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Chemotherapy efficacy in metastatic neuroendocrine colorectal cancer

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ABSTRACT *AIM: to evaluate the effectiveness of first-line chemotherapy in patients with colorectal neuroendocrine cancer (NEC).*
PATIENTS AND METHODS: a retrospective study included patients with metastatic colorectal NEC (2000-2020). The main analyzed parameter was the response rate to treatment according to the RECIST criteria, depending on the regimen used in the first line. The overall survival was additional parameter.
RESULTS: the study included 27 patients (13 with initial stage IV disease and 14 with progression after primary radical treatment). Ten patients in the 1st line underwent chemotherapy according to the EP scheme, 4 — XELOX, 2 — FOLFIRI, 2 — Irinotecan and Cisplatin, 1 — Samarium, 1 — Nivolumab, 1 — 5-FU-LV. Most often, the treatment effect (partial response or stabilization) was observed against the background of chemotherapy according to the EP scheme — in 60% of patients. The median OS was 7 months.
CONCLUSION: the use of chemotherapy according to the EP regimen is the preferred options for the treatment of metastatic colorectal NEC. The median OS in this group of patients remains extremely low, and new clinical trials are needed.

KEYWORDS: *neuroendocrine cancer, first-line chemotherapy, metastatic cancer*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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INTRODUCTION

Colorectal neuroendocrine cancer (NEC) is a rare malignant neoplasm. Only a small number of clinical cases series are available in the scientific literature [1–7].

An important issue in the treatment of colorectal NEC is the choice of the optimal first-line CT regimen. There are a small number of articles that consider the effectiveness of first-line chemotherapy (CT) for colorectal neuroendocrine cancer, mainly in the framework of publications that combine various types of NEC of the gastrointestinal tract. The main treatment regimen is a combination of etoposide and cisplatin [8,13]. At the same time, the effectiveness of CT and the prognosis of the disease may vary significantly depending on the tumor site, and the data on colorectal NEC are limited to small retrospective studies [9, 10].

AIM

The aim of our study was to evaluate the response rate of metastatic colorectal NEC to the first line of chemotherapy, as well as to study the clinical

characteristics of a group of patients with metastatic colorectal NEC.

PATIENTS AND METHODS

The study is based on a retrospective study of the medical histories of patients treated at the N.N. Blokhin Oncology Research Center and the Tyumen Medical City State Medical Institution in the period from 2000 to 2020.

According to the ICD codes-0 1.4.1 8249/3, 82401, 8240/1, 8240/3.1, 8240/3, 82403, 82443, 8045/3.2, 8013/3, 80123, 85103, 8510/3, 8041/3.3, 80413, 8041/3, 8246/3, 8240/3.2 and ICD-X C20, C21.1 a request was sent to archive for the selection of patient case histories for the period 2000–2020. The criteria for inclusion in the study group were: histologically verified colorectal neuroendocrine cancer (Ki-67 > 20%, moderate or low degree of tumor differentiation). Staging was carried out on the basis of pelvic MRI, chest and abdominal CT with intravenous contrast. Histology was carried out due to WHO pathomorphological classification 2019 [11]. Staging was carried out due to the UICC TNM system (8th edition). Also, an IHC study was conducted in all patients, which finally confirmed the diagnosis of neuroendocrine cancer.

The following chemotherapy regimens were used: EP (Etoposide 100 mg/m^2 i/v on days 1–3 + cisplatin 75 mg/m^{2}i/v on day 1 once every 3 weeks, 6 cycles), XELOX (Oxaliplatin 130 mg/m^2 i/v on day 1 + capecitabine 2000 mg/m^2 inside on days 1–14, 1 time in 3 weeks, 6 cycles), FOLFIRI (Irinotecan 180 mg/m^2 i/v on day 1 + calcium folinate 400 mg/m^2 i/v on day 1 + 5-fluorouracil 400 mg/m^2 i/v on day 1-day 5 + fluorouracil 2400 mg/m^2 i/v 46-hour infusion once every 2 weeks, 9 cycles), *cisplatin and irinotecan* (Cisplatin 60 mg/m^2 i/v on day 1 + irinotecan 65 mg/m^2 i/v on days 1 and 8, every 3 weeks), 5-FU-LV (5–fluorouracil 370–400 mg /m^2 1–5 days, in combination with a high dose of leucovorin (200 mg/m^2 1–5 days) 6 cycles with an interval of 4 weeks), *Nivolumab* (240 mg i/v 30-minute infusion every 14 days), *Samarium* (1.5 mCi/kg weight of the patient's body).

