Ann Surg Oncol
https://doi.org/10.1245/s10434-019-08049-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Surgery with Radical Intent: Is There an Indication for G3 Neuroendocrine Neoplasms?

Elettra Merola, MD, PhD[1,2,3], Anja Rinke, MD[4], Stefano Partelli, MD, PhD[5], Thomas M. Gress, MD, PhD[4], Valentina Andreasi, MD[5], Attila Kollár, MD, PhD[6], Aurel Perren, MD, PhD[7], Emanuel Christ, MD, PhD[8], Francesco Panzuto, MD, PhD[3], Andreas Pascher, MD, PhD[9,10], Henning Jann, MD[11], Ruza Arsenic, MD[12], Birgit Cremer, MD[13], Daniel Kaemmerer, MD[14], Patrizia Kump, MD[15], Rainer W. Lipp, MD[16], Abbas Agaimy, MD[17], Bertram Wiedenmann, MD, PhD[11], Massimo Falconi, MD, PhD[5], and Marianne E. Pavel, MD, PhD[2,11]

[1]Department of Gastroenterology, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy; [2]Department of Medicine 1, Division of Endocrinology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [3]Digestive and Liver Diseases Unit, Sant'Andrea Hospital, Rome, Italy; [4]Department of Gastroenterology, Endocrinology, Metabolism and Infectiology, University Hospital Marburg and Philipps University Marburg, Marburg, Germany; [5]Pancreatic Surgery Unit, Vita-Salute University, San Raffaele Hospital IRCCS, Milan, Italy; [6]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [7]Institute of Pathology, University of Bern, Bern, Switzerland; [8]Department of Endocrinology, Diabetology and Metabolism, Center of Endocrine and Neuroendocrine Tumors, University Hospital of Basel, Basel, Switzerland; [9]Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Münster, Münster, Germany; [10]Department of Surgery, Charité Universitätsmedizin, Berlin, Germany; [11]Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum and Campus Mitte, Charité Universitätsmedizin, Berlin, Germany; [12]Department of Pathology, Campus Mitte, Charité Universitätsmedizin, Berlin, Germany; [13]Department of Internal Medicine I, Center for Integrated Oncology Cologne/Bonn, University Hospital of Cologne, Cologne, Germany; [14]Department of General and Visceral Surgery, Zentralklinik Bad Berka, Bad Berka, Germany; [15]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University, Graz, Austria; [16]Division of Oncology, Department of Internal Medicine, Medical University, Graz, Austria; [17]Institute of Pathology, Friedrich-Alexander University Erlangen-Nuremberg, University Hospital, Erlangen, Germany

ABSTRACT

Background. While platinum-based chemotherapy represents the standard treatment for advanced grade 3 (G3) neuroendocrine neoplasms (NENs) according to the European Neuroendocrine Tumor Society guidelines, the role of radical-intended surgery in these patients, as well as the use of adjuvant chemotherapy, are still controversial. The aim of the present work is to describe, in a retrospective series of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) G3, the overall survival (OS) rate and risk factors for death after radical surgery. Secondary aims are the description of median recurrence-free survival (RFS) and of the role of adjuvant chemotherapy.

Patients and Methods. Multicenter analysis of a series of stage I–III GEP-NEN G3 patients receiving radical surgery (R0/R1) with/without adjuvant chemotherapy was performed.

Results. Sixty patients from eight neuroendocrine tumor (NET) referral centers, with median follow-up of 23 months (5–187 months) were evaluated. While 28.6% of cases had NET G3, 71.4% had neuroendocrine carcinoma G3 (NEC G3). The 2-year OS rate after radical

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-08049-5) contains supplementary material, which is available to authorized users.

First Received: 26 March 2019

E. Merola, MD, PhD
e-mail: elettra.merola@gmail.com

Published online: 12 November 2019

surgery was 64.5%, with a statistically significant difference in terms of Ki67 threshold (cut-off 55%, $P = 0.03$) and tumor differentiation (NEC G3 vs. NET G3, $P = 0.03$). Median RFS after radical surgery was 14 months, and 2-year RFS rate was 44.9%. Use of adjuvant chemotherapy provided no benefit in terms of either OS or RFS in this series.

Conclusions. Surgery with radical intent might represent a valid option for GEP-NEN G3 patients with locoregional disease, especially with Ki67 value $\leq$ 55%.

