with primary surgery; LD - primary plus Lnm neo-adjuvant chemo followed by surgery

Large cell variant: treatment like adenocarcinoma – in very poorly differentiated variant probably and in ED only chemo – no data available on the type of drugs

**Q25:** When is curative surgery NOT recommended?

In ED and all very poorly differentiated variants – ad chemo; see also Q 24

**Q26:** Which type of surgical resection would you recommend?

Follow oncological principles

**Q27:** Is surgery for liver metastases recommended along with elective surgery?

No because of the very poor prognosis

**Q28:** In advanced stages, are debulking surgical strategies recommended and to what extent?

There is no indication for debulking operations

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*Cytoreductive therapy*

**Ileum**

Na: define (not available).

**Colon-rectum**

Na: define (not available).

**Q29:** Is loco-regional ablative therapy recommended for liver metastases secondary to PDECs? If so, which type?

No – poor prognosis

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*Medical therapy*

Systemic chemotherapy

**Ileum**

Na: define (not available).

**Colon-rectum**

The efficacy of systemic chemotherapy is best in fast-growing or poorly differentiated tumours. In these tumours cisplatin plus etoposide have proven to be effective [23].

**Q30:** When should chemotherapy be employed for patients with PDEC?

ASAP in all pts.

**Q31:** Which cytotoxic agents and protocols are recommended?

Cisplatin/etoposide (Moertel-scheme)

FOLFOX-IV or XELOX may be an option in the future (Pape UF et al. JCO, ProcASCO, 2006; 24:14074; Bajetta E et al. Cancer Chemother Pharmacol 2006, e-pub-ahead of print)

Paclitaxel-triple scheme needs validation in phase III-trials (no recommendation) in view of toxicity

**Q32:** Can chemotherapy be proposed in an adjuvant setting?

No data available

**Q33:** Is there a role for somatostatin analog or interferon therapy?

No

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**All locations**

*Follow-up during/ after treatment*

Na: define (not available).

**Q34:** What is the scheduled follow-up for patients with PDEC? Which minimal examinations are required and for how long?

Every 2 months (every 1 to 2 cycles)

Clinical examination, CT-scan

Bone scan according to symptoms

Brain-MRI according to symptoms