

# Poorly-Differentiated Endocrine Carcinomas of Midgut and Hindgut Origin

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## Introduction

### *Epidemiology and Classification*

Retrospective clinical and epidemiological studies show that the rectum is the third most common site for carcinoid tumors, overrepresented in black and Asian populations [1, 2]. Risk factors for malignancy are tumor size exceeding 2 cm and invasion beyond the muscularis propria; the 5-year survival relates to tumor stage [3, 4]. However, detailed information regarding poorly-differentiated endocrine carcinomas (PDEC) in the colon and rectum is greatly lacking. Most series report an increasing incidence of rectal carcinoids, which include both well-differentiated (WDEC) and PDEC tumors, over the

last decades; from SEER cancer database colonic carcinoids are uncommon with a rather constant incidence [2]. These trends may relate to an increased awareness about rectal carcinoids and an increased number of diagnostic examinations and endoscopic polypectomies. In western Sweden, the number of patients with clinically diagnosed rectal carcinoids were studied over three decades (1959–1988) showing a rising trend with 11, 21 and 37 cases per decade – only 1 patient had metastatic disease [5]. In contrast, during a recent 5-year period (2000–2005) 7 patients with PDEC tumors of the colon and rectum were diagnosed in the same geographical region. These figures indicate that PDEC may have been misdiagnosed as adenocarcinoma prior to the publication of the WHO 2000 criteria [6]. Two histological types of PDEC of the gastrointestinal tract can be identified: small or large cell carcinomas [6]. A nationwide SEER study on rare tumors of colon and rectum from the USA showed

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an incidence rate of 2 'neuroendocrine carcinomas' per million; this term corresponds to PDEC, but does not distinguish between small or large cell variants [7]. Other limitations of SEER studies are absence of data on comorbidity, heredity and chemotherapy, which may closely relate to survival. Data on the true incidence of PDEC in relation to carcinomas with neuroendocrine (NE) differentiation are still lacking. PDEC of midgut origin are very rare [8].

#### *Minimal Consensus Statement on Epidemiology*

The incidence rate of colorectal PDEC (small and large cell variants) is 2 per million and even lower for the midgut/appendiceal sites. Like for WDEC, the trend may be rising. Data on the true incidence of PDEC vs. carcinomas with NE differentiation is lacking.

#### *Prognosis and Genetics*

In reports and reviews of colorectal PDEC, several statements and hypotheses have been made: (1) Patients usually present with metastatic disease and few are cured by surgery or chemotherapy [9]. (2) The tumors may be derived from endocrine-committed primitive cells and have low expression of large dense core granules containing chromogranin A (CgA) or synaptophysin but maintained expression of cytosolic markers, e.g. neuron-specific enolase (NSE), and protein gene product 9.5. This may be a consequence of lost NE differentiation ('the CgA switch-gene') leading to decreased hormone synthesis and secretion [10, 11]. (3) Loss at heterozygosity of TP53, DCC and APC suppressor loci may indicate common genetic events in the development of colorectal PDEC and adenocarcinoma [12]. (4) PDEC have high chromosomal instability [13] and are often synchronous with adenoma/adenocarcinoma [2]. (5) Investigations of PDEC arising in tubulovillous adenomas indicate clonal divergence of these two tumor types [14]. It is evident that genetic studies on larger series of well-characterized PDEC with access to clinical data are required to better understand the etiology of this tumor type.

#### *Minimal Consensus Statement on Prognosis*

The prognosis of PDEC (small and large cell variants) is poor due to frequent presentation with metastases and relative lack of effective therapy. The tumor type may be derived from endocrine-committed progenitor cells with loss of NE differentiation, but due to common genetic events it cannot be excluded that they develop during stepwise progression of adenocarcinoma.

#### *Small Cell PDEC*

In a review of gastrointestinal small cell carcinomas (1970–2003), Brenner et al. [15] found 138 reports on 544 cases; the first description of small cell carcinomas in the esophagus was credited to McKeown [16] in 1951. This tumor type constitutes <1% of all gastrointestinal malignancies and is most common in the esophagus (53%), followed by the colorectum (13 + 7 = 20%) and stomach (11%). Malignant and site-specific symptoms dominate, but ectopic hormonal secretion may occur [17]. The tumors are usually metastatic at presentation. The TNM classification can be used for staging of tumors [18], but in the USA the classification of pulmonary oat-cell carcinoma, according to the VA Lung Study Group [19], is often used also for gastrointestinal small cell carcinoma: limited disease (LD) means the primary tumor with, or without, regional lymph node metastases, and extensive disease (ED) includes distant metastases. A proposal for a TNM classification for endocrine tumors of colon and rectum will soon be published [Rindi et al., in press, 2007].

