Chemotherapy in resected neuroendocrine carcinomas of the digestive

Anna Pellat, Thomas Walter, Jeremy Augustin, Vincent Hautefeuille, Olivia Hentic, Christine Do cao, Astrid Lièvre, Romain Coriat, Pascal Hammel, Olivier Dubreuil, et al.

► To cite this version:

Anna Pellat, Thomas Walter, Jeremy Augustin, Vincent Hautefeuille, Olivia Hentic, et al.. Chemotherapy in resected neuroendocrine carcinomas of the digestive. *Neuroendocrinology*, 2020, 110 (5), pp.404-412. 10.1159/000502825 . hal-02996214

HAL Id: hal-02996214

<https://hal.sorbonne-universite.fr/hal-02996214>

Submitted on 9 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Anna Pellat ¹⁻², Thomas Walter ³, Augustin Jérémy ⁴, Vincent Hautefeuille ⁵, Olivia Hentic ⁶, Christine Do Cao ⁷, Astrid Lievre ⁸, Romain Coriat ⁹, Pascal Hammel ¹⁰, Olivier Dubreuil ¹¹, Romain Cohen ¹⁻², Anne Couvelard ¹², Thierry André ¹⁻², Magali Svrcek ¹³⁻², Eric Baudin ¹⁴, Pauline Afchain ¹⁻²

¹ Medical oncology department, Saint Antoine hospital, Paris, France

² Sorbonne Université, Paris, France

³ Medical oncology department, Edouard Herriot hospital, Lyon, France

⁴ Pathology department, La Pitié Salpêtrière hospital, Paris, France

⁵ Gastroenterology and Digestive Oncology department, Amiens University Hospital, Amiens, France

⁶ Gastroenterology and pancreatology department, Beaujon hospital, Clichy, France

⁷ Endocrinology department, CHU of Lille, Lille France

⁸ Gastro enterology department, CHU of Rennes, Rennes, France; Rennes 1 University, Rennes, France

⁹ Gastro enterology and digestive oncology, Cochin hospital, Paris, France

¹⁰ Digestive oncology department, Beaujon hospital, Clichy, France

¹¹ Gastro enterology and digestive oncology, La Pitié Salpêtrière hospital, Paris France

¹² Pathology department, Bichat hospital and University Paris Diderot, Paris, France

¹³ Pathology department, Saint Antoine hospital, Paris, France

¹⁴ Endocrinology department, Institut Gustave Roussy, Villejuif, France

Short title: Chemotherapy in digestive neuroendocrine carcinomas

Corresponding author:

Dr Anna Pellat, MD

[Medical oncology department, Saint Antoine hospital
184 rue du Faubourg Saint Antoine, 75012, Paris, France](#)

Tel: +33149282345

Fax: +33149283498

anna.pellat@aphp.fr

Keywords: chemotherapy, neuroendocrine carcinomas, ki-67 index

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 $\pm$ 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 $\geq$ 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.

INTRODUCTION

Neuroendocrine neoplasms (NEN) of the digestive tract are rare tumours with a rising incidence due to their better identification [1–3]. They are classified according to their differentiation and proliferation rate (mitotic count and Ki-67 index) and divided in 3 grades (G): G1 and G2 tumours ($Ki-67 \leq 20\%$) and G3 ($Ki-67 > 20\%$) [4]. The WHO classification has recently been updated for pancreatic NEN integrating a new entity of G3 well differentiated tumours, or NET-G3 [5–8]. Therefore, the term of neuroendocrine carcinoma (NEC) only applies to G3 poorly differentiated tumours [8].

Among NEN of the digestive tract, about 15% are NEC with values varying from 7 to 21% depending on studies [1,2,9]. NEC represent the most aggressive subgroup, accounting for 80% of all G3 NEN and are often diagnosed at a metastatic state [9]. Median overall survival (OS) is about 34 months for patients with a localised disease [1,10,11] and 5 months for patients with metastatic disease [10–12]. The majority of therapeutic guidelines for NEC derive from studies in small cell lung cancer (SCLC), which is the closest tumour entity [13–15]. Few retrospective clinical studies have focused on the therapeutic management of localised and resectable NEC of the digestive tract and the role of neoadjuvant or adjuvant chemotherapy is not well known [13]. For localised NEC, international guidelines recommend surgery, followed by adjuvant systemic chemotherapy combining platinum salts with etoposide (VP16) [14,16]. There are no recommendations on neoadjuvant chemotherapy. Surgery is offered when tumours can be entirely resected and after performing a thoraco-abdomino-pelvic computerised tomography (CT) and a positron emission tomography (PET) scanner, if available, to evaluate the preoperative node status and research distant metastasis. In France, adjuvant chemotherapy was proposed as an option before 2016 and is now recommended based on expert consensus. Nevertheless, there are no prospective (randomised 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 ≤ 1 mm 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.