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are characterized as G3 in 10–20% of cases, with median OS ranging between 10 and 23 months.[1,2] Several publications describe them as a heterogeneous population, with prognosis depending on stage, proliferation index (Ki67),[3] and differentiation.[1,2,4–6] The World Health Organization (WHO) had previously established a classification (WHO 2017) distinguishing two subgroups of pancreatic NENs G3: well-differentiated neuroendocrine tumors (NET G3) versus poorly differentiated neuroendocrine carcinomas (NEC G3).[7] This distinction has been recently applied to all GEP-NENs G3 by the novel WHO 2019 classification.[8] Among NEC G3, cell morphology can further be differentiated into two subtypes: small cell and large cell NEC.

While platinum-based chemotherapy represents the standard treatment for advanced G3 cases according to the European Neuroendocrine Tumor Society (ENETS) guidelines,[9] the role of radical-intended surgery for G3 patients as well as the use of adjuvant chemotherapy are still controversial.[10–21] Data in literature are in fact scanty and derive from small series, leaving many questions unanswered.

The aim of the present work is to retrospectively analyze a series of nonmetastatic GEP-NENs G3 treated at diagnosis with radical surgery. OS was the primary endpoint, along with possible associated risk factors. Secondary aims include median RFS and RFS rates, and to investigate the role of adjuvant chemotherapy.

PATIENTS AND METHODS

Patient Selection

In this multicenter retrospective analysis, patients who fulfilled the following inclusion criteria were included: newly diagnosed sporadic GEP-NENs G3, with stage I–III disease and receiving upfront surgery with radical intent (R0–R1).

The exclusion criteria were: presence of genetic syndromes (i.e., type I multiple endocrine neoplasia, von Hippel–Lindau syndrome), tumor primary site other than GEP, G1–G2 tumors, presence of distant metastases, non-radical surgery (R2 resection), use of neoadjuvant treatment, follow-up time shorter than 6 months for alive patients and/or lack of follow-up information.

All the patients signed an informed consent for treatment. The study was approved by the scientific committee of ENETS, whilst ethical approval was waived due to the retrospective design of the study according to the regulations of the single centers.

Patients were classified according to the ENETS tumor–node–metastasis (TNM) staging system.[22,23] The definition (NEC G3 vs. NET G3) established for GEP-NENs G3 using the WHO 2019 classification[8] was applied in the present study by expert referral pathologists in each center.

After surgery, patients were followed up with imaging (CT or MRI) every 3–6 months.

Disease recurrence was determined based upon the results of all imaging tests and pathological findings obtained during the postsurgical follow-up of each patient.

OS was defined as the time between radical surgery and death or last follow-up, while RFS was calculated as the interval between radical surgery and disease recurrence or last follow-up.

Data Collection

The variables were retrospectively retrieved from paper and/or electronic patient files in different centers, collected in a shared database and analyzed focusing on: demographics (age, gender), tumor features (presence of a clinical syndrome, primary site and primary size), histological features (Ki67, differentiation, cell morphology, R status, and lymph node status and ratio), use of adjuvant chemotherapy/radiochemotherapy (if performed), survival data, disease recurrence, and first-line therapy after recurrence.

According to lymph node ratio, patients were classified into three categories: category 1 when ratio was 0; category 2 with ratio > 0 but ≤ 0.20 for pancreatic NENs (Pan-NENs), or 0.60 for other primaries; category 3 with ratio > 0.20 and 0.60 for pancreas or other sites, respectively.[24,25]

Statistical Analysis

Statistical analysis was performed using a dedicated software program (Medcalc 15.6.1, www.medcalc.be). The distribution of continuous variables is reported as median and range. Comparison between the subgroups was carried out using Fisher's exact test or the Chi squared test for noncontinuous variables, while the Mann–Whitney *U* test or Kruskal–Wallis analysis of covariance was adopted for

continuous variables. *P* value was considered as statistically significant when lower than 0.05. Survival analysis was performed according to the Kaplan–Meier method; log-rank test was used for comparison of survival curves. The Cox regression model was used to investigate a possible correlation between tumoral features and disease recurrence or death. All variables significant on univariate analysis were included in the multivariate model.

RESULTS

Patient Features

Out of 108 patients screened in eight NET referral centers, a total of 60 stage I–III patients fulfilled the inclusion criteria (Supplementary Fig. 1). Main patient and tumor features at surgery are presented in Table 1.

Primary tumor site was pancreatic in 25/60 (41.7%) cases, and colorectal in 20/60 (33.3%). Other cases included appendiceal (3/60, 5.0%), gastroesophageal (5/60, 8.4%), duodenal (2/60, 3.3%), papilla of Vater (3/60, 5.0%), or ileal (2/60, 3.3%) primary locations.