The main analyzed parameter was the frequency of response to treatment according to the RECIST 1.1 criteria [12], additional parameters were the overall survival. The effect of treatment according to

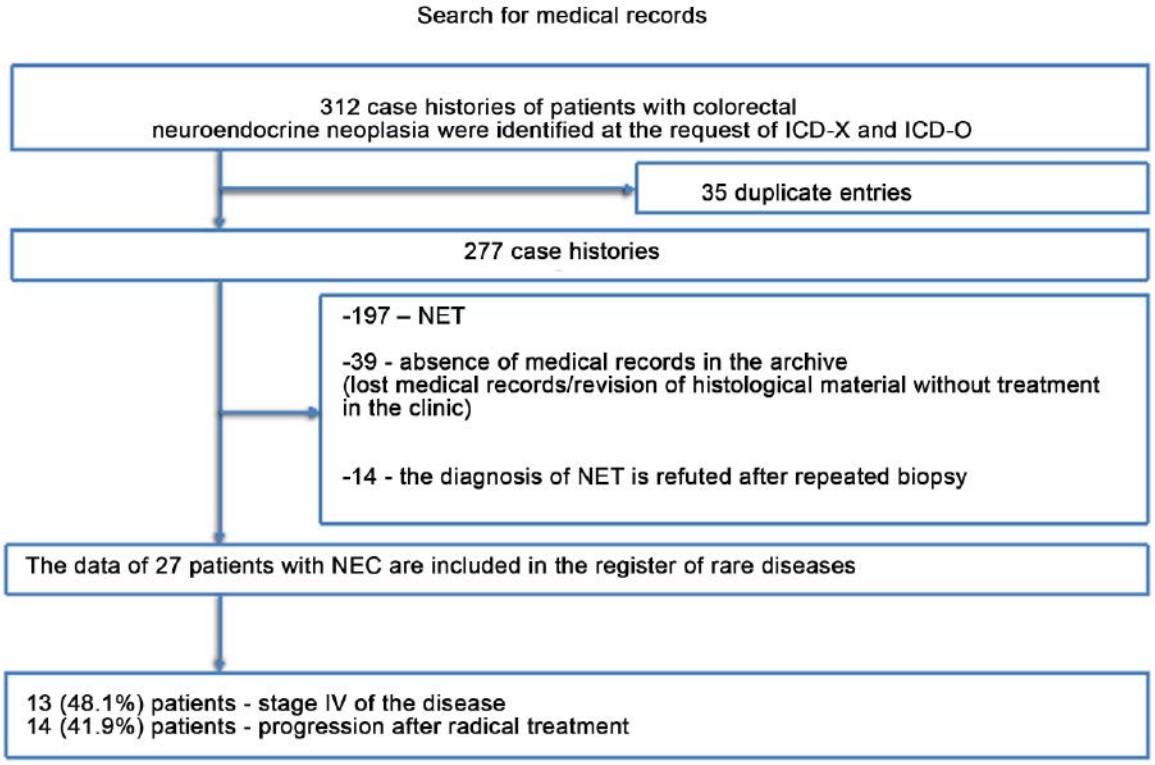

Figure 1. *Recruitment of patients to the study group*

Table 1. *Characteristics of the group of patients with colorectal NEC*

Characteristic	N = 27 (100%)
Gender	
Male	12 (44.6%)
Female	15 (55.6%)
Age	
30-50 years	9 (33.3%)
50–70 years	16 (59.3%)
> 70 years	2 (7.4%)
ECOG	
0-1	23 (85.2%)
2-3	4 (14.8%)
Initial Stage	
IA-IIB	4 (14.81%)
IIIA-IIIB	10 (37.04%)
IV	13 (48.15%)
Localization	
rectum and anal canal	16 (59.3%)
left colon	6 (22.2%)
right colon	5 (18.5%)
Dimensions	
2-5 cm	12 (44.4%)
> 5 cm	15 (55.6%)
cT	
1-2	8 (29.6%)
3-4	19 (70.4%)
cN	
0	6 (22.2%)
1	21 (77.8%)
Histological structure	
Microcellular cancer	8 (29.6%)
Macrocellular cancer	8 (29.6%)
No data	11 (40.8%)

