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# Survival of patients managed in France for duodenal neuroendocrine tumors (D-NET): a 20-year multicenter cohort study from the GTE group: a cohort study

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**Introduction:** Duodenal neuroendocrine tumours (D-NETs) have a low incidence; however, their diagnosis has been increasing. Features such as tumour location, size, type, histological grade, and stage were used to adapt the treatment to either endoscopic (ER) or surgical (SR) resections. There is no consensus regarding the definitive treatment. The authors' study aimed to describe the management of non-metastatic, well-differentiated D-NETs in France and its impact on patient survival.

**Methods:** A registry-based multicenter study using prospectively collected data between 2000 and 2019, including all patients managed for non-metastatic G1 and G2 D-NETs, was conducted in the GTE group.

**Results:** A total of 153 patients were included. Fifty-eight benefited from an ER, and 95 had an SR. No difference in recurrence-free survival (RFS) was observed regardless of treatment type. There was no significant difference between the two groups (ER vs. SR) in terms of location, size, grade, or lymphadenopathy, regardless of the type of incomplete resection performed or regarding the pre-therapeutic assessment of lymph node invasion in imaging. The surgery allowed for significantly more complete resection (patients with R1 resection in the SR group: 9 vs. 14 in the ER group,  $P < 0.001$ ). Among the 51 patients with positive lymph node dissection after SR, tumour size was less than or equal to 1 cm in 25 cases. Surgical complications were more numerous ( $P = 0.001$ ). In the subgroup analysis of G1–G2 D-NETs between 11 and 19 mm, there was no significant difference in grade ( $P = 0.977$ ) and location ( $P = 0.617$ ) between the two groups (ER vs. SR). No significant difference was found in both morphological and functional imaging, focusing on the pre-therapeutic assessment of lymph node invasion ( $P = 0.387$ ).

**Conclusion:** Regardless of the resection type (ER or SR) of G1–G2 non-metastatic D-NETs, as well as the type of management of incomplete resection, which was greater in the ER group, long-term survival results were similar between ER and SR. Organ preservation seems to be the best choice owing to the slow evolution of these tumours.

**Keywords:** duodenal neuroendocrine tumours (D-NET), France, management, survival

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## Introduction

Well-differentiated duodenal neuroendocrine tumours (D-NETs) are rare and are often found incidentally. NETs constitute part of around 2% of all the NETs. Over the last few decades, their prevalence has increased following improvements in diagnostic methods, modifications of histological classifications, improved knowledge of them, and systematic recording in national registers. Currently, the NET incidence is higher in localized and low-grade tumours than in metastatic tumours. Therapeutic management of D-NET depends on localization, size, tumour grade, tumour wall invasiveness, node involvement, presence or absence of genetic disorders, and functional status.

Their definitive treatment is non-consensual. According to the latest European Guidelines, ENETS management for G1–G2 D-NETs less than 1 cm, greater than or equal to 2 cm, or metastatic ones is well codified<sup>[1]</sup>. D-NETs greater than or equal to 2 cm are at greater risk of metastatic spread<sup>[2]</sup>, thus requiring surgical resection (SR)<sup>[3]</sup>. Similarly, the specific location of peri-ampullary tumours tends to be of an intermediate grade or poor differentiation, and therefore, they have a worse prognosis, calling for SR<sup>[4]</sup>. Endoscopic resection (ER) is indicated for D-NETs that are less than or equal to 1 cm, non-functional, and without locoregional or distant invasion<sup>[5–7]</sup>.

However, the debate persists for D-NETs between 11 and 19 mm in size. ER exposes the risk of incomplete resection (IR) and prevents lymph node dissection (LND). The completeness of excision depends on the endoscopic technique used. Endoscopic submucosal dissection (ESD) enables better quality resection; however, this procedure exposes a higher risk of perforation and, therefore, should be reserved for trained teams<sup>[8,9]</sup>. In addition, it is uncertain whether positive resection margins directly lead to an increased risk of disease recurrence<sup>[10]</sup>. Conversely, patients with sterile specimens after new ER for IR may subsequently present with lymph node metastases (LNM)<sup>[5]</sup>, emphasizing the controversial prognostic importance of LNM, according to some authors<sup>[11–13]</sup>.