A functioning tumor was observed in only two patients: one glucagonoma and one gastrinoma.

Somatostatin receptors (SRs) were investigated pre-surgery in 28 cases (7 by Octreoscan®, 13 by ^{68}GaDOTA-PET/CT, and 8 by immunohistochemistry), and SR expression was observed in 15/28 (53.6%). The SR-positive neoplasms were pancreatic in 60.0% of cases and were mainly NET G3 ($P = 0.03$).

NET G3 neoplasm was identified in 16/56 (28.6%) cases, while 40/56 (71.4%) were NEC G3 (differentiation was unknown in 4 cases). Small cell histomorphology was shown in 14/40 (35.0%) NEC G3 patients, large cell NEC

TABLE 1 Patient features at surgery, with stratification according to treatment received

Feature	All patients ($n = 60$)	Curative surgery ($n = 40$)	Curative surgery + adjuvant therapy ($n = 20$)	*P*-value
Gender [male; *n* (%)]	28 (46.7)	19 (47.5)	9 (45.0)	0.25
Age [years; median (range)]	57 (26–81)	56.5 (31–81)	58 (26–76)	0.97
Tumor primary site				
Pancreas, *n* (%)	25 (41.7)	23 (57.5)	2 (10.0)	
Colorectal, *n* (%)	20 (33.3)	7 (17.5)	13 (65.0)	
Others, *n* (%)	15 (25.0)	10 (25.0)	5 (25.0)	< 0.01
T[22,23]				
T1, *n* (%)	6 (10.0)	3 (7.5)	3 (15.0)	0.49
T2, *n* (%)	9 (15.0)	6 (15.0)	3 (15.0)	
T3, *n* (%)	37 (61.7)	24 (60.0)	13 (65.0)	
T4, *n* (%)	8 (13.3)	7 (17.5)	1 (5.0)	
TNM staging [22,23]				
Stage I/II, *n* (%)	15 (25.0)	12 (30.0)	3 (15.0)	0.34
Stage III, *n* (%)	45 (75.0)	28 (70.0)	17 (85.0)	
Lymph node ratio*				
Ratio = 0, *n* (%)	14 (25.0)	11 (29.7)	3 (15.8)	0.09
Ratio > 0 but ≤ 0.20 (for pancreas) or 0.60 (for others), *n* (%)	30 (53.6)	16 (43.3)	14 (73.7)	
Ratio > 0.20 (for pancreas) or 0.60 (for others), *n* (%)	12 (21.4)	10 (27.0)	2 (10.5)	
R status*				
R0, *n* (%)	43 (76.8)	29 (76.3)	14 (77.8)	1.00
R1, *n* (%)	13 (23.2)	9 (23.7)	4 (22.2)	
Ki67 [%; median (range)]	54 (25–100)	50 (25–90)	75 (25–100)	< 0.01
Tumor differentiation[8]*				
NET G3, *n* (%)	16 (28.6)	15 (40.5)	1 (5.3)	< 0.01
NEC G3, *n* (%)	40 (71.4)	22 (59.5)	18 (94.7)	

*Unknown in four cases

NET neuroendocrine tumor, *NEC* neuroendocrine carcinoma

affected 14/40 (35.0%), while in 12/40 (30.0%) cell morphology could not be determined. Patient features according to tumor differentiation (NEC G3 vs. NET G3) are reported in Supplementary Table 1.

Treatment Details

Surgical procedures are summarized in Table 2. Median postoperative follow-up time was 23 months (range 5–187 months).

Adjuvant therapy was adopted in 20 (33.3%) cases (Supplementary Fig. 1), with a median of 4 chemotherapy cycles (range 2–12). Most patients receiving adjuvant treatment had a colorectal primary and a higher Ki67 value (mainly NEC G3 patients) (Table 1).

Primary Endpoint: Overall Survival

Twenty-five out of 60 (41.7%) patients had died at last follow-up, 17 (28.3%) were alive but with recurrence, and 18 (30%) were alive and still disease free.

The 2-year OS rate of the study population after first radical resection was 64.5%, with a median OS which was not reached (Fig. 1a).

A statistically significant different OS was observed according to Ki67, when the cut-off was set at 55%, and based on tumor differentiation (NEC G3 vs. NET G3) ($P = 0.03$; Fig. 1b, c).