#### *Histopathology and Genetics*

Histologically small cell carcinoma is indistinguishable from pulmonary oat-cell carcinoma with tumor cells less than the size of three lymphocytes and with scant cytoplasm. Nuclei can be round-, ovoid-, or spindle-shaped with granular chromatin and small nucleoli and typically showing nuclear molding. Small cell carcinomas usually have >10 mitoses/10 HPF (average 40–50) and show lymphovascular invasiveness. Half of the tumors contain non-small cell carcinoma components, e.g. adenocarcinoma components can dominate and colorectal tumors may even contain foci of squamous differentiation [20]. The NE differentiation of tumor cells can show immunoreactivity for CgA and synaptophysin and is often also positive for the carcinoembryonic antigen (CEA). Keratin expression (AE1:AE3, Cam 5.2) is common in these tumors, but not of the high molecular forms. In contrast to pulmonary small cell carcinoma (85–100%), thyroid transcription factor-1 (TTF-1) is only occasionally positive (17%) in gastrointestinal small cell carcinoma [21]. Otherwise, gastrointestinal and lung small cell carcinoma both overexpress p53, have high proliferation, telomerase activation and Rb loss; p16 loss and K-ras amplification are infrequent. The etiology is unknown, but besides origin in pluripotent stem cells a late stage phenomenon during stepwise progression of adenocarcinoma cannot be excluded [22, 23]. In a recent study of 15 cases with colorectal small cell carcinoma, the phenotype

was not generally associated with loss of mismatch repair proteins and the tumors are thus more likely to develop through chromosomal rather than microsatellite instability [24].

#### *Minimal Consensus Statement on Clinical Presentation, Histopathology and Genetics*

Small cell PDEC can be clinically divided into those with LD and those with ED including metastases. The tumors have high proliferation and are lymphoinvasive. They can express CgA, synaptophysin and often CEA and low-molecular keratins. They are likely to develop through chromosomal instability.

#### *Diagnostic Procedures and Therapy*

When a patient presents with a small cell carcinoma tumor it is of prime importance to exclude a primary pulmonary small cell carcinoma and assess if the patient has LD or ED. Diagnostic studies are aimed at the affected site, e.g. endoscopy and spiral CT. There are no studies other than case reports on the sensitivity of other imaging modalities, i.e. MRI, FDG-PET, or octreotide scintigraphy. However, available data suggest that PDEC mostly do not express somatostatin receptors in quantities that will allow octreotide scintigraphy. On the other hand, these tumors commonly demonstrate intense metabolism mirroring their proliferative activity, thus offering reasonable FDG-PET results in the majority of cases. In patients with LD, there is a potential role for radical surgery, while patients with ED are best treated with chemo-radiotherapy. However, judging from the limited patient series available it seems as if surgically-treated patients rapidly develop recurrence [cf. 15]. In fact, in one series surgical treatment was a significant predictor of death [25]. In the experience from the M.D. Anderson Memorial Hospital, a period of chemo-radiotherapy prior to surgery was proposed for patients with esophageal small cell carcinoma and LD [26]. Chemotherapy combining several agents seems to result in the best response rates; in a survey of the literature only 12 of 52 patients had colorectal small cell carcinoma. The most commonly used drugs were cisplatin (45 mg/m<sup>2</sup> per day × 3 days i.v.) and etoposide (130 mg/m<sup>2</sup> per day on days 2 and 3 i.v.), sometimes combined with cyclophosphamide, doxorubicin and vincristine. The overall response rates with cisplatin-based or CAV/ACE chemotherapy (cyclophosphamide/doxorubicin with vincristine or etoposide) in ED were 70–90% [cf. 15]. These data correlate well with the early study of Moertel et al. [27], who reported 67% response rate in 18 patients with ‘anaplastic NE carcino-

ma’; of 12 responders, 3 showed complete regression. Drug toxicity was significant with nausea, sensory neuropathy, alopecia and bone marrow suppression. To date there have been no prospective randomized studies, nor more specific drug combinations recommended for colorectal PDEC.

