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ORIGINAL ARTICLE

Neuroendocrine neoplasms of the jejunum: a heterogeneous group with distinctive proximal and distal subsets

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Abstract Neuroendocrine tumors (NETs) of the jejunum are rare and usually grouped with either duodenal or ileal NETs. We aimed at better evaluating their characteristics by studying 116 cases of small-bowel NETs for which a precise anatomical location was available. Thirty-four cases were duodenal. Eighty-two were located after the duodenojejunal ligament, including ten cases in the first 50 cm, four cases between 50 and 100 cm, and six cases between 100 and 250 cm. All tumors located after 50 cm from the duodenojejunal ligament were enterochromaffin neoplasms. In contrast, the ten tumors located before this point formed a heterogeneous group. They included two cases of gastrin-expressing tumors in the first 10 cm and one case of enterochromaffin tumor located at 45 cm. The seven remaining cases were large tumors, located between 10 and 50 cm, of intermediate or high histological grade (four out of seven G2 or G3), locally invasive and usually metastatic (five out of seven with liver metastases); their survival was comparable to that of duodenal NETs. Patients with tumors located in the duodenum or the first 50 cm of the jejunum had longer survivals than those with lower jejunal and ileal tumors (p=0.024). In conclusion, our study underlines the heterogeneity of jejunal NETs and supports the distinction between "upper" and "lower" jejunal tumors, which, for prognostic purposes, might be grouped with, respectively, duodenal and ileal NETs. Our data suggest that the arbitrary limit between upper and lower jejunal tumors might be fixed at 50 cm from the duodenojejunal ligament.

Keywords Neuroendocrine neoplasms · Jejunum · Small bowel · Enterochromaffin tumors

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Introduction

Neuroendocrine tumors of the jejunum are much rarer than those of the other segments of the small intestine and remain poorly characterized [1–3]. In the earlier literature, they usually have been lumped with either duodenal [4] or ileal [5, 6] neuroendocrine neoplasms. In the 2000 [7] and 2010 [8]

editions of the WHO classification of digestive neuroendocrine tumors as well as in the European Neuroendocrine Tumor Society (ENETS) proposals for the staging of gastroenteropancreatic neuroendocrine tumors [9], they have been split into two distinct groups: tumors of the "upper jejunum" are associated with those of the duodenum, and tumors of the "lower jejunum," with those of the ileum. However, in several recent clinical guidelines, jejunal neuroendocrine tumors are considered together with ileal tumors [10–12].

Little evidence has been provided to substantiate any of these statements. Two main difficulties have hampered the study of jejunal neuroendocrine neoplasms: their rarity and the absence of a clear-cut definition of the jejunum. Anatomically, the upper limit of this intestinal segment is defined as the duodenojejunal ligament (or ligament of Treitz), but no precise lower limit can be identified. Moreover, the length of the jejunum is variable from one individual to another: by convention, it is estimated to be about 40 % of the whole length of the small intestine and may therefore vary from 100 to 250 cm from one individual to another [13–15]. It may therefore be difficult for the surgeon to decide whether a tumor is located in the distal jejunum or in the proximal ileum. Histology is not helpful to solve the issue, in the absence of any clear-cut boundary between the various segments. Difficulties are even major in distinguishing the "upper" and the "lower" jejunum, as proposed by the recent WHO classifications, in the absence of any reliable anatomical or histological definition of these two supposed segments of the jejunum.

Several questions remain, therefore, to be addressed: (a) Do "jejunal" neuroendocrine neoplasms form a homogeneous or a heterogeneous group? (b) Is it possible to identify, according to the upper or lower location of the primary, two tumor subsets similar to, respectively, duodenal and ileal neuroendocrine tumors? (c) On the contrary, is there any evidence for the existence of a distinctive subset of specifically jejunal neuroendocrine neoplasms? To address these questions, we decided to analyze the clinical, pathological, and functional characteristics of the large series of small-bowel neuroendocrine neoplasms referred to our institution between 1991 and 2007, and for which a precise anatomical location could be determined from the endoscopical, surgical, and/or pathological reports.

Material and methods

Inclusion criteria

Two hundred thirty-four patients with a primary neuroendocrine tumor located in the segment of the digestive tract comprised between the pylorus and the ileocecal valve, who were referred to our institution for diagnosis and/or treatment between 1991 and 2007, were retrieved from the database of the Center for Diagnosis and Treatment of Neuroendocrine Tumors, Hôpital Edouard Herriot, Lyon (ENETS Center of Excellence). Patients with ampullary and periampullary tumors were excluded from the study group; patients with tumors of Meckel's diverticulum were included.

Criteria for inclusion in the study group were the following: (a) precise anatomical location available from the endoscopical, surgical, and/or pathological reports; (b) availability of clinical charts and complete pathological reports; and (c) availability of formalin-fixed, paraffin-embedded tissue material for histological review and additional investigations, if necessary. One hundred eighteen patients were excluded: (a) 108 referred only after surgery, for whom no tissue material was available in our center, and (b) 10 in whom the precise anatomical location could not be obtained. One hundred sixteen patients were included in the study.

