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Chemotherapy in resected neuroendocrine carcinomas of the digestive tract: a national study from the French Group of Endocrine Tumours (GTE)

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Short title: Chemotherapy in digestive neuroendocrine carcinomas

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ABSTRACT

Background. Neuroendocrine carcinomas of the digestive tract are rare and aggressive tumours. In localised disease, the treatment is surgery. Based on expert consensus, international guidelines recommend the administration of adjuvant chemotherapy combining etoposide and platinum salts, justified by the high risk of metastatic relapse. However, no clinical study has proven the benefit of neoadjuvant or adjuvant chemotherapy.

Objectives. We aimed to evaluate their effect in this indication.

Methods. We performed a retrospective observational French study to evaluate overall and disease-free survivals, prognostic factors for survival and chemotherapy toxicity.

Results. Seventy-three patients had surgical resection of a localised digestive neuroendocrine carcinoma between 2000 and 2016. The majority of patients presented colorectal (35%) tumours and median Ki-67 value was 70%. Forty-three patients received chemotherapy, either perioperative (neoadjuvant ± adjuvant) or adjuvant. Median overall and disease-free survivals for the whole population were 24 and 9 months, respectively. Median overall and disease-free survivals for patients receiving chemotherapy were 62 and 13 months, respectively. Positive postoperative node status and Ki-67≥ 80% had a negative prognostic impact on overall and disease-free survivals. Administration of chemotherapy had a positive prognostic impact on overall and disease-free survivals. Sixteen grade 3/4 toxicities were reported without toxic death.

Conclusions. Our results suggest a positive effect on survival of chemotherapy in resected digestive neuroendocrine carcinomas, but further studies are needed to confirm these results.

69 **INTRODUCTION**

70 Neuroendocrine neoplasms (NEN) of the digestive tract are rare tumours with a rising
71 incidence due to their better identification [1–3]. They are classified according to their
72 differentiation and proliferation rate (mitotic count and Ki-67 index) and divided in 3 grades
73 (G): G1 and G2 tumours (Ki-67≤20%) and G3 (Ki-67>20%) [4]. The WHO classification has
74 recently been updated for pancreatic NEN integrating a new entity of G3 well differentiated
75 tumours, or NET-G3 [5–8]. Therefore, the term of neuroendocrine carcinoma (NEC) only
76 applies to G3 poorly differentiated tumours [8].
77 Among NEN of the digestive tract, about 15% are NEC with values varying from 7 to 21%
78 depending on studies [1,2,9]. NEC represent the most aggressive subgroup, accounting for 80
79 % of all G3 NEN and are often diagnosed at a metastatic state [9]. Median overall survival
80 (OS) is about 34 months for patients with a localised disease [1,10,11] and 5 months for
81 patients with metastatic disease [10–12]. The majority of therapeutic guidelines for NEC
82 derive from studies in small cell lung cancer (SCLC), which is the closest tumour entity [13–
83 15]. Few retrospective clinical studies have focused on the therapeutic management of
84 localised and resectable NEC of the digestive tract and the role of neoadjuvant or adjuvant
85 chemotherapy is not well known [13]. For localised NEC, international guidelines
86 recommend surgery, followed by adjuvant systemic chemotherapy combining platinum salts
87 with etoposide (VP16) [14,16]. There are no recommendations on neoadjuvant chemotherapy.
88 Surgery is offered when tumours can be entirely resected and after performing a thoraco-
89 abdomino-pelvic computerised tomography (CT) and a positron emission tomography (PET)
90 scanner, if available, to evaluate the preoperative node status and research distant metastasis.
91 In France, adjuvant chemotherapy was proposed as an option before 2016 and is now
92 recommended based on expert consensus. Nevertheless, there are no prospective (randomised
93 or not) studies with adjuvant chemotherapy available in localised SCLC or in NEC of the

digestive tract. Trials are difficult to conduct because of the rarity and diversity of these tumours. Minor progress in therapeutic strategy and management has been made in the past 4 decades for NEC, which makes them a priority of research. This is underlined by their poor prognosis and the description of new entities such as NET-G3 or mixed neuroendocrine-non neuroendocrine neoplasms (MINEN) [8]. Moreover, these 2 entities show better prognosis and could benefit from a different therapeutic approach [6,17]. The aim of our study was to evaluate the effect of chemotherapy, perioperative (defined as neoadjuvant +/-adjuvant) or adjuvant chemotherapy, in patients operated for a localised NEC of the digestive tract.