Thus, the management is diverse, with more or less invasive procedures ranging from simple ER to cephalic duodenopancreatectomy (CDP, Whipple procedure). The main objective of our study was to describe the management of non-metastatic G1–G2 D-NETs in France and patient outcomes in terms of overall survival (OS) and recurrence-free survival (RFS).

## Material and methods

### Study design

A French multicenter retrospective study was conducted between the 5 February 2021 and the 3 July 3, 2021, regarding the management of patients diagnosed with a D-NET within 14 centres of the GTE group between 2000 and 2019.

### Patients

The inclusion criteria were patients with duodenal tumours, including ampullary, NET (s), and non-metastatic (s).

Patients with metastatic, grade 3 NETs, poorly differentiated neuroendocrine carcinomas, mixed neuroendocrine and non-neuroendocrine lesions (MiNEN), and patients with a genetic predisposition, such as Multiple Endocrine Neoplasia Type 1 (MEN1) and neurofibromatosis type 1 (NF1), were excluded.

## HIGHLIGHTS

- Therapeutic management of G1–G2 duodenal neuroendocrine tumours (D-NETs) requires consideration of tumour size, grade, and distant dissemination.
- Regional lymph node invasion does not seem to be a poor prognostic factor and questions its specific role in D-NET.
- Prospective studies with systematic functional and structural imaging are necessary to underline the oncological importance of lymph nodes and adapt therapeutic management to patients' comorbidities.
- Regarding D-NETs between 11 and 19 mm, it seems that endoscopic resection should be chosen first if these tumours are G1–G2 without regional lymph node invasion present at the preoperative imaging assessment.

### Data collection

Clinical, biological, and radiological data were collected prospectively at the time of diagnosis. The use of somatostatin analogues or proton pump inhibitors has also been reported. The presence of regional lymph nodes (periduodenal-pancreatic, pyloric, and hepatic) on endoscopy or imaging was studied. The accumulation of a radiotracer on octreoscan, PET-68Ga-DOTATOC, and PET-18-FDG was collected.

The WHO 2019 and TNM 2017 classifications were used to classify the tumour grade and stage, respectively.

The work has been reported in line with the STROCSS criteria<sup>[14]</sup>.

### Therapeutic management

ER was performed using endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic ampullectomy, or a full-thickness resection device (FTRD).

SR consisted of wedge duodenal resection, cephalic duodenopancreatectomy (CDP), antrectomy, surgical ampullectomy, or duodenal resection combined with other resections.

Additional endoscopic or surgical treatment could be offered if the initial treatment is not optimal (microscopic or macroscopic invasion at histology analysis: R1/R2).

Endoscopic and surgical complications arising during the initial treatment were noted. Complications were classified according to their onset time: strictly less than 1 month from treatment, and they were recorded as “early”; or “late” if it was greater than or equal to 1 month. Surgical complications were classified according to the Clavien–Dindo classification.

### Follow-up

Follow-up started with the first endoscopic or surgical resection.

A recurrence was defined thanks to the histological results of endoscopic or surgical specimens (and not imaging results since resections were not done in the same centre as the follow-up) taken during the follow-up.

The main criterion of analysis was the OS of patients managed for D-NET according to their therapeutic management, either ER or SR.

### Statistical analyses

Statistical analyses were performed using the Stata 11 software. The significance level for all statistical analyses was set

at  $P$  less than 0.05. The data were described as numbers and percentages (%) for qualitative variables or medians with interquartile ranges for quantitative variables. Pearson's  $\chi^2$  test (or Fisher's test if the size was less than 5) was used to compare qualitative variables, and the Wilcoxon–Mann–Whitney nonparametric test was used to compare quantitative variables between the two groups. OS and RFS were estimated using the Kaplan–Meier model. A log-rank test was used to compare RFS between the two groups.

Ethics

This was a non-interventional retrospective study in which the collection of patients' non-opposition to the analysis of their medical data was performed. This approach has been validated by the ethics committee and registered under number 461-2021-117.

Results

In total, 110 patients were excluded from the study. In total, 153 patients were included (flowchart. Fig. 1) and the median follow-up was 40.6 months (1–237 months).

Patients' characteristics

Patient characteristics are described in Table 1. The median age of the cohort was 62 years, which included more than 50% of males, approximately 50% of incidental tumours, and bulb localization. One-third of tumours were in the Ampulla or peri-ampulla region, two-third of them were removed surgically.