Determination of the anatomical location

For neoplasms located in the duodenum, defined as the segment of the small intestine located before the ligament of Treitz, the exact location was determined according to the informations provided either by the diagnostic and/or therapeutic endoscopic procedure or at surgery; upper duodenum was defined as the part of the duodenum located above the papilla; lower duodenum as the part of the duodenum located below the papilla.

For neoplasms located after the ligament of Treitz, the location was determined during surgery and/or during the macroscopic examination of the surgical specimen. It was expressed as the distance (in centimeter) measured between the tumor center and either the duodenojejunal junction or the ileocecal valve, according to the type of surgical procedure. In the absence of objective criteria to distinguish between the distal jejunum and the proximal ileum, we decided to use the arbitrary limits of 100 and 250 cm after the ligament of Treitz, because they have been proposed as, respectively, the minimal and maximal lengths of the jejunum in the anatomical literature. This means that all neoplasms located before 100 cm from the ligament of Treitz can be confidently considered jejunal, whereas those originating between 100 and 250 cm may be either jejunal or ileal, depending on the total length of the small intestine in the individual patient. The tumors located after 250 cm from the ligament of Treitz can be confidently considered ileal.

Clinical data

The following clinical parameters were recorded from the original clinical charts or from a specific database maintained

in our institution for all patients referred for neuroendocrine tumor: sex, age at diagnosis, functional syndrome, presence of multiple endocrine neoplasia type 1 (MEN1) syndrome, evidence of regional and distant metastases, duration of follow-up, and status at the end of follow-up period. Serum hormonal levels were recorded when available. The end of the follow-up period was 1 September 2011. Complete follow-up data were obtained for 108 of the 116 patients. The median duration of follow-up was 45 months.

Pathological data

The original macroscopical reports and all the available archival histological material were reviewed; additional immunohistochemical studies were performed if necessary. The following pathological features were noted: number of tumors, maximum diameter, degree of morphological differentiation, extent of local invasion, evidence of angioinvasion, and/or perineural invasion. If multiple tumors were present, the data presented here refer to the largest and/or the most locally invasive lesion.

All cases were reviewed in order to evaluate the type of tumor architecture according to the classification of Soga and Tazawa [16]: insular, trabecular, tubuloglandular, and solid (preferred to the original term undifferentiated). In all cases, the expression of the following immunohistochemical markers and hormones was recorded from the original report or assessed from additional investigations: chromogranin A (clone DAK-A3, Dako, Glostrup, DK), synaptophysin (clone 27G12, Novocastra, Newcastle Upon Tyne, UK), serotonin (clone 5HT-H209, Dako), somatostatin (polyclonal, INSERM U45, Lyon, France), gastrin (polyclonal, INSERM U45), glucagon (clone K79bB10, Sigma, St. Louis, MI, USA), pancreatic polypeptide (polyclonal, INSERM U45, Lyon, France), and Ki67 (clone MIB-1, Dako). Finally, all cases were reviewed in order to evaluate the mitotic index and the Ki67 index according to the current recommendations [17, 18]. For each case, the following informations were provided: differentiation status, histological grade [17, 18], histological classification according to WHO 2010 guidelines [18], and pTNM stage according to ENETS proposals [9] and to the seventh edition of AJCC/Unio Internationalis Contra Cancrum (UICC) classification [19].

Statistical analysis

Categorical variables were expressed as percentages and compared by the chi-squared test or with Fisher's exact test when appropriate. Continuous variables were expressed as means ± standard deviation, or median with range if not normally distributed, and compared by performing the two-sample *t* test or with the Mann–Whitney *U* test when appropriate.

The overall survival of the patients was assessed using Kaplan–Meier analysis, and comparisons were performed using the log-rank test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (Chicago, IL).

Results

Anatomical location

Thirty-four patients presented with tumors located in the duodenum, before the ligament of Treitz. Fourteen tumors were located in the first 100 cm after the ligament of Treitz and could be, therefore, confidently considered jejunal; 11 out of these tumors were located in the first 50 cm, and only 3 were detected between 50 and 100 cm. Sixty-eight tumors were located between 100 cm from the ligament of Treitz and the ileocecal valve; 6 tumors were located between 100 and 250 cm from the ligament of Treitz, and 62 were located after 250 cm (Fig. 1).

Tumors located before the ligament of Treitz: correlations with clinical, histological, and biological features

There were 34 patients; 20 (58 %) were male, and 14 (42 %) female. The median age was 66 years (range, 34–81). Six patients (17 %) presented with Zollinger–Ellison syndrome. MEN1 syndrome was diagnosed in three patients (9 %). Six patients presented with multiple tumors. Fourteen patients had endoscopical resections, and 20 had surgical resections.

Tumors were located in the upper duodenum in 30 patients and in the lower duodenum in 4 patients. Median tumor size was 9.7 mm (range, 3–28). At histological examination, the architecture was trabecular in all cases, except four, characterized by a tubuloglandular pattern. All tumors were made of well-differentiated neoplastic cells displaying a typical endocrinoid appearance: they were monomorphic, medium-sized, with a large eosinophilic cytoplasm, and a regular nucleus containing salt and pepper chromatin. Gastrin was detected by immunohistochemistry in 25 cases, alone or in association with another digestive hormone. Somatostatin was the only hormone expressed in three cases; two were periampullary and presented a tubuloglandular architecture. None of the hormones tested, including serotonin, was detected by immunohistochemistry in the other cases (22 %).