119 **Histology**

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

127 **Evaluation criteria**

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

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

139 **Study flow**

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

Statistical analysis

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

RESULTS

Patients characteristics

Ninety patients from 21 medical centres in 18 French cities were screened, and 73 patients were included in the final analysis. Seventeen patients were excluded: 10 patients were misdiagnosed (7 patients had MINEN and 2 had well differentiated tumours; 1 patient had pancreatic adenocarcinoma after reviewing of surgical specimen), 6 patients had metastatic disease, and 1 patient was lost to follow-up just after surgery. Regarding the 59 patients treated after 2010 in our population, 78% were diagnosed by an expert pathologist member of the TEN path network because they were treated in a NEN expert centre.

Patients characteristics are reported in **Table 1**. Median age was 68 years old with 62% of males. Regarding tumour site, 35 % of patients had colorectal NEC, 34% had pancreatic or ampullary NEC and 31 % had NEC at other sites (oesophagus, stomach, anal, gall bladder). The majority of patients had large cells NEC (58%) and a positive node status (pN+) after surgery (62%). Median value of Ki-67 was 70% [25-100].

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

Time-related parameters

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

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

Study of potential prognostic factors

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

surgical specimens (pN+), Ki-67 index, initial site of NEC and surgical margin (R0 or R1). In univariate analysis, a postoperative positive node status (pN+) had a negative impact on both OS (**Table 2**, HR=3.11, p=0.0046) and DFS (**Table 3**, HR=2.04, p=0.033). Administration of chemotherapy (all modalities) had a positive impact on both OS and DFS (**Table 2**, HR=0.38, and **Table 3**, HR=0.44). Administration of perioperative chemotherapy (n=16) and adjuvant chemotherapy (n=27) also had a positive impact on OS and DFS compared to no chemotherapy (n=30). For Ki-67 we used 3 thresholds for evaluation: 55%, 70% and 80%. We did not find any impact on OS whichever the threshold used while Ki-67 $\geq 80\%$ had a negative impact on DFS (p=0.026). Age, sex, large cells and R1 resection margin had no impact on survival. The initial tumour site did not show impact on survival either. In multivariate analysis (**Tables 2 and 3**), Ki-67 $\geq 80\%$, positive node status on surgical specimens (pN+) and administration of chemotherapy (all modalities, n=43) were independent prognostic factors on OS and DFS. Administration of chemotherapy showed a positive impact on survival for both OS and DFS (aHR=0.32 p=0.00055 and aHR=0.36, p=0.00099) while Ki-67 $\geq 80\%$ and pN+ were poor prognostic factors. Analysis was also performed after exclusion of the 6 patients who had received fluorouracil-based chemotherapy. In multivariate analysis, administration of chemotherapy showed a positive impact on survival for both OS and DFS (p=0.0032 and p=0.0039).

Toxicity

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

DISCUSSION

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

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

Our study was retrospective, which is an important limitation. Also, we had to include patients treated over 16 years, time during which pathological classifications have evolved.

We did not perform a centralised review for histology and Ki-67, therefore creating a risk of bias in interpretation. Nevertheless, the majority of patients treated after 2010 in our population were diagnosed by an expert pathologist member of the TENpath network, because they were treated in a NEN expert centre. This illustrates the centralised therapeutic management of these tumours in France. Platinum salts and etoposide have been used in these tumours for more than 20 years without new combinations emerging as a new standard. One phase III clinical trial in extensive SCLC found no difference in survival with the association of cisplatin and irinotecan compared to etoposide and platinum salts [20]. The combination of

cisplatin and irinotecan can be administered as first line treatment in extensive SCLC in Japan [20,21]. In our work, 6 patients did not receive the recommended regimen of platinum salts and etoposide, with heterogeneous dose and schedule of platinum salts and etoposide. Also, the decision to administer chemotherapy depended on patient's general condition, which creates a selection bias. Finally, data on post-operative performance status was lacking in our work.