Significant differences were found between the two techniques in terms of tumour localization, size, resection margins, TNM stages, and complications but not in terms of tumour grade (Table 1). Functional tumours and tumours with a size greater than 11 mm were significantly more removed surgically.

Impact of lymph node invasion in the SR group of patients who had a lymph node analysis

Fifty-one patients (53.6%) underwent a positive lymph node dissection. Among these, ~50% had a tumour size less than 10 mm. Moreover, at the initial workup with structural body imaging, 14 patients out of 51 (27%) had a positive lymph node: 10 with TDM, 4 on EUS, and 7 with both exams (Table 2).

Post-procedure complications after endoscopic or surgical resection

Complications were more frequent after SR than after ER, 6 (13.0%) versus 40 (42.1%) ( $P=0.001$ ). The most common endoscopic complications were perforation and bleeding. These were most often early (83.3%). The most frequent surgical complications included bleeding, pancreatic and biliary leaks, gastroparesis, and, which were most often early (within 30 days postoperatively) (77.5%). Among surgical complications, 18.4% were classified as grade 1 and 44.7% as grade 2 according to Clavien–Dindo classification.

A comparison of patients who presented with complications according to either ER or SR did not show any differences in tumour localization (including ampulla or peri-ampulla region), grade, or size. However, the presence of a positive lymph node on initial imaging was significantly greater in the SR group (Table 3).

Cases of patients with initial R1 or Rx specimens

33 patients out of 58 (%) in the ER group presented with an incomplete resection margin (R1) or undefined margin (Rx), whereas in the SR group, they represented 14 patients out of 95 (%). Patients with an incomplete resection margin (R1) or undefined margin (Rx) were placed under surveillance more if they were first treated surgically, contrary to those with endoscopy, where a secondary treatment was proposed most of the time (Table 4).

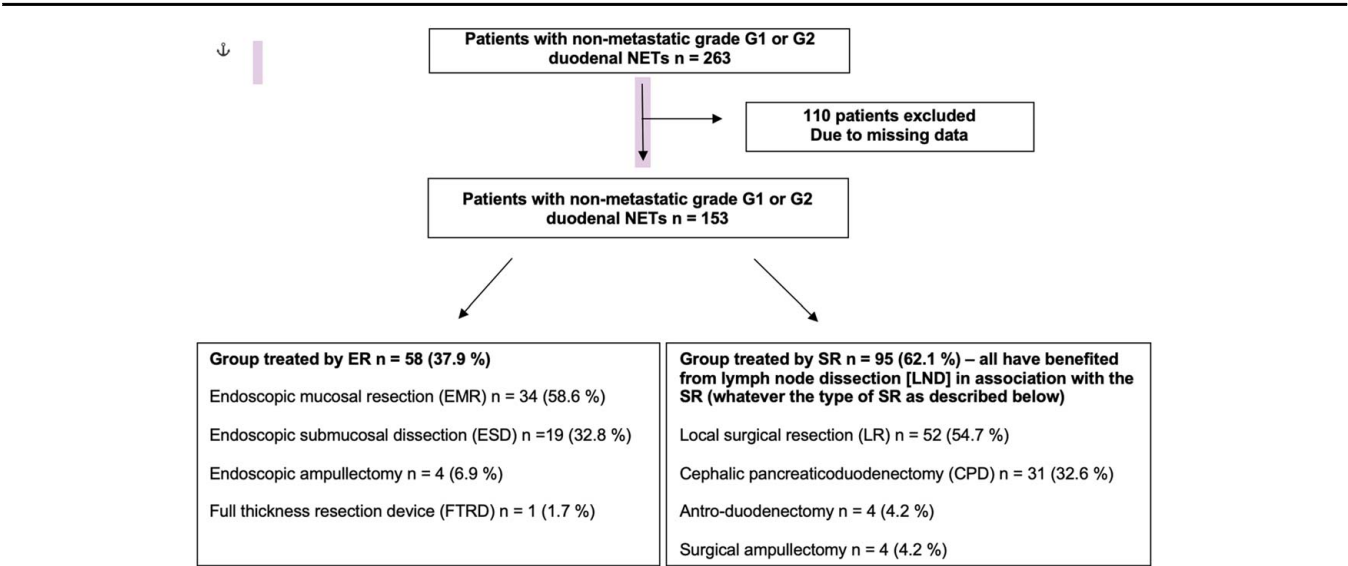


Figure 1. Flowchart. ER, endoscopic resection; SR, surgical resection.