According to the 2010 WHO classification, tumors were classified as neuroendocrine neoplasms G1 in 33 patients and neuroendocrine neoplasm G2 in 1 patient. Among tumors for which the pTNM stage (according to both ENETS and UICC classifications) could be determined, 17 were pT1; 6, pT2; and 3, pT3; 14 were stages I and II, and 12, stages III and IV. In

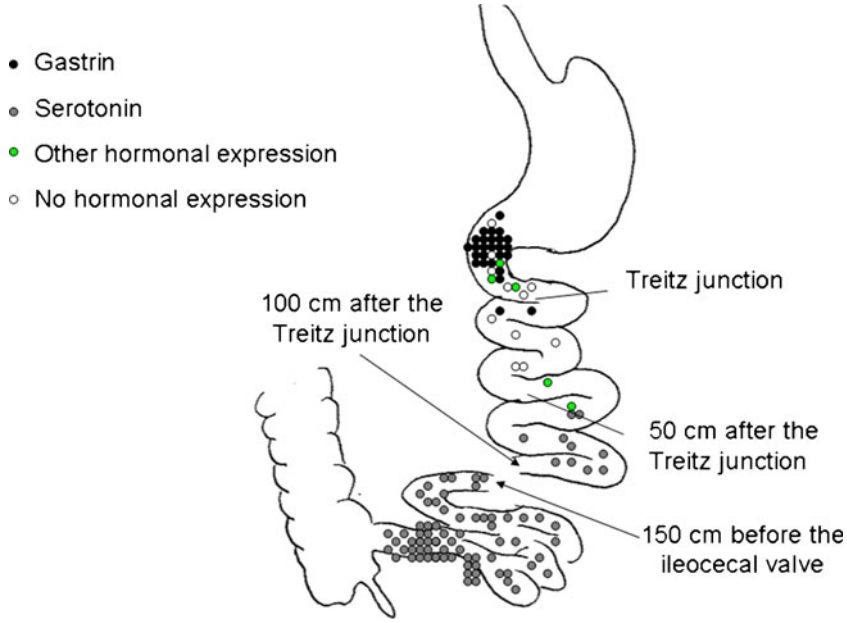

Fig. 1 Location of the small-bowel neuroendocrine tumors included in this series, with their hormonal profile as assessed by immunohistochemistry

eight cases, only incomplete endoscopical resections were available, and an accurate TNM stage could not be determined. Twenty-five patients were still alive at the end of the follow-up period; the median overall survival was 154 months (Table 1).

Tumors located before 100 cm after the ligament of Treitz: correlations with clinical, histological, and biological features

Fourteen patients presented with tumors located before 100 cm after the ligament of Treitz and could therefore be confidently considered jejunal. Ten were male, and four, female. The median age was 57.5 years (range, 48–76). All patients had surgical resections. Two patients presented with multiple tumors. According to their histological patterns and/or hormonal profile, three groups of tumors could be recognized in our series. Each of these groups was associated with a different anatomical distribution (Table 1).

A first group was formed by gastrin-expressing tumors (Fig. 2). Only two cases were observed. In the first patient, the tumor was unique, measured 8 mm in diameter, and was located at 9 cm from the ligament of Treitz; it was classified as a neuroendocrine neoplasm G1; regional lymph node metastases were present; no distant metastasis was detected; the patient was rapidly lost from follow-up. The other patient, with the MEN1 syndrome, presented with two digestive neuroendocrine tumors, one in the lower duodenum and one 7 cm after the ligament of Treitz; the duodenal tumor measured 15 mm in diameter, expressed gastrin, and was classified as neuroendocrine neoplasm G1, pT3, stage IV; the jejunal tumor measured 7 mm in diameter, expressed gastrin, and was strictly submucosal; it was classified as neuroendocrine neoplasm G1. This patient presented with regional lymph node involvement and metastatic liver disease, which, on a clinical basis, were considered to be more likely related to the duodenal tumor than to the jejunal neoplasm. The patient was alive at the end of the follow-up period, with an overall survival of 41 months.

A second group was formed by typical enterochromaffin tumors, showing clinical and/or immunohistochemical evidence of serotonin expression (Fig. 3). Five cases were observed. Only one was located before 50 cm from the ligament of Treitz (at 45 cm), while all others were located after 50 cm. There were four males and one female, with a median age of 59 years (range, 49–76). No patient showed evidence of the carcinoid syndrome. Median tumor size was 15.2 mm (range, 3–110). All tumors displayed a well-differentiated morphological appearance and a typical insular or micronodular architecture, characterized by the presence of tumor cell nests separated by fibrous septa containing numerous vessels. All tumors expressed serotonin by immunohistochemistry. According to the 2010 WHO classification, all cases were classified as neuroendocrine neoplasms G1. One case was pT1, and four, pT3. Four patients had lymph node and liver metastases and were stage IV. Three patients were alive at the end of the follow-up period, with a median overall survival of 58.3 months.