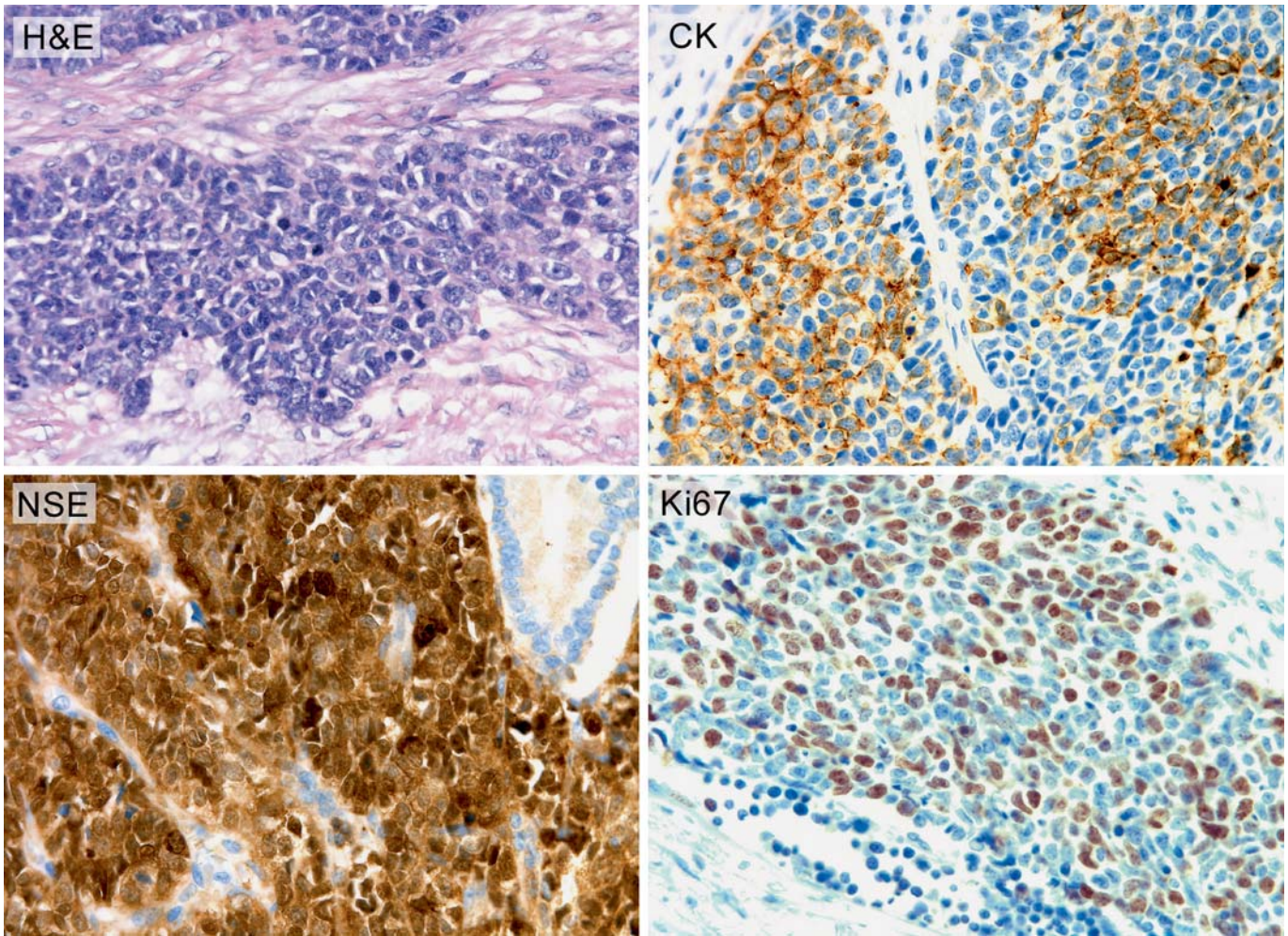
Thus, chemotherapy based on cisplatin and etoposide is the mainstay of treatment for ED; the initial response rate is high, but of short duration (6–9 months) [cf. 9]. In pulmonary small cell carcinoma, combined chemo- and radiotherapy may offer a better treatment alternative than chemotherapy alone, but requires a good performance status of the patient. However, there are molecular differences between small cell carcinoma of different origin that might imply divergent management, e.g. patients with gastrointestinal small cell carcinomas seem to have better survival after surgical resection. Since many gastrointestinal small cell carcinomas have a non-small cell carcinoma component, chemotherapy directed against both components, e.g. cisplatin, may offer a therapeutic advantage. The prognosis is still dismal and the response to second-line therapy poor [15]. Therefore, aggressive primary chemotherapy is recommended. If radical resection can be performed, it seems reasonable to continue with adjuvant chemotherapy during a period in an attempt to obtain a more durable effect. In a recent phase II study, patients with PDEC and WDEC tumors were treated with XELOX (oxaliplatin and the 5-FU precursor, capecitabine) irrespective of the site of the primary tumor. Patients with PDEC seemed to have a low responsiveness to this treatment in contrast to patients with WDEC [28].