### Patients' characteristics.

Bold values are Statistical significance of *p* value.  
max, maximum; min, minimum; NA, non-applicable analysis.

There was no significant difference in recurrence-free survival between the two groups: either surgical or endoscopic resection (Fig. 2) (Table 5).

There was no significant difference in the grade ( $P=0.977$ ) or location (including ampulla or peri-ampulla region) ( $P=0.617$ ) between the two groups (ER vs. SR). There was also no significant difference in the pre-therapeutic assessment of lymph node invasion [computed tomography (CT) scan and/or endoscopy] ( $P=0.387$ ) between the two groups. More than 50% of patients with SR had pathological lymph node invasion. There was a

### Pre-operative assessment of lymph node invasion.

CT, computed tomography; EUS, endoscopic ultrasound.

## Discussion

The comparison between the two types of resection (SR and ER) showed differences in terms of tumour localization, size, and TNM stage. This was in accordance with the guidelines for therapeutic management<sup>[1,18]</sup>. For example, surgical management

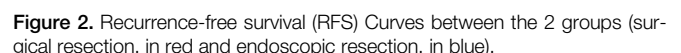
**Analysis of potential complications factors according to the type of resection: tumours' characteristics for patients with complications after either initial ER or SR.**

CT, computed tomography; ER, endoscopic resection; EUS, endoscopic ultrasound; SR, surgical resection.

### Management and follow-up of patients with incomplete or undefined margins after first resection.

ER, endoscopic resection; NA, not applicable; SR, surgical resection.

In the surgical group, higher complication rates were observed, similar to the findings of Margonis and colleagues. The presence of lymph nodes on pre-therapeutic imaging was associated with the risk of surgical complications ( $P=0.017$ ). The presence of an LNM may lead to difficulties during dissection. This finding implies that SR in our cohort was most often due to the presence of lymph nodes. More precisely, it was structural imaging alone





**Table 5**  
**Analysis of survival: OS and RFS between the two groups.**

	ER group (n = 58)	SR group (n = 95)	P
Median OS	Non reached <sup>a</sup>	7 years	NA
Median RFS	3.2 years	1.2 years	0.709

ER, endoscopic resection; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; SR, surgical resection

<sup>a</sup>No death.

which seemed to point to the presence of lymph nodes, as functional imaging only fixed tumour tissue and not lymph nodes. However, among patients with a positive lymph node dissection, 49.0% had a size of less than or equal to 1 cm, which is in contradiction with some studies describing LNM more commonly in tumours greater than 1.5 cm<sup>[13]</sup>. Overall, we can

**Table 6**  
**Patients' characteristics with D-NET sized between 11 and 19 mm according to the type of resection.**

Characteristics	Patients with ER n = 13, n (%)	Patients with SR n = 28, n (%)	P
Stage cTNM before any treatment			
Local stage uT2 (n = 15)	7 (53.8)	8 (28.6)	1.000
Missing data	6	20	
Presence of lymph node at initial imaging (CT scan and/or echo-endoscopy) (n = 8)	1 (7.7)	7 (25)	0.387
Missing data	2	4	
Stage pTNM after treatment (n = 27)			<b>0.003</b>
Stage I	13 (100)	12 (44.4)	
Stage II	0	1 (3.7)	
Stage III	0	14 (51.9)	
Missing data	0	1	
Grade			0.977
G1	12 (92.3)	25 (89.3)	
G2	1 (7.7)	3 (10.7)	
Functional secretion	0	9 (32.1)	<b>0.038</b>
Localization (n = 27)			0.617
Bulb	6 (46.2)	12 (44.4)	
Ampulla or peri-ampullary	6 (46.2)	11 (40.8)	
Duodenal D3/D4	0	3 (11.1)	
Multifocal	1 (7.7)	1 (3.7)	
Missing data	0	1	
Resection margins			NA
R0	6 (46.2)	26 (92.9)	
R1	2 (15.4)	2 (7.1)	
R2	0	0	
Undefined margins	5 (38.5)	0	
Lymph node resection (n = 25)			NA
Performed	NA	25 (92.6)	
Positive	NA	14 (51.9)	
Missing data	NA	1	
Theoretical indication of complementary treatment (n = 9)	7 (53.8)	2 (7.1)	NA
Surveillance	2 (28.6)	2 (100)	
New endoscopy	0	0	
New surgery	5 (71.4)	0	
Residual tumour (n = 5)	4 (80)	0	<b>0.007</b>

Bold values are Statistical significance of p value.