The risk factor analysis (Table 3) showed the Ki67 value [as continuous variable, hazard ratio (HR): 1.02, confidence interval (CI): 1.00–1.04, $P = 0.01$] as a significant prognostic factor, and there was a tendency towards significance for age at surgery (as continuous variable) and tumor differentiation (NEC G3 vs. NET G3: HR 4.24, $P = 0.05$).

TABLE 2 Description of surgical procedures

Surgical procedure	$N = 60$
Pancreaticoduodenectomy	18
Abdominoperineal resection	11
Right hemicolectomy	11
Left pancreatectomy	9
Gastroesophageal resection	2
Total gastrectomy	2
Rectosigmoidal resection	1
Resection of transverse colon	1
Right hemicolectomy + ovariectomy	1
Left pancreatectomy + renal resection	1
Left pancreatectomy + adrenal resection	1
Duodenal resection	1
Partial esophagectomy	1

FIG. 1 Overall survival (OS) after radical surgery for the overall population (**a**), according to Ki67 (cut-off value: 55%) (**b**), tumor differentiation (**c**), treatment for overall population (**d**), and NEC G3 subgroup (**e**): **a** Median OS was not reached, and 2-year OS rate was 64.5%; **b** Median OS for Ki67 $\leq$ 55% was not reached versus 26 months for Ki67 > 55%. The 2-year OS rates were 75.6% versus 53.1%, respectively ($P = 0.03$); **c** Median OS for NET G3 patients was not reached, while NEC G3 cases showed a median OS of 33 months. The 2-year OS rates were 90.9% versus 58.5%, respectively ($P = 0.03$); **d** Median OS for patients treated with radical surgery only was not reached versus 40 months for patients also receiving adjuvant therapy. 2-Year OS rates were 62.0% versus 69.1%, respectively ($P = 0.87$); **e** Median OS for the NEC G3 patients treated with radical surgery only was 19 months versus 40 months for the NEC G3 patients also receiving adjuvant therapy. The 2-year OS rates were 47.7% versus 64.0%, respectively ($P = 0.35$) ▶

Secondary Endpoints

Disease recurrence was observed in 40/60 (66.7%) patients. Recurrent disease was intra-abdominal in 80.0% of cases and extra-abdominal in 20.0% (chest lymph nodes observed in five patients, bone lesions in one, ocular metastasis in one, and lung metastasis in one).

First-line approach after disease recurrence was characterized by a further radical-intended surgery in 7/40 (17.5%) patients. In 29/40 (72.5%) a systemic treatment was started: 25 patients received systemic chemotherapy, 1 everolimus, 1 peptide receptor radionuclide therapy (PRRT), and 2 somatostatin analogs. The latter two patients were NET G3, with Ki67 of 25% and 40%, and disease recurrence was limited to abdominal lymph nodes. In four patients, best supportive care was applied.

Median RFS was 14 months, with a 2-year RFS rate of 44.9% (Fig. 2a). No statistically significant risk factors for disease recurrence were identified.

A limited number of patients ($n = 20$) had received adjuvant therapy. These were mainly patients with NEC ($n = 18$) and colorectal primary tumor ($n = 13$), with a median Ki67 of 75% (Table 1). Use of adjuvant therapy did not provide any benefit in terms of either OS or median RFS in comparison with patients receiving only surgery (Fig. 1d and 2b, respectively). The survival curves might suggest a potential benefit of the adjuvant treatment for the NEC G3 subgroup, but a statistical significance was missed ($P = 0.35$ for OS, Fig. 1e; $P = 0.45$ for RFS, Fig. 2c).

DISCUSSION

The present study supports the idea that radical-intended resection might be a valid therapeutic option also for GEP-NEN G3 patients. A statistically significant different OS was observed according to Ki67 value (cut-off: 55%) and tumor differentiation (NEC G3 vs. NET G3), while median