METHODOLOGY

We conducted an observational, retrospective, multicentre, French study. Patients were recruited with the help of the expert network "*groupe des tumeurs neuroendocrines*" (GTE) and French pathology and oncology departments. Ethical approval was provided by Saint Antoine hospital's ethics committee on November 8th, 2016. Data was recovered for patients treated for NEC of the digestive tract between the 1st of January 2000 and the 31st of December 2016.

Inclusion and exclusion criteria

Patients included in the study were adults over 18 years old presenting a localised NEC of the digestive tract, surgically resected, with residual margins R0 or R1 (according to the R residual tumour classification, R1 was defined as a ≤1mm margin). We included both patients receiving chemotherapy (perioperative or adjuvant) or not. Exclusion criteria were as follows: patients with MINEN, well differentiated tumours, presence of distant metastasis at the time of diagnosis, R2 margin, non-digestive NEC.

Histology

Given the rarity of NEN and the difficulties in pathological diagnosis, a specialised French pathology network has been created in 2010 (TENpath network). Sections reviewing by an expert pathologist from the TENpath network is now recommended for difficult cases (NET-G3, MINEN, and NEC with low Ki-67 values) without delaying treatment. Interpretation by a pathologist from the TENpath network was not mandatory for inclusion in our study, even for patients treated after 2010. Similarly, a centralised review for pathology was not performed for practical purposes.

Evaluation criteria

We evaluated the overall survival (OS), defined as the time between histological diagnosis of NEC and time of death. Pathological diagnosis was made on tumour biopsies or surgical specimens. Then, we evaluated disease free survival (DFS) defined as the time between histological diagnosis of NEC and relapse or death from any cause. May 31st 2017 was the data cut off.

We performed a univariate analysis followed by a multivariate analysis in order to study the impact of 10 potential prognostic factors on OS and DFS: age, sex, administration of chemotherapy (all modalities), of adjuvant chemotherapy alone, of perioperative chemotherapy, size of cells, node status on surgical specimens (pN), Ki-67 index, initial site of NEC and surgical margin (R0 or R1). Toxicity was graduated according to the NCI-CTCAE v4, and only grades 3 and 4 toxicities were reported.

Study flow

Patients data were recovered from medical files in each centre: clinical, pathological and imaging data. Imaging exams performed to evaluate disease staging, mainly thoraco-abdomino-pelvic computed tomography (CT), were not centralized for independent review. Finally, we recovered therapeutic data and information on follow-up for each patient.

144 **Statistical analysis**

145 This study was observational and groups were not compared (chemotherapy versus no
146 chemotherapy). Time-related parameters, OS and DFS, were assessed by Kaplan-Meier
147 methods with the associate p-value of log-rank test. Values are expressed as median (range).
148 Univariate and multivariate analysis were assessed by Cox model. Kaplan-Meier curves were
149 drawn using Medcalc 18.2.1. The association between time-related parameters (OS and DFS)
150 and variables were evaluated using univariate and multivariate Cox proportional hazards
151 regression models (R survival package, R Foundation for Statistical Computing, 3.3.1-R
152 Studio). Variables with a p value <0.05 were selected as covariates for the multivariate
153 analysis. Statistical significance was defined by a p value of 0.05 or less.