CT, computed tomography; D-NET, duodenal neuroendocrine tumour; ER, endoscopic resection; NA, not applicable; SR, surgical resection.

wonder if regional lymph nodes have to be taken into account for SR indication, especially for extended SR. It is worth noting that only 76% of the cohort had functional imaging, but this finding follows the timing of the study and the technological advances over time. Thus, a prospective analysis encompassing systematic functional imaging must be conducted to confirm our findings regarding the importance of lymph node invasion.

We were not able to undertake survival analysis in subgroups of D-NETs, such as R1 tumours or those between 11 and 19 mm, due to the low number of patients. For the latter group of tumours sized between 11 and 19 mm, it is difficult to conclude the importance of lymph nodes due to their low number at initial structural imaging (especially in the ER group: only one patient). However, it seems that ER may be considered in the first instance if lymph nodes are not found in the imaging, whereas if present, as the prognosis is good with a median OS of 41 months, SR may be performed but as limited as possible, especially for frail and elderly patients.

### Limitations

This was a retrospective study with specific bias. All the choices were discussed in the local endocrine/digestive MDT, but not specifically in the RENATEN MDT, which is a national French-specific MDT for such pathologies. Recurrences were only defined by histological assessment and not by imaging, as this latter was performed most of the time in centres different from the one where ER or SR was initially performed. In addition, the follow-up was not sufficient (median follow-up: 40.6 months), as these tumours are at slow evolution. Finally, these tumours are rare, and the low number of patients within our cohort made it difficult to conduct a propensity score analysis to avoid confusion.

### Strengths

Despite the low incidence of D-NET, our study encompassed 14 French centres with a cohort size that was not insignificant (most recent study: 102 in the UK cohort of Mandair and colleagues. All of these centres are part of the French GTE group (Endocrine Tumour Group), which encompasses specialized gastroenterologists, anatomical pathologists, and surgeons in the field of neuroendocrine tumours with updated management of such diseases.

### Conclusion

Therapeutic management of G1–G2 D-NETs requires consideration of tumour size, grade, and distant dissemination. Regional lymph node invasion does not seem to be a poor prognostic factor and questions its specific role in D-NET. Prospective studies with systematic functional and structural imaging are necessary to underline the oncological importance of lymph nodes and adapt therapeutic management to patients' comorbidities. Moreover, it is worth noticing the development of endoscopic resections: the feasibility and expertise of such procedures need to be assessed in each centre before using it in clinical routine. Regarding D-NETs between 11 and 19 mm, it seems that ER should be chosen first if these tumours are G1–G2 without regional lymph node invasion present at the preoperative imaging assessment, whatever their location (including ampulla or peri-ampulla regions).

## Human and animal rights

This article does not contain any animal studies performed by any of the authors.

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### Author contribution

N.C. conceived and designed the study. M.M.B.H. acquired the data. N.C. and M.M.B.H. analyzed the data. M.M.B.H., M.M. and N.C. interpreted data. M.M.B.H., M.M., D.L., d.M.L., L.D., W.T., P.M., C.G., G.B., P.M., L.A., C.R., V.S., G.R., C.N., B.-O.O., B.G., S.D., L.S., H.S., J.C., T.M.P., T.J., F.A., E.C. contributed to writing the manuscript and its critical revision. M.M.B.H., M.M., N.C., D.L., d.M.L., L.D., W.T., P.M., C.G., G.B., P.M., L.A., C.R., V.S., G.R., C.N., B.-O.O., B.G., S.D., L.S., H.S., J.C., T.M.P., T.J., F.A., E.C. approved the final version of this manuscript.

**Research registration unique identifying number (UIN)**

Our research has been registered through <https://www.researchregistry.com/> Under research registry UIN : researchregistry9779.

**Guarantor**

N. Christou.

## Data availability statement

Data are available upon reasonable request. Patients were informed that their medical data were anonymized. The data were stored in a specialized data bank within the coordinator University Hospital, protected against network intrusion.

## Provenance and peer review

Not commissioned, externally peer-reviewed.