Poorly differentiated neuroendocrine tumours, such as SCLC and NEC of the digestive tract, are chemosensitive to etoposide and cisplatin combination with overall responses ranging from 40% to 67% [22,23]. This effect is however temporary and patients rapidly progress, often at a distant site, underlining the spreading potential of these tumours. In our population, 66% of patients relapsed with a majority of hepatic or node metastases. Recent data were also obtained by the *poorly differentiated neuroendocrine carcinoma* (CEPD) French cohort in which 39% of 25 patients with operated NEC had relapsed [23].

A review from 1997 on localised small cells NEC of the oesophagus showed higher survival for patients treated with a combined treatment of surgery and chemotherapy vs surgery alone (median OS of 20 months vs 5 months respectively, $p < 0.001$) [24]. The types and protocols of chemotherapy were not described in this study. In Haugvik's work [25], all patients operated for pancreatic NEC had received adjuvant chemotherapy; median OS was 24 months, which is similar to our result. Without consensual recommendations, the therapeutic strategy was heterogeneous in clinical practice. The administration of neoadjuvant chemotherapy could help select patients with less aggressive tumours who could benefit from surgery, like the strategy adopted for borderline and locally advanced pancreatic adenocarcinomas. However, the proportion of patients showing progressive disease during neoadjuvant chemotherapy was 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-¹⁸FDG-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-¹⁸FDG-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

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

ACKNOWLEDGMENTS

We thank all members of the GTE for their contribution to this work, including David Tougeron and Come Lepage. We also thank Delphine Lees for editorial assistance.

STATEMENT OF ETHICS

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

DECLARATIONS OF INTEREST

The authors declare no following competing interests for this work

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

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

317 The main part of data was provided by Dr Anna Pellat, Pr Thomas Walter, Dr Vincent
318 Hautefeuille, Dr Olivia Hentic, Dr Christine Do Cao, Pr Astrid Lievre, Dr Olivier Dubreuil,
319 Pr Romain Coriat, and Pr Eric Baudin.
320 Statistics were done by Dr Jérémy Augustin.
321 The article was written by Dr Anna Pellat.
322 It was reviewed by Pr Thierry André, Dr Pauline Afchain, Pr Thomas Walter, Dr Vincent
323 Hautefeuille, Dr Olivia Hentic, Pr Pascal Hammel, Dr Jérémy Augustin, Dr Romain Cohen,
324 Pr Anne Couvelard and Pr Magali Svrcek.
325

326 REFERENCES

- 327 1 Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al.: One hundred years
328 after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in
329 35,825 cases in the United States. *J Clin Oncol* 2008;26:3063–72.
- 330 2 Korse CM, Taal BG, van Velthuysen ML, Visser O: Incidence and survival of
331 neuroendocrine tumours in the Netherlands according to histological grade: experience of
332 two decades of cancer registry. *Eur J Cancer* 2013;49:1975–83.
- 333 3 T. Walter J-YS C Lepage: Epidemiology of digestive neuroendocrine tumors with focus
334 on French data. *Hepato-Gastro* 2013;20 (2013):160–166.
- 335 4 Rindi G, Inzani F, Solcia E: Pathology of gastrointestinal disorders. *Endocrinol Metab*
336 *Clin North Am* 2010;39:713–27.
- 337 5 Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, et al.: The high-grade
338 (WHO G3) pancreatic neuroendocrine tumor category is morphologically and
339 biologically heterogenous and includes both well differentiated and poorly differentiated
340 neoplasms. *Am J Surg Pathol* 2015;39:683–90.
- 341 6 Coriat R, Walter T, Terris B, Couvelard A, Ruszniewski P: Gastroenteropancreatic Well-
342 Differentiated Grade 3 Neuroendocrine Tumors: Review and Position Statement.
343 *Oncologist* 2016; DOI: 10.1634/theoncologist.2015-0476
- 344 7 Perren A, Couvelard A, Scoazec J-Y, Costa F, Borbath I, Delle Fave G, et al.: ENETS
345 Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology:
346 Diagnosis and Prognostic Stratification. *Neuroendocrinology* 2017; DOI:
347 10.1159/000457956
- 348 8 Klöppel G: Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. *Visc*
349 *Med* 2017;33:324–330.
- 350 9 Scoazec J-Y, Couvelard A, Monges G, Guyétant S, Bisot-Locard S, Parot X, et al.:
351 Professional Practices and Diagnostic Issues in Neuroendocrine Tumour Pathology:
352 Results of a Prospective One-Year Survey among French Pathologists (the PRONET
353 Study). *Neuroendocrinology* 2017;105:67–76.
- 354 10 Dasari A, Mehta K, Byers LA, Sorbye H, Yao JC: Comparative study of lung and
355 extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database
356 analysis of 162,983 cases. *Cancer* 2017; DOI: 10.1002/cncr.31124
- 357 11 Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC: Gastroenteropancreatic high-
358 grade neuroendocrine carcinoma. *Cancer* 2014;120:2814–23.
- 359 12 Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al.: Predictive
360 and prognostic factors for treatment and survival in 305 patients with advanced
361 gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann*
362 *Oncol* 2013;24:152–60.