154

155 **RESULTS**

156 **Patients characteristics**

157 Ninety patients from 21 medical centres in 18 French cities were screened, and 73 patients
158 were included in the final analysis. Seventeen patients were excluded: 10 patients were
159 misdiagnosed (7 patients had MINEN and 2 had well differentiated tumours; 1 patient had
160 pancreatic adenocarcinoma after reviewing of surgical specimen), 6 patients had metastatic
161 disease, and 1 patient was lost to follow-up just after surgery. Regarding the 59 patients
162 treated after 2010 in our population, 78% were diagnosed by an expert pathologist member of
163 the TEN path network because they were treated in a NEN expert centre.
164 Patients characteristics are reported in **Table 1**. Median age was 68 years old with 62% of
165 males. Regarding tumour site, 35 % of patients had colorectal NEC, 34% had pancreatic or
166 ampullary NEC and 31 % had NEC at other sites (oesophagus, stomach, anal, gall bladder).
167 The majority of patients had large cells NEC (58%) and a positive node status (pN+) after
168 surgery (62%). Median value of Ki-67 was 70% [25-100].

169 In total, 43 patients (59%) received chemotherapy and 37 (86%) received the combination of
170 platinum salts (cisplatin or carboplatin) and etoposide. Six patients (14%) received
171 fluorouracil-based chemotherapy: in neoadjuvant setting, 1 received FOLFOX and 1 received
172 capecitabine along with radiotherapy; the 4 others received capecitabine in adjuvant setting.
173 Among the 43 patients, 16 received perioperative chemotherapy (22%): 16 patients received
174 neoadjuvant chemotherapy and 8 also received adjuvant chemotherapy. Four patients also
175 received radiotherapy combined with chemotherapy in neoadjuvant setting. Twenty-seven
176 patients (37%) received adjuvant chemotherapy alone **(Supplementary Figure)**. The median
177 number of cycles of chemotherapy per patient was 4. Regarding the 30 other patients: 21
178 (70%) were not offered chemotherapy; 1 patient refused treatment and the others presented
179 surgery complications or alteration of general state.

180 **Time-related parameters**

181 With a median follow up of 48 months (0-130), median OS for all patients (n=73) was 24
182 months **(Figure 1a).** Forty-one patients died (56%). Median DFS was 9 months. **(Figure 1b)**.
183 There were 48 events (relapse or death), so an events rate for DFS of 66%. The majority of
184 patients presented metastatic relapse: hepatic (54%), bone (15%), brain (6%), often associated
185 with a local node relapse.

186 Regarding the population who received chemotherapy (all modalities), median OS and DFS
187 were 62 and 13 months respectively (**Figures 2 and 3**). Regarding the 30 patients who did not
188 receive any chemotherapy, median OS and DFS were 19 and 5 months respectively (**Figures**
189 **2 and 3**).

190 **Study of potential prognostic factors**

191 We evaluated 10 potential prognostic factors: age ≥ 68 years (median age of the population),
192 male sex, administration of chemotherapy, administration of adjuvant chemotherapy alone,
193 administration of perioperative chemotherapy, large cells NEC, positive node status on

194 surgical specimens (pN+), Ki-67 index, initial site of NEC and surgical margin (R0 or R1). In
195 univariate analysis, a postoperative positive node status (pN+) had a negative impact on both
196 OS (**Table 2**, HR=3.11, p=0.0046) and DFS (**Table 3**, HR=2.04, p=0.033). Administration of
197 chemotherapy (all modalities) had a positive impact on both OS and DFS (**Table 2**, HR=0,38,
198 and **Table 3**, HR=0,44). Administration of perioperative chemotherapy (n=16) and adjuvant
199 chemotherapy (n=27) also had a positive impact on OS and DFS compared to no
200 chemotherapy (n=30). For Ki-67 we used 3 thresholds for evaluation: 55%, 70% and 80%.
201 We did not find any impact on OS whichever the threshold used while Ki-67 ≥80% had a
202 negative impact on DFS (p=0.026). Age, sex, large cells and R1 resection margin had no
203 impact on survival. The initial tumour site did not show impact on survival either.
204 In multivariate analysis **(Tables 2 and 3)**, Ki-67≥80%, positive node status on surgical
205 specimens (pN+) and administration of chemotherapy (all modalities, n=43) were
206 independent prognostic factors on OS and DFS. Administration of chemotherapy showed a
207 positive impact on survival for both OS and DFS (aHR=0,32 p=0.00055 and aHR=0,36,
208 p=0.00099) while Ki-67≥80% and pN+ were poor prognostic factors.
209 Analysis was also performed after exclusion of the 6 patients who had received fluorouracil-
210 based chemotherapy. In multivariate analysis, administration of chemotherapy showed a
211 positive impact on survival for both OS and DFS (p=0,0032 and p=0,0039).