The seven remaining tumors originated in a short segment of the proximal jejunum, located between 10 and 50 cm from the ligament of Treitz. They were two male and five female patients, with a median age of 59 years (range, 48–64). Tumor diameter ranged from 20 to 120 mm (mean±SD=50±42); tumor size was therefore significantly larger than in duodenal tumors (mean±SD=9.6±5.4 mm, p=0.0017) and in enterochromaffin tumors, either jejunal or ileal (mean±SD=22.1±17.6 mm, p=0.0009). The architectural pattern was variable (Fig. 4). In four cases, the proliferation was made of an

Table 1 Clinical, histological, and immunohistochemical features

	Duodenal tumors	Jejunoileal tumors			
		Proximal jejunal tumors (<10 cm)	Other upper jejunal tumors (10–50 cm)	Enterochromaffin tumors	
				<100 cm	>100 cm
Patients, *n*	34	2	7	5	68
Sex (F/M), *n*	14/20	1/1	2/5	1/4	27/41
Age, median (range)	66 (34–81)	50 (50–50)	59 (48–64)	59 (49–76)	60 (36–82)
Functioning syndrome					
Carcinoid, *n* (%)	0	0	0	0	32 (47 %)
ZES, *n* (%)	6 (17 %)	1 (50 %)	0	0	0
MEN1 syndrome, *n* (%)	3 (9 %)	1 (50 %)	0 (0 %)	0 (0 %)	0 (0 %)
Multiple tumors, *n* (%)	6 (18 %)	1 (50 %)	1 (14 %)	1 (20 %)	16 (24 %)
Mean size (range) (mm)	9.7 (3–28)	7.5 (7–8)	50 (20–120)	15.2 (3–21)	22.6 (5–110)
Architecture, *n* (%)					
Trabecular	30 (88 %)	2 (100 %)	2 (29 %)	–	–
Insular	–	–	1 (14 %)	5 (100 %)	68 (100 %)
Tubuloglandular	4 (12 %)	–	4 (57 %)	–	–
Hormone expression, *n* (%)					
Serotonin	–	–	–	5 (100 %)	68 (100 %)
Gastrin	25 (69 %)	2 (100 %)	–	–	2 (3 %)
Somatostatin	7 (19 %)	–	–	–	6 (10 %)
Glucagon	2 (6 %)	–	2 (29 %)[a]	–	–
Insulin	1 (3 %)	–	–	–	–
Pancreatic polypeptide	1 (3 %)	–	–	–	1 (2 %)
WHO 2010, *n* (%)					
NET G1	33 (97 %)	2 (100 %)	3 (43 %)	5 (100 %)	56 (82 %)
NET G2	1 (3 %)	0	3 (43 %)	0	12 (18 %)
NEC	0	0	1 (14 %)	0	0
pT, *n* (%) (ENETS-UICC)					
pT1	17 (50 %)	1 (50 %)	0	1 (20 %)	3 (4 %)
pT2	6 (17.6 %)	0	1 (14 %)	0	6 (9 %)
pT3	3 (8.8 %)	1 (50 %)	6 (86 %)	4 (80 %)	59 (87 %)
pT4	0	0	0	0	0
n/a	8 (23.4 %)	0	0	0	0
Lymph node metastasis, *n* (%)	11 (32 %)	2 (100 %)	2 (29 %)	4 (67 %)	59 (87 %)
Liver metastases, *n* (%)	3 (9 %)	1 (50 %)	5 (71 %)	4 (80 %)	42 (62 %)
TNM stage (ENETS)					
I	11 (32.5 %)	–	–	–	1 (1.5 %)
II	3-2A/1B- (9 %)	1-1B- (50 %)	–	–	2-1A/1B- (3 %)
III	9-9B- (26.5 %)	–	1 -1B- (14 %)	1-1B- (20 %)	19-19B- (28 %)
IV	3 (9 %)	1 (50 %)	6 (86 %)	4 (80 %)	46 (67.5 %)
n/a	8 (24 %)	–	–	–	–
Alive, *n* (%)	25 (73 %)	1 (50 %)	6 (86 %)	3 (60 %)	50 (74 %)
Lost of follow-up, *n*	7	1	0	0	0
Median follow-up in months (range)	38.8 (3–327)	32.9 (1–64.9)	46.4 (15–177)	58.3 (2–200)	41.7 (3–183)

F female, *M* male, *WHO* World Health Organization, *NET* neuroendocrine tumor, *NEC* neuroendocrine carcinoma, *ENETS* European Neuroendocrine Tumor Society, *UICC* Unio Internationalis Contra Cancrum, *n/a* not assessable, *ZES* Zollinger-Ellison syndrome

[a] Positivity in about 5 and 10 % of tumor cells

admixture of solid and tubuloglandular areas; hemorrhagic areas of variable size were visible; cystic spaces were constantly present but showed variable degrees of development, from focal dilatations of tubuloglandular structures to cystic degeneration visible at macroscopical examination (Fig. 4). In two cases, glucagon was detected in less than 10 % of tumor cells; in the two other cases, none of the hormones tested was detected. In addition to the typical neuroendocrine component,