- 363 13 Pellat A, Wislez M, Svrcek M, Hammel P, Afchain P, Andre T: [Therapeutic
364 management of poorly differentiated neuroendocrine lung tumors and neuroendocrine
365 carcinomas of the digestive system]. *Bull Cancer* 2016; DOI:
366 10.1016/j.bulcan.2016.06.006
- 367 14 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et
368 al.: ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic
369 Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology*
370 2016;103:186–94.
- 371 15 Cicin I, Karagol H, Uzunoglu S, Uygun K, Usta U, Kocak Z, et al.: Extrapulmonary
372 small-cell carcinoma compared with small-cell lung carcinoma: a retrospective single-
373 center study. *Cancer* 2007;110:1068–76.
- 374 16 Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvolts LK: Prognostic validity of a
375 novel American Joint Committee on Cancer Staging Classification for pancreatic
376 neuroendocrine tumors. *J Clin Oncol* 2011;29:3044–9.
- 377 17 Coriat R, Terris B, Walter T: In Reply. *The Oncologist* 2017;22:359–360.
- 378 18 Smith JD, Reidy DL, Goodman KA, Shia J, Nash GM: A retrospective review of 126
379 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol*
380 2014;21:2956–62.
- 381 19 Shafqat H, Ali S, Salhab M, Olszewski AJ: Survival of patients with neuroendocrine
382 carcinoma of the colon and rectum: a population-based analysis. *Colon Rectum*
383 2015;58:294–303.
- 384 20 Lara PN Jr, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al.: Phase III
385 trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-
386 cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*
387 2009;27:2530–5.
- 388 21 Moertel CG, Kvolts LK, O’Connell MJ, Rubin J: Treatment of neuroendocrine carcinomas
389 with combined etoposide and cisplatin. Evidence of major therapeutic activity in the
390 anaplastic variants of these neoplasms. *Cancer* 1991;68:227–32.
- 391 22 Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P, Aparicio T, et al.: Treatment of
392 poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*
393 1999;81:1351–5.
- 394 23 Walter T, Tougeron D, Baudin E, Le Malicot K, Lecomte T, Malka D, et al.: Poorly
395 differentiated gastro-entero-pancreatic neuroendocrine carcinomas: Are they really
396 heterogeneous? Insights from the FFCD-GTE national cohort. *Eur J Cancer Oxf Engl*
397 1990 2017;79:158–165.
- 398 24 Casas F, Ferrer F, Farrus B, Casals J, Biete A: Primary small cell carcinoma of the
399 esophagus: a review of the literature with emphasis on therapy and prognosis. *Cancer*
400 1997;80:1366–72.
- 401 25 Haugvik S-P, Janson ET, Österlund P, Langer SW, Falk RS, Labori KJ, et al.: Surgical
402 Treatment as a Principle for Patients with High-Grade Pancreatic Neuroendocrine

403 Carcinoma: A Nordic Multicenter Comparative Study. *Ann Surg Oncol* 2016;23:1721–
404 1728.

405 26 Jesinghaus M, Konukiewitz B, Keller G, Kloor M, Steiger K, Reiche M, et al.: Colorectal
406 mixed adenoneuroendocrine carcinomas and neuroendocrine carcinomas are genetically
407 closely related to colorectal adenocarcinomas. *Mod Pathol Off J U S Can Acad Pathol Inc*
408 2017;30:610–619.

409 27 Takizawa N, Ohishi Y, Hirahashi M, Takahashi S, Nakamura K, Tanaka M, et al.:
410 Molecular characteristics of colorectal neuroendocrine carcinoma; similarities with
411 adenocarcinoma rather than neuroendocrine tumor. *Hum Pathol* 2015;46:1890–1900.

412 28 Brieu B, Lepere C, Walter T, Lecomte T, Guimbaud R, Manfredi S, et al.:
413 Radiochemotherapy Versus Surgery in Nonmetastatic Anorectal Neuroendocrine
414 Carcinoma: A Multicenter Study by the Association des Gastro-Enterologues
415 Oncologues. *Med Baltim* 2015;94:e1864.

416

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