the RECIST criteria was evaluated in the presence of at least 1 control examination within 4 months after the start of chemotherapy. Statistical analysis was performed using the IBM SPSS software package (version 25). Qualitative criteria were compared using a chi-squared test, using a two-sided R. Overall survival was calculated from the date of detection of metastatic disease to the date of death of the patient. Progression-free survival was calculated from the date of detection of metastatic disease to the date of disease progression or the date of death from other causes. Survival was analyzed using the Kaplan-Meier method.

RESULTS

The study included 27 patients (Fig. 1), 14 of whom had progression after primary radical surgery, 13 had initially metastatic NEC. Most of the patients were aged in the range of 50–70 years (59%). Primary multiple malignant neoplasms occurred in 4 (14.8%) patients, among whom in 1 (25%) patient NEC was synchronous and in 3 (75%) — metachronous. The most frequent site were the rectum and anal canal (59%). Lymph node lesion occurred in 21 (78%) patients (Table 1).

The nature of distant metastasis was diverse (Table 2). However, isolated liver lesion was most often occurred, in 10 (76.9%) patients.

Other, the rarest location of distant metastasis in patients in the study were isolated metastases in the left lateral pelvic lymph node, left internal iliaclymph nodes, on the peritoneum along the right-common iliac vessels, peritoneal carcinomatosis, metastases to the anterior abdominal wall, metastatic lesion of cervical and supraclavicular lymph nodes, ovarian metastases, bone metastases.

Table 2. *Pattern of metastasis in patients with metastatic colorectal NEC*

Metastasis zones	N(%), (*n* = 27)
Liver	11 (40.7%)
Retroperitoneal lymph nodes	7 (26.0%)
Brain	2 (7.4%)
Lungs	1 (3.7%)
Other	6 (22.2%)

Table 3. *Types of treatment performed in patients with NEC*

Type of Treatment	N (*n* = 27)	%
Removal of the primary tumor		
Was not carried out	13	48.15
Local excision	1	3.7
Colorectal resection	13	48.15
Radiation therapy for the pelvic area		
RT to I Line CT	3	10.3
RT in parallel with the I line CT	2	6.9
RT after the I line CT	1	3.4
First-lined rug treatment		
EP	10	37.1
XELOX	4	14.8
FOLFIRI	2	7.4
IP	2	7.4
Others	3	11.1
The scheme is unknown	1	3.7
Without treatment	5	18.5
Other treatment		
CT 2 line was carried out	5	18.5
Resection of liver metastases	4	14.8

Note: EP — etoposide and cisplatin, XELOX — capecitabine and oxaliplatin, FOLFIRI — 5-fluorouracil, leucovorin and irinotecan, IP — irinotecan and cisplatin.

TREATMENT

Table 3 presents the characteristics of the treatment performed in a group of patients with metastatic NEC. Removal of the primary tumor was performed in 16 (55.2%) patients, 15 (93.8%) of whom underwent colorectal resection, and in 1 (6.3%) patient local excision of the tumor was performed.

Five (18.5%) patients were unable to start 1st line CT due to low functional status. Initially, there were 3 patients with stage IV disease, 2 of whom had primary tumor removal, both urgently (tumor perforation in 1 patient and bleeding in the other) after surgery. So, the patients were unable to start CT due to low functional status. One (20%) of those patients had multiple liver metastases, and the other two (40%) had widespread lung lesion. Two patients with an initially local process also did not start CT. One patient (20%) showed tumor progression in the liver and, as a result, a low functional status.The second (20%) patient refused the treatment