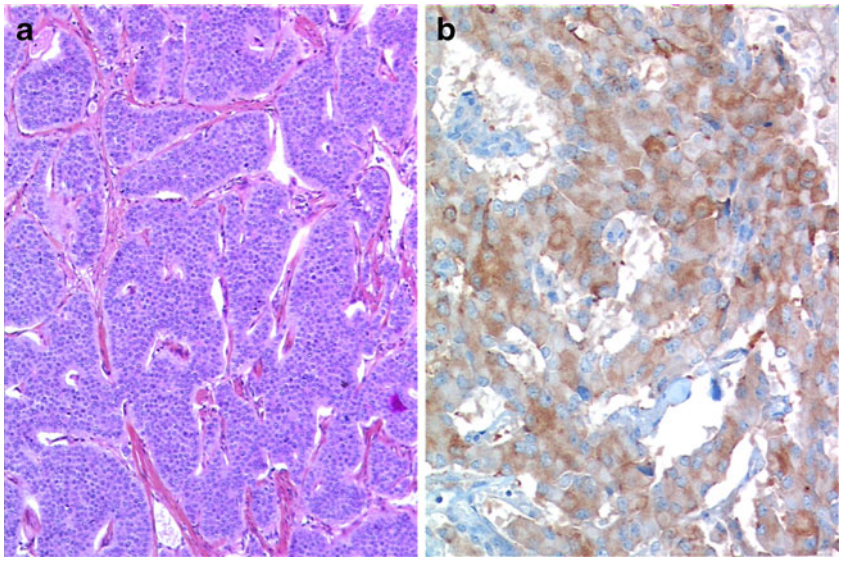

Fig. 2 Gastrin-expressing neuroendocrine tumor of the upper jejunum. This tumor, located 9 cm *after* the ligament of Treitz, shows the typical appearance of a well-differentiated neuroendocrine tumor; mitoses are absent (**a**). Gastrin is detected by immunohistochemistry in most neoplastic cells (**b**). **a** Hematoxylin–eosin–saffron, original magnification, ×190; **b** immunoperoxidase, original magnification, ×320

cells with a dendritic morphology, expressing vimentin and S100 protein and resembling sustentacular cells, were detected in two cases. A second architectural pattern was observed in two out the seven cases. It was purely trabecular, with small amounts of fibrous, well-vascularized stroma. No hormone was detected by immunohistochemistry. In the last case, the architecture was characterized by the presence of tumor nests of variable size, separated by large fibrous septa. No hormone, including serotonin, was detectable in our technical conditions.

Four out of the seven cases presented a high histological grade despite their well-differentiated morphological appearance: three were G2, and one was G3. This proportion was significantly higher than for duodenal tumors (1 G2 tumor out of 36 cases, $p=0.0003$) and for enterochromaffin jejunal and ileal tumors (12 G2 out of 73 cases, $p=0.035$). All seven tumors were locally invasive; six were pT3, and six were stage IV. These proportions were significantly higher than in duodenal tumors (3 pT3 and stage IV tumors out of 36, $p=0.0002$) but were similar to that observed in enterochromaffin jejunal and ileal tumors (62 pT3 or pT4 tumors and 50 stage IV tumors out of 73 cases).

Despite the apparently unfavorable histoprognostic factors associated with these seven cases (large size, high histological grade, evidence of local invasion, and metastatic dissemination), only one patient was deceased at the end of the follow-up period. The six other patients were alive, with survivals ranging from 7 to 192 months; median overall survival was 68 months.

Tumors located after 100 cm after the ligament of Treitz: correlations with clinical, histological, and biological features

All tumors were typical enterochromaffin tumors, characterized by a micronodular/insular architecture and by the

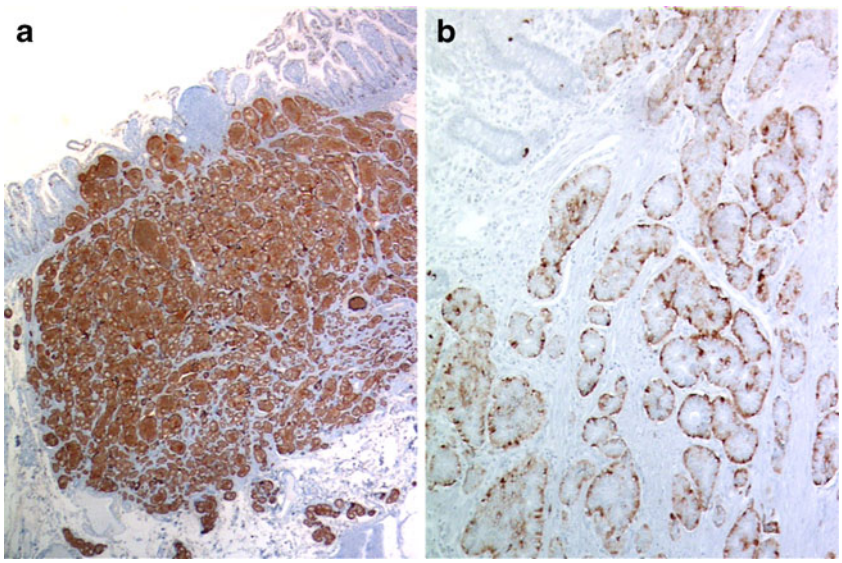

Fig. 3 Enterochromaffin tumor of the jejunum. This tumor, located 45 cm after the ligament of Treitz, shows a typical insular architecture (**a**). Neoplastic cells strongly express chromogranin A (**a**) and serotonin (**b**). Immunoperoxidase, original magnifications: **a**×110, **b**×250