#### *Minimal Consensus Statement on Diagnostic Procedures and Therapy*

In patients with distant metastases, pulmonary small cell carcinoma should first be excluded (usually immunopositive for thyroid transcription factor 1). Diagnostic studies by endoscopy and CT are aimed at the affected site. Due to high proliferation, FDG-PET may be helpful. Patients with LD may be amenable for surgical treatment, while patients with ED are best treated with chemotherapy. The initial response rate for cisplatin and etoposide is usually high but associated with significant toxicity. The prognosis is still dismal and response to second-line therapy poor.

#### *Large Cell PDEC Variant*

The large cell PDEC variant also includes so-called medullary tumors. In a series from the University of Michigan, the highest age incidence was around 60 years



**Fig. 1.** PDEC of small cell type in the right colon from patient No. 1. Tumor cells are of small to intermediate size with scant cytoplasm (H&E). A majority of tumor cells are positive for cytokeratin (CK) (antibody AE1/AE3) and NSE. Proliferative activity is high with more than 30% Ki67-positive tumor cell nuclei.

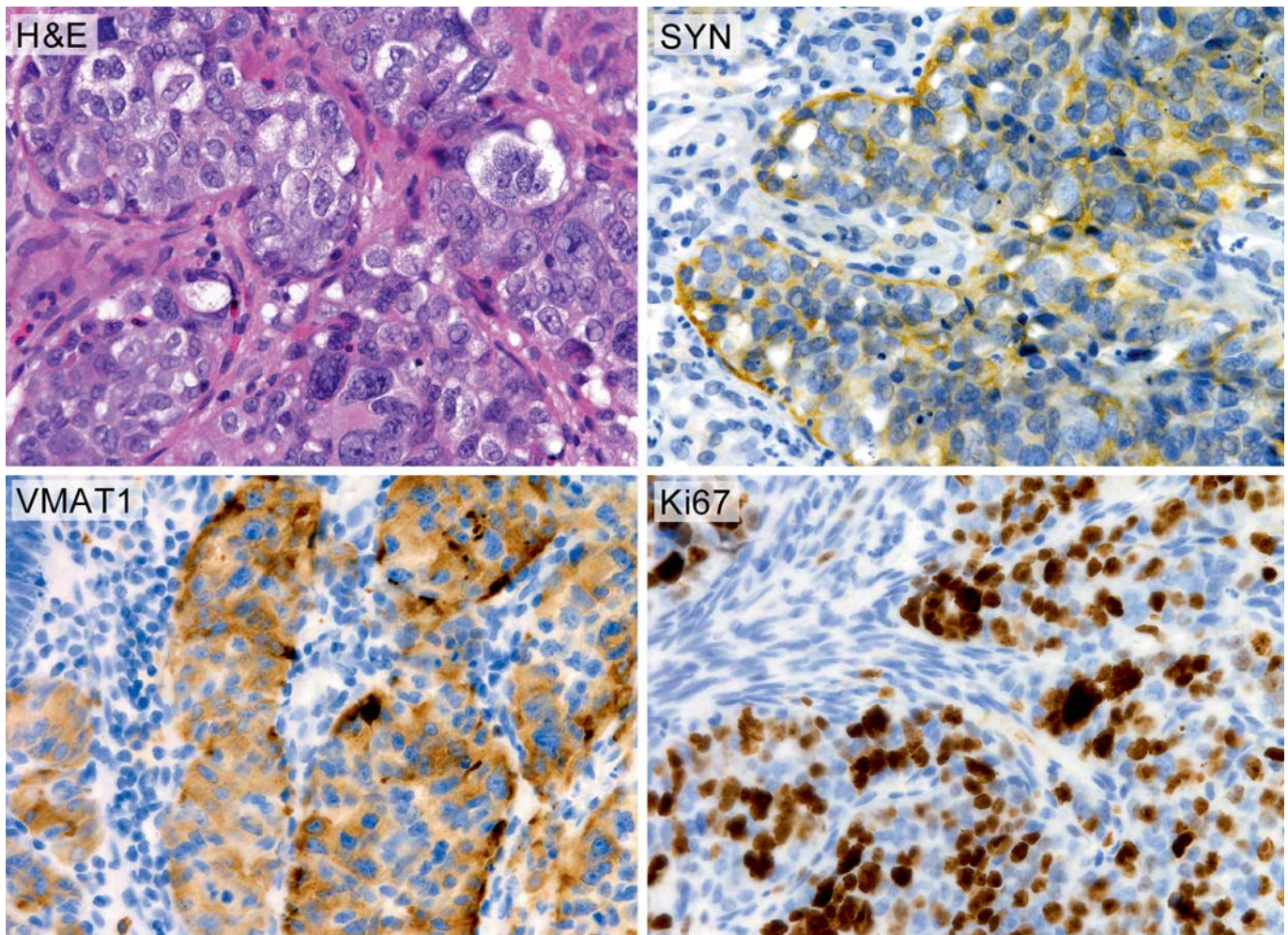
with large variations [29]. The average survival was similar as for differentiated adenocarcinoma, but reduced expression of the transcription factor CDX2 and high microsatellite instability were much more common for large cell PDEC than for differentiated adenocarcinoma. There also seemed to be a preponderance of right-sided colonic tumors. It was suggested at the meeting that these patients should be treated according to the guidelines of small cell carcinoma based on the lack of larger experience.