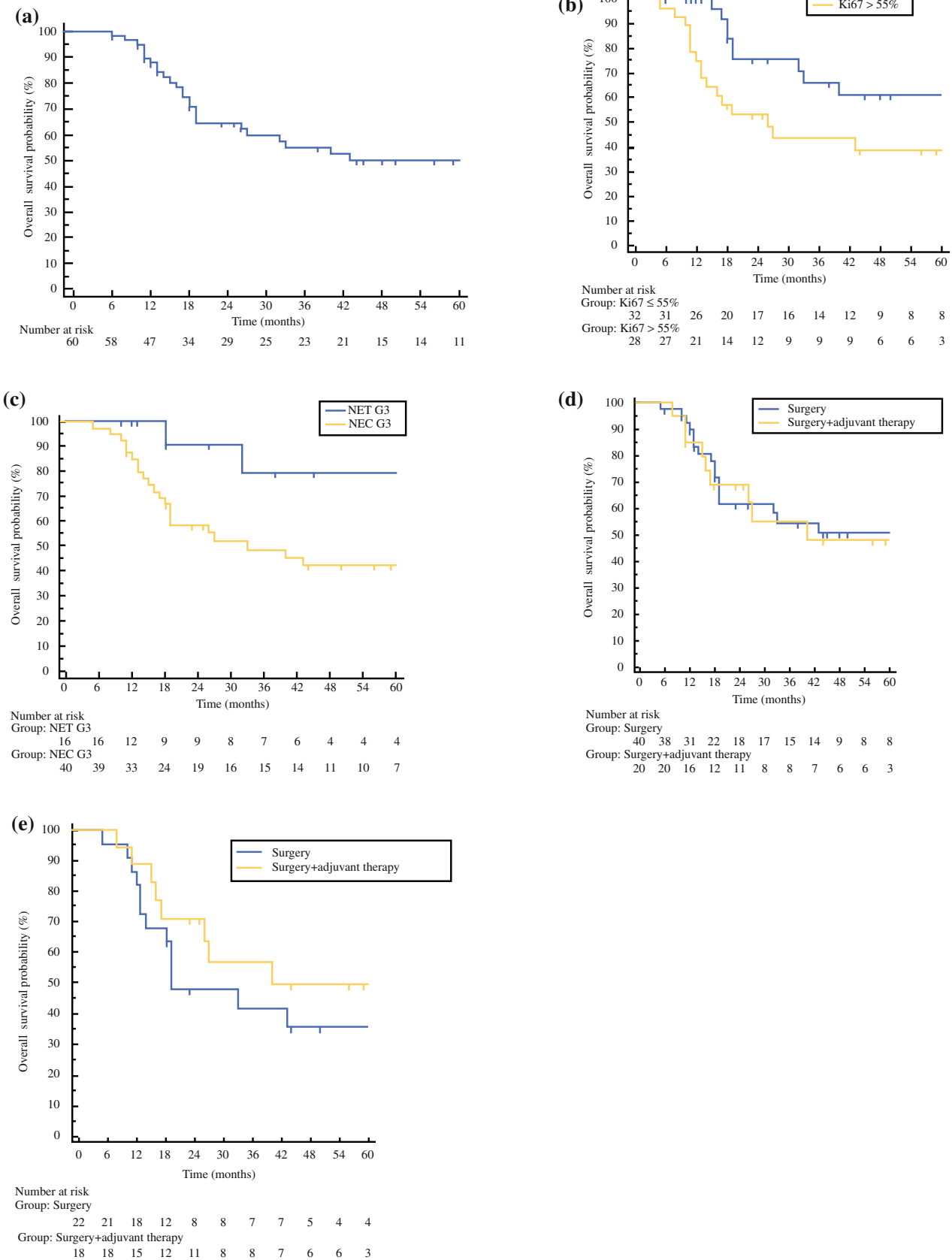

(a)
Overall survival probability (%)
Time (months)
Number at risk
60 58 47 34 29 25 23 21 15 14 11
(b)
Ki67 ≤ 55%
Ki67 > 55%
Overall survival probability (%)
Time (months)
Number at risk
Group: Ki67 ≤ 55%
32 31 26 20 17 16 14 12 9 8 8
Group: Ki67 > 55%
28 27 21 14 12 9 9 9 6 6 3
(c)
NET G3
NEC G3
Overall survival probability (%)
Time (months)
Number at risk
Group: NET G3
16 16 12 9 9 8 7 6 4 4 4
Group: NEC G3
40 39 33 24 19 16 15 14 11 10 7
(d)
Surgery
Surgery+adjuvant therapy
Overall survival probability (%)
Time (months)
Number at risk
Group: Surgery
40 38 31 22 18 17 15 14 9 8 8
Group: Surgery+adjuvant therapy
20 20 16 12 11 8 8 7 6 6 3
(e)
Surgery
Surgery+adjuvant therapy
Overall survival probability (%)
Time (months)
Number at risk
Group: Surgery
22 21 18 12 8 8 7 7 5 4 4
Group: Surgery+adjuvant therapy
18 18 15 12 11 8 8 7 6 6 3

TABLE 3 Risk factors for death (outcome = overall survival)