212 **Toxicity**

213 There were no toxic deaths in our study. We reported 16 grades 3 and 4 toxicities for the 43
214 patients who received chemotherapy (**Supplementary table**) excluding alopecia. Neutropenia
215 was the most common toxicity. We also observed 3 deaths within the month following
216 surgery for patients with pancreatic NEC (2 cephalic duodenopancreatectomies and 1
217 splenopancreatectomy).

218

219 **DISCUSSION**

220 In this retrospective study of resected NEC of the digestive tract, administration of
221 chemotherapy (all modalities) showed better prognosis for OS and DFS. For the whole
222 population, median OS and DFS were 24 and 9 months respectively. There were no toxic
223 deaths with chemotherapy.

224 This study is one of the largest observational cohort of resected digestive NEC and only a few
225 retrospective studies have been conducted [18,19]. Conducting studies on these tumours is
226 difficult because of their rarity and their diversity, but also because of the recent description
227 of the new histological entity of well differentiated tumours of grade 3, bearing better
228 prognosis, that must be separated from NEC. European and French guidelines recommend the
229 administration of an adjuvant chemotherapy, by analogy with SCLC, despite a lack of proof
230 of efficacy, and in relation with the bad prognosis of NEC of the digestive tract [7]. To our
231 knowledge, this work is the first focusing on the role of perioperative or adjuvant
232 chemotherapy in resected NEC and no clinical prospective study has ever been conducted
233 comparing adjuvant and perioperative chemotherapy with surgery to surgery alone.

234 Our study was retrospective, which is an important limitation. Also, we had to include
235 patients treated over 16 years, time during which pathological classifications have evolved.
236 We did not perform a centralised review for histology and Ki-67, therefore creating a risk of
237 bias in interpretation. Nevertheless, the majority of patients treated after 2010 in our
238 population were diagnosed by an expert pathologist member of the TENpath network,
239 because they were treated in a NEN expert centre. This illustrates the centralised therapeutic
240 management of these tumours in France. Platinum salts and etoposide have been used in these
241 tumours for more than 20 years without new combinations emerging as a new standard. One
242 phase III clinical trial in extensive SCLC found no difference in survival with the association
243 of cisplatin and irinotecan compared to etoposide and platinum salts [20]. The combination of

244 cisplatin and irinotecan can be administered as first line treatment in extensive SCLC in Japan
245 [20,21]. In our work, 6 patients did not receive the recommended regimen of platinum salts
246 and etoposide, with heterogeneous dose and schedule of platinum salts and etoposide. Also,
247 the decision to administer chemotherapy depended on patient's general condition, which
248 creates a selection bias. Finally, data on post-operative performance status was lacking in our
249 work.
250 Poorly differentiated neuroendocrine tumours, such as SCLC and NEC of the digestive tract,
251 are chemosensitive to etoposide and cisplatin combination with overall responses ranging
252 from 40% to 67% [22,23]. This effect is however temporary and patients rapidly progress,
253 often at a distant site, underlining the spreading potential of these tumours. In our population,
254 66% of patients relapsed with a majority of hepatic or node metastases. Recent data were also
255 obtained by the *poorly differentiated neuroendocrine carcinoma* (CEPD) French cohort in
256 which 39% of 25 patients with operated NEC had relapsed [23].
257 A review from 1997 on localised small cells NEC of the oesophagus showed higher survival
258 for patients treated with a combined treatment of surgery and chemotherapy vs surgery alone
259 (median OS of 20 months vs 5 months respectively, $p<0.001$) [24]. The types and protocols of
260 chemotherapy were not described in this study. In Haugvik's work [25], all patients operated
261 for pancreatic NEC had received adjuvant chemotherapy; median OS was 24 months, which
262 is similar to our result. Without consensual recommendations, the therapeutic strategy was
263 heterogeneous in clinical practice. The administration of neoadjuvant chemotherapy could
264 help select patients with less aggressive tumours who could benefit from surgery, like the
265 strategy adopted for borderline and locally advanced pancreatic adenocarcinomas. However,
266 the proportion of patients showing progressive disease during neoadjuvant chemotherapy was
267 not evaluated. For now, little data is available on neoadjuvant and/or perioperative