#### *Minimal Consensus Statement on Large Cell PDEC*

The large cell PDEC variant should be treated similar to small cell PDEC in the absence of larger experience.

#### *Therapeutical Results*

There are two large retrospective clinical series on colorectal NE carcinomas, one from Chicago [39 patients with NE tumors out of 988 resected colorectal neoplasms (1983–1993)] [30] and one from MSKCC, New York [38 patients out of 6,495 resected (1975–1998)] [31]. The incidence figures differ markedly (3.9 vs. 0.6%), while the average patient age was similar, 65 vs. 57 years. The Chicago series, which also included a few WDEC and mixed endocrine-exocrine (amphicrine) tumors, showed an equal distribution of small cell and intermediate cell tumors with preferential site in the colon. In the MSKCC series, there were 22 small cell and 16 large cell tumors with equal distribution between the colon and rectum.



**Fig. 2.** PDEC of large cell type in the rectum from patient No. 2. Tumor cells are of large size with moderate amount of cytoplasm (H&E). A majority of tumor cells are positive for synaptophysin (SYN) and vesicular monoamine transporter I (VMAT1). Proliferative activity is high with more than 30% Ki67-positive tumor cell nuclei.

The immunohistochemical studies were incomplete in the Chicago series and in the MSKCC only 15–19 tumors were investigated with expression of CgA and NSE in almost all, while synaptophysin was expressed in about two-thirds. In both series, 80% of the patients presented with metastatic disease (Duke C and D or stage III–IV). The median survival was low: 7 and 10 months, respectively. The survival analysis in the first series was 58% at 6 months, 15% at 3 years and 6% at 5 years; in the second series the survival after 1 and 3 years was 46 and 13%, respectively [30, 31].

#### *Minimal Consensus Statement on Survival*

Despite active therapeutic efforts, the median survival of high-stage PDEC tumors (ED) is very low (7–10 months). Survival beyond 5 years is scarce.

#### *Cases Illustrated in Figures 1 and 2*

In figures 1 and 2, patients with small or large cell PDEC are presented with histopathological details. Patient No. 1 (small cell carcinoma) was initially thought to have right-sided colonic adenocarcinoma as a cause of ileus and underwent removal of the primary tumor and resectable nodes. Due to asthma and poor general condition, he rejected chemotherapy. After a progression-free

interval of 27 months, he agreed to chemotherapy tailored for a WDEC (streptozotocin + 5-FU and interferon- $\alpha$ ) without any objective response and died a few months thereafter. It may be claimed that this patient would have done better with cisplatin + etoposide in an adjuvant setting after R1 resection.

Patient No. 2 (large cell carcinoma) was initially diagnosed with rectal adenocarcinoma from tumor biopsies. After R0 resection, he received adjuvant therapy with streptozotocin + 5-FU alternated with adriamycin. After a tumor-free interval of 7 months, he underwent radiofrequency ablation of liver metastases, followed by chemoembolization (doxorubicin). A short-lasting tumor regression was seen after this procedure and the patient died 4 months later. Since the recurrent tumors were somatostatin receptor-positive, radiotherapy with  $^{177}\text{Lu}$ -octreotate, followed by cisplatin + etoposide, might have been a better treatment alternative.

### List of Participants

*List of Participants of the 'Consensus Conference on the ENETS Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumors, Part 2: Midgut and Hindgut Tumors' Held in Frascati (Rome, Italy), November 1-4, 2006*

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