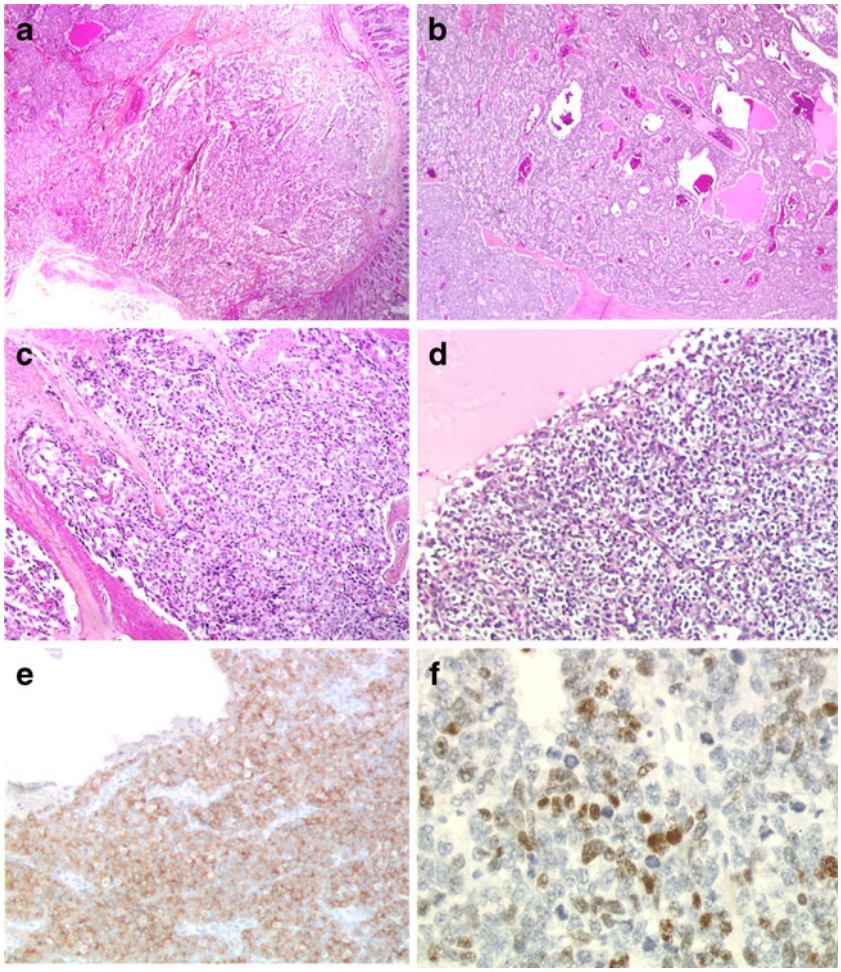

Fig. 4 Upper jejunal neuroendocrine tumors. At low magnification, these two large tumors, respectively located at 12 cm (**a**) and 35 cm (**b**) from the ligament of Treitz show a variable degree of cystic degeneration. In the first case (**a**, **c**), the tumor is mainly solid, with scattered hemorrhagic cysts (a); tumor cells show a significant degree of atypia (**c**). In the other cases (**b**, **d**–**f**), the tumor has a microcystic appearance. Cystic spaces are directly lined by neoplastic cells (**d**) expressing synaptophysin (**e**); Ki67 index is high (**f**). **a**–**d** Hematoxylin–eosin–saffron, original magnifications: **a**×60, **b**×90, **c**×180, **d**×210. **d**–**f** Immunoperoxidase, original magnifications: **e**×210, **f**×280

expression of serotonin. Sixty-eight cases were observed, including eight cases discovered in a Meckel's diverticulum. There were 41 males and 27 females, with a median age of 60 years (range, 36–82). Thirty-two patients had clinical evidence of carcinoid syndrome. Seventeen patients (23 %) presented with multiple tumors. Median tumor size was 22.6 mm (range, 5–110). All tumors displayed a well-differentiated morphological appearance and a typical micronodular architecture, characterized by the presence of tumor cell nests separated by fibrous septa containing numerous vessels. All tumors expressed serotonin, alone or in association with another hormone (somatostatin in six cases, gastrin in two, and pancreatic polypeptide in one). According to the 2010 WHO classification, 56 cases were classified as neuroendocrine neoplasms G1 and 12 as neuroendocrine neoplasms G2. Fifty-nine cases were pT3 (85 %) according to either ENETS or UICC TNM classifications (Table 1). At diagnosis, 59 patients presented with regional lymph node involvement, and 42 had liver metastases; 65 were staged as stage III or IV. Fifty patients were alive at the end of the follow-up period; median overall survival was 135 months (Table 1).

Prognostic relevance

We first compared the tumors according to their clinical, histological, and functional characteristics. Three groups were considered: (a) duodenal tumors (n=34), (b) upper jejunal tumors located before 50 cm from the ligament of Treitz (n=9), and (c) enterochromaffin tumors, both jejunal and ileal (n=73). The survival curves are shown in Fig. 5. There was no difference between duodenal tumors, on one hand, and upper jejunal tumors, on the other hand (p=0.63, log-rank test).