268 chemotherapy in NEC and its administration is not recommended by guidelines (it is only an
269 option in French recommendations).
270 Regarding other prognostic factors, we found that a positive nodal status (pN+) was a
271 pejorative factor for both OS and DFS. Current guidelines do not take this factor into account
272 for the therapeutic decision. French guidelines have changed and now recommend, when
273 available, the performance of a PET-^{18}FDG-CT before surgery in order to improve the
274 detection of preoperative node involvement and/or distant metastases. We did not report the
275 number of patients with a PET-^{18}FDG-CT before surgery in our work. We did not find any
276 impact on survival with a threshold of 55%. In the NORDIC study, patients with a Ki-
277 67<55% showed lower response rate to chemotherapy combining etoposide and platinum
278 salts but better OS (14 months versus 10 months) [12]. On the contrary, in Haugvik's work
279 [25], a Ki-67 55% threshold did not show any impact on survival in the 28 patients who
280 underwent surgery for pancreatic NEC. The NORDIC study included patients with metastatic
281 and localised NEC regardless of their histological differentiation status, which might explain
282 this difference. In addition to the Ki-67 threshold, recent studies in colon and other locations
283 suggested that the tumour molecular profile may help to adapt chemotherapy regimen in
284 patients with NEC. A subgroup of NEC are genetically closely related to adenocarcinomas
285 and better respond to chemotherapies used for exocrine tumours [26,27].These genetic tests
286 were not possible to perform in our study.
287 Initial site of NEC was not a prognostic factor in our study, as in the CEPD cohort [24]. One
288 retrospective study found that exclusive administration of chemotherapy or
289 radiochemotherapy were associated with a similar survival than surgery in a small population
290 of localised anorectal NEC [28].
291 In conclusion, our work suggests a positive prognostic impact of adjuvant or perioperative
292 chemotherapy on survival, for patients operated for a localised NEC. Patients treated for NEC

293 of the digestive tract should be rigorously selected before surgery and some patients might
294 benefit from an alternative treatment such as radiochemotherapy. This underlines the need for
295 prospective studies comparing these therapeutic strategies in different sites of NEC. We plan
296 to conduct a prospective cohort of localised NEC of the digestive tract evaluating the role of
297 neoadjuvant chemotherapy, followed by surgery or radiochemotherapy, or adjuvant
298 chemotherapy in case of surgery first.
299

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303

304 **STATEMENT OF ETHICS**

305 Ethical approval was provided by Saint Antoine hospital's ethics committee on November
306 8th, 2016. The authors have no ethical conflicts to disclose?

307
308 **DECLARATIONS OF INTEREST**

309 The authors declare no following competing interests for this work
310

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314

315 **AUTHOR CONTRIBUTIONS**

316 The project was initiated by Pr Thierry André, Dr Pauline Afchain and Dr Anna Pellat.

The main part of data was provided by Dr Anna Pellat, Pr Thomas Walter, Dr Vincent Hautefeuille, Dr Olivia Hentic, Dr Christine Do Cao, Pr Astrid Lievre, Dr Olivier Dubreuil, Pr Romain Coriat, and Pr Eric Baudin.

Statistics were done by Dr Jérémy Augustin.

The article was written by Dr Anna Pellat.

It was reviewed by Pr Thierry André, Dr Pauline Afchain, Pr Thomas Walter, Dr Vincent Hautefeuille, Dr Olivia Hentic, Pr Pascal Hammel, Dr Jérémy Augustin, Dr Romain Cohen, Pr Anne Couvelard and Pr Magali Svrcek.

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417 # FIGURE LEGENDS

418 **Figure 1.** Overall survival and disease-free survivals of the whole population (73 patients)

419 **Figure 2.** Overall survivals according to chemotherapy administration

420 **Figure 3.** Disease-free survivals according to chemotherapy administration