Variable	Univariate analysis		
	HR	95% CI	*P*
Gender (male vs. female)	0.75	0.34–1.65	0.48
Age at surgery, years*	1.03	0.99–1.06	0.05
Pancreatic versus other primary sites	0.84	0.37–1.89	0.67
Colorectal versus other primary sites	1.09	0.45–2.49	0.82
T (ref. T1)†[22,23]			
T2	1.40	0.23–8.40	0.71
T3	1.52	0.35–6.69	0.57
T4	3.53	0.68–18.3	0.13
TNM staging (ref. stage I)[22,23]†			
Stage II	1.08	0.13–9.03	0.94
Stage III	0.87	0.11–6.59	0.89
Lymph nodal ratio (ref. ratio = 0)†			
Ratio > 0 but ≤ 0.20 (for pancreas) or 0.60 (for others)	0.60	0.23–1.60	0.31
Ratio > 0.20 (for pancreas) or 0.60 (for others)	0.71	0.22–2.27	0.57
R1 versus R0	1.77	0.72–4.30	0.21
Ki67, %*	1.02	1.00–1.04	0.01
Ki67 > 55%	2.30	1.01–5.21	0.04
Tumor differentiation (NEC G3 vs. NET G3)[8]	4.24	0.99–18.09	0.05
Small cell versus large cell	0.89	0.33–2.41	0.82
Adjuvant therapy	1.07	0.47–2.42	0.87
Number of cycles of adjuvant therapy*	1.11	0.85–1.45	0.42

*Continuous variables

†Categorical variables

HR hazard ratio, *CI* confidence interval, *NEC* neuroendocrine carcinoma, *NET* neuroendocrine tumor

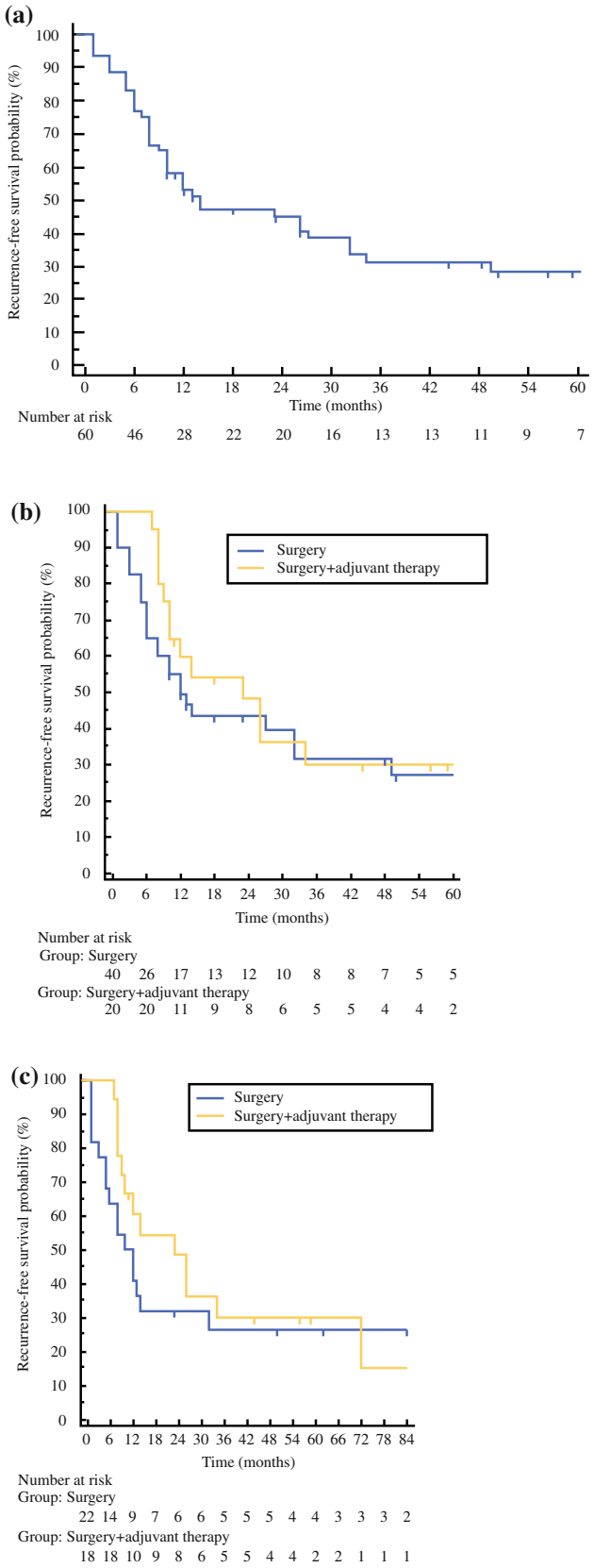
RFS after surgery was 14 months. In addition, the present data did not show any benefit in terms of survival rates for adjuvant therapy in comparison with the radical resection alone, although the number of patients with adjuvant therapy was rather low in our study.