We then evaluated the prognostic relevance of grouping duodenal and upper jejunal tumors, on one hand, and lower jejunal and ileal tumors, on the other hand, as proposed by recent histopathological classifications [7–9]. For this purpose, we compared the following groups: (a) patients with tumors located in the duodenum or in the first 50 cm after the ligament of Treitz (n=44) and (b) patients with tumors located beyond 50 cm from the ligament of Treitz (n=72). The limit of 50 cm was retained because of the marked differences in tumors observed before and after this point. In our series, patients with duodenal and upper jejunal tumors had significantly longer survivals than those with

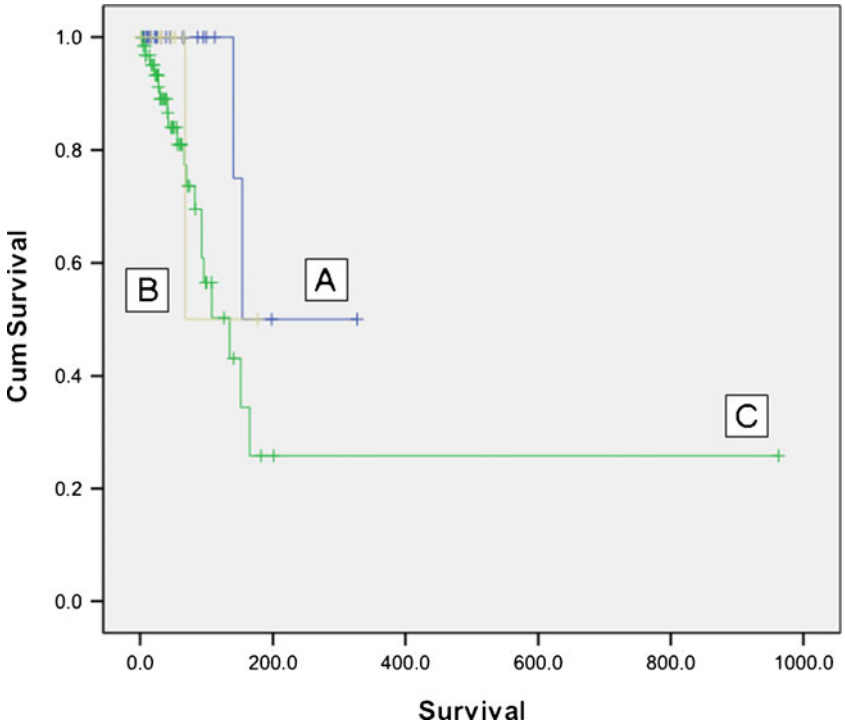

Fig. 5 Survival curves in three groups of patients: *A* patients with duodenal tumors (n=34), *B* patients with upper jejunal neoplasms located before 50 cm from the duodenojejunal ligament (n=9), *C* patients with enterochromaffin tumors, both jejunal and ileal (n=73)

lower jejunal and ileal tumors (p=0.024, log-rank test) (Fig. 6).

Discussion

Our series confirms the rarity of jejunal neuroendocrine neoplasms. In our group, only 14 tumors could be confidently classified as jejunal because of their location before 100 cm from the ligament of Treitz; an additional six cases were located between 100 and 250 cm from the ligament of Treitz and may have been either jejunal or ileal depending on the anatomical characteristics of the patient. In contrast, our series contains 34 cases of neuroendocrine tumors originating in the duodenum, and 62, in the ileum. In addition to being rare, jejunal neoplasms are also markedly heterogeneous; our series

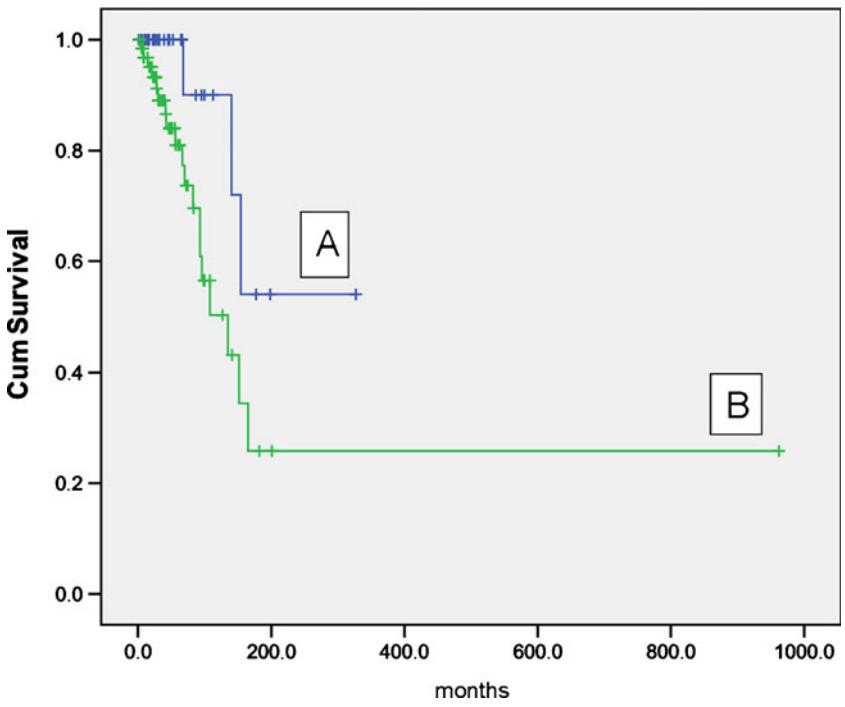

Fig. 6 Survival curves in two groups of patients: *A* patients with duodenal tumors and tumors located in the first 50 cm after the ligament of Treitz (n=44), *B* patients with tumors located after 50 cm from the ligament of Treitz (n=72). The difference is statistically significant (p=0.024, log-rank test)

contains no less than three distinct subgroups with largely non-overlapping distributions: (a) tumors located in the most proximal segment of the jejunum, resembling duodenal neuroendocrine tumors; (b) enterochromaffin tumors, observed in our series after 45 cm from the ligament of Treitz, closely similar to their ileal counterparts; and (c) upper jejunal tumors, usually non-functioning, originating in a short segment of about 50 cm after the ligament of Treitz.

In our series, gastrin-expressing tumors were the most frequent duodenal neuroendocrine neoplasms. We observed only two cases after the ligament of Treitz. Both cases were located in the very proximal part of the jejunum, less than 10 cm from the duodenojejunal ligament; one of those two cases was a minute tumor observed in a MEN1 patient. The existence of upper jejunal neuroendocrine tumors sharing features with duodenal tumors has been acknowledged in a number of case reports [4, 20–27]. Like their duodenal counterparts, "duodenal-like" tumors of the upper jejunum are usually small and synthesize gastrin [4] or, more rarely, other hormones typical of the duodenopancreatic area [4, 20, 25, 28–30]. The few data available from the literature suggest that duodenal-like tumors of the upper jejunum share the same general behavior than their duodenal counterparts [4].

The second group of jejunal neuroendocrine neoplasms observed in our series was formed by typical enterochromaffin tumors, most of which were located in the lower jejunum, mainly after 50 cm from the duodenojejunal ligament; only one case was observed before this point, at 45 cm. In the literature, the existence of jejunal enterochromaffin tumors is well acknowledged [1, 6, 31–33]. In our series, we observed five enterochromaffin tumors before the arbitrary limit of 100 cm from the ligament of Treitz, as compared to 68 cases after this point. This proportion is comparable to that reported in previous studies [31, 34]. In keeping with literature data [6, 31], the cases of jejunal enterochromaffin tumors included in our study shared the same presentation and general clinical behavior than their ileal counterparts, including a strong tendency to local invasion, regional lymph node involvement, and metastatic dissemination.

The third group of jejunal neuroendocrine tumors observed in our study is made of seven cases originating from a short segment of the upper jejunum comprised between 10 and 50 cm after the ligament of Treitz. These tumors had several features in common: they were large, non-functioning, of intermediate or high histological grade, locally invasive, and usually metastatic. They were significantly larger than duodenal tumors and than enterochromaffin tumors, either jejunal or ileal. The proportion of G2 and G3 tumors was significantly higher than for duodenal tumors and for enterochromaffin jejunal and ileal tumors. The proportion of invasive tumors was significantly higher than that in duodenal tumors but was similar to that observed in enterochromaffin jejunoileal tumors. Another distinctive feature frequently observed in this tumor subset was the presence of cystic degeneration, present in four cases of our series: this feature, more typical of pancreatic tumors [35, 36], is exceptionally encountered in gastrointestinal neuroendocrine neoplasms.

A literature search retrieved only a small number of cases that could be confidently ascribed to the same segment of the proximal jejunum [37–41]. Like our own cases, the tumors described in these reports were large, locally invasive, and usually metastatic. Moreover, some of them also presented with unusual features, such as cystic degeneration [42], presence of reactive multinucleated cells [38], or of cells resembling sustentacular cells [37], as also observed in two of our cases. As in most of our cases, no hormone was detected in any of the cases reported in the literature. Our data, in keeping with previous ones [43], suggest that, despite the presence of many unfavorable histoprognostic factors (large size, high histological grade, evidence of local invasion, and metastatic dissemination), upper jejunal tumors have a prolonged clinical course, more similar to that of duodenal tumors than to that of ileal enterochromaffin tumors.

Our findings lend strong support to the distinction between upper and lower jejunal neoplasms proposed by recent histopathological classifications [7–9]. We observed marked differences in clinical, histological, and biological characteristics between the tumors located before and after 50 cm from the ligament of Treitz. Upper jejunal neuroendocrine tumors, located before 50 cm, were heterogeneous and comprised a small subset of duodenal-like tumors, a subset of large, locally invasive, and usually metastatic tumors of unexpectedly good prognosis and even rare cases of enterochromaffin tumors. In contrast, lower jejunal neuroendocrine tumors formed a homogeneous group of enterochromaffin tumors, similar to their ileal counterparts. Our findings show that the distinction between the two groups is of prognostic value. Upper jejunal neuroendocrine tumors, despite their heterogeneity, are associated with a better prognosis than lower jejunal tumors; in our retrospective series, the difference in overall median survival was statistically significant.

In conclusion, our study confirms the rarity and heterogeneity of jejunal neuroendocrine neoplasms. Our data lend strong support to the distinction between upper jejunal neoplasms, on one hand, and lower jejunal neoplasms, on the other hand, as proposed by recent histopathological classifications.

Conflict of interest We declare that we have no conflict of interest.

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