At the end of follow-up, the observed mortality was 41.7%, with half of the population still alive 5 years after resection, independent of the primary tumor site. These results can hardly be compared with data in the literature, since previous papers investigating the role of surgery for GEP-NENs G3 analyzed mixed patient populations with different disease stages (stage I–III and stage IV), different grading (G1–G2 and G3), and with short post-surgical follow-up.[6,10–12,15–17,20,21] The present study instead includes a population without stage IV disease, receiving R0–R1 surgery with median follow-up of 23 months (range 5–187 months) after resection.

Yoshida et al. [21] reported a benefit from radical surgery in comparison with systemic therapies for non-metastatic pancreatic NENs G3, showing an increased benefit in NETs G3 in comparison with NECs G3. Performing a subanalysis of our data focusing only on pancreatic cases, OS rates are similar to the results from Yoshida et al. Median OS for pancreatic NETs G3 was not reached either in Yoshida et al. or in the present study, while for pancreatic NECs G3 such median was 16 and 19 months, respectively. The post-surgical follow-up was longer, however, in our study (median 23 months) in comparison with Yoshida et al. (13.2 for NETs G3 and 9.2 months for NECs G3, respectively), and we analyzed cases receiving adjuvant treatments separately from patients receiving surgery only.

The Ki67 value was herein confirmed as the major prognostic factor also in these NEN G3 patients, and in agreement with Sorbye et al.,[3] the cut-off of 55% was able to distinguish two subsets of patients with significantly different OS ($P = 0.03$) (Fig. 1b). On the contrary, tumor primary site showed no prognostic impact in terms of OS (Table 3). This discrepancy may be due to the different populations included in the two studies: 60 patients with localized disease in the present population, and 305 patients with advanced unresectable NENs in the study by Sorbye and coworkers.[3]

A statistically significant difference in OS was observed with respect to tumor differentiation (NEC G3 vs. NET G3), which can be considered as another valuable



◀**FIG. 2** Recurrence-free survival (RFS) after radical surgery for the overall population (**a**), according to treatment in the overall population (**b**), and in the NEC G3 subgroup (**c**): **a** Median RFS was 14 months, and 2-year RFS rate was 44.9%; **b** Median RFS for patients treated with radical-intended surgery only was 12 months versus 23 months for patients also receiving adjuvant therapy. The 2-year RFS rates were 43.5% versus 48.1%, respectively ($P = 0.62$); **c** Median RFS for the NEC G3 patients treated with radical intended surgery only was 10 months versus 23 months for the NEC G3 patients also receiving adjuvant therapy. The 2-year RFS rates were 31.8% versus 36.4%, respectively ($P = 0.43$)

prognostic factor for OS ($P = 0.03$) (Fig. 1c), consistent with literature for stage IV disease.[1,2,21] The results of the present study show the prognostic impact of the recent WHO 2019 classification,[8] which has officially established this distinction for all GEP-NENs G3.

Current evidence regarding the indications for adjuvant treatment in NENs is still limited.[14,17–19] In our population, a significant benefit in terms of OS or disease recurrence obtained with adjuvant therapy was not observed in comparison with patients receiving radical surgery alone. However, these results should be taken with caution due to the limitations of the present study: the low number of patients who received an adjuvant therapy, the retrospective design, and the preselection bias represented by the use of adjuvant treatment in case of higher Ki67 and non-pancreatic neoplasms (Table 1). These limitations might also explain why use of adjuvant treatment was not confirmed as a statistically significant prognostic factor for the NEC G3 subgroup, although the survival curves might suggest a potential benefit of this therapeutic strategy in comparison with surgery alone (Figs. 1e and 2c). The potential benefit of adjuvant treatment can only be evaluated within a prospective trial, while our results rather reflect a "real-world" setting, showing how, in NET referral centers, use of adjuvant therapy was mainly adopted in cases of aggressive disease.

CONCLUSIONS

Radical surgery represents a valid option for GEP-NENs G3 with locoregional disease, especially for those with Ki67 $\leq$ 55%. In this series, use of adjuvant therapy did not significantly affect either OS or RFS, but prospective studies are warranted to confirm these results.

ACKNOWLEDGEMENTS The study was endorsed by unrestricted support from the Ipsen Scientific Exchange Program (2016–2018).

DISCLOSURES The study was supported by the European Neuroendocrine Tumor Society (ENETS) "Excellence Academy Fellowship Grant" (2017). Dr. Anja Rinke declared: honoraria for

presentations and attendance of advisory boards from Novartis and IPSEN; coverage of travel costs/congress costs from IPSEN; Notice: As this manuscript is about surgery there is no connection of the content with drug treatment/drug companies, and therefore no conflict of interest to the content of this manuscript. All other authors have no conflicts of interest to declare.

REFERENCES

1. Velayoudom-Cephise FL, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer.* 2013;20(5):649–657.
2. Heetfeld M, Chougnet CN, Olsen IH, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer.* 2015;22(4):657–664.
3. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24(1):152–160.
4. Basturk O, Yang Z, Tang LH, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol.* 2015;39(5):683–690.
5. Tang LH, Untch BR, Reidy DL, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Cancer Res.* 15 2016;22(4):1011–1017.
6. Crippa S, Partelli S, Bassi C, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: Morphology matters. *Surgery.* 2016;159(3):862–871.
7. Klöppel G et al. WHO classification of tumours of endocrine Organs. 4th ed., vol. 10. Lyon:WHO/IARC;2007.
8. WHO classification of Tumors Editorial Board: digestive system tumors. 5th ed;2019.
9. Garcia-Carbonero R, Rinke A, Valle JW, et al. ENETS Consensus guidelines for the standards of care in neuroendocrine neoplasms. systemic therapy 2: chemotherapy. *Neuroendocrinology.* 2017;105(3):281–294.
10. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg.* 2014;101(11):1405–1412.
11. Xu X, Li J, Han X, Shi C, Jin D, Lou W. Clinical characteristics and prognostic factors of patients with gastric neuroendocrine carcinoma treated with radical surgery. *Chin Med J (Engl).* 2014;127(13):2419–2422.
12. Yang M, Zeng L, Zhang Y, Su AP, Yue PJ, Tian BL. Surgical treatment and clinical outcome of nonfunctional pancreatic neuroendocrine tumors: a 14-year experience from one single center. *Medicine (Baltimore).* 2014;93(22):e94.
13. Kim BS, Park YS, Yook JH, Kim BS. Comparison of relapse-free survival in gastric neuroendocrine carcinoma (WHO grade 3) and gastric carcinoma. *Therap Adv Gastroenterol.* 2017;10(5):407–415.
14. Maire F, Hammel P, Kianmanesh R, et al. Is adjuvant therapy with streptozotocin and 5-fluorouracil useful after resection of liver metastases from digestive endocrine tumors? *Surgery.* 2009;145(1):69–75.
15. Yang M, Ke NW, Zeng L, et al. Survival analyses for patients with surgically resected pancreatic neuroendocrine tumors by World Health Organization 2010 Grading Classifications and American Joint Committee on Cancer 2010 Staging Systems. *Medicine (Baltimore).* 2015;94(48):e2156.
16. Shen C, Chen H, Chen H, et al. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. *BMC Gastroenterol.* 9 2016;16:111.
17. Deng HY, Li G, Luo J, Li XR, Alai G, Lin YD. The role of surgery in treating resectable limited disease of esophageal neuroendocrine carcinoma. *World J Surg.* 16 2018.
18. Filosso PL, Guerrera F, Evangelista A, et al. Adjuvant chemotherapy for large-cell neuroendocrine lung carcinoma: results from the European Society for Thoracic Surgeons Lung Neuroendocrine Tumours Retrospective Database. *Eur J Cardiothorac Surg.* 2017;52(2):339–345.
19. Galleberg RB, Knigge U, Tiensuu Janson E, et al. Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol.* 2017;43(9):1682–1689.
20. Partelli S, Inama M, Rinke A, et al. Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. *Neuroendocrinology.* 2015;102(1-2):68–76.
21. Yoshida T, Hijioka S, Hosoda W, et al. Surgery for pancreatic neuroendocrine tumor g3 and carcinoma g3 should be considered separately. *Ann Surg Oncol.* 12;2019.
22. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449(4):395-401.
23. Rindi G, Kloppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2007;451(4):757-762.
24. Boninsegna L, Panzuto F, Partelli S, et al. Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. *Eur J Cancer.* 2012;48(11):1608-1615.
25. Wu L, Chen F, Chen S, Wang L. The Lymph node ratio optimizes staging in patients with small intestinal neuroendocrine tumors. *Neuroendocrinology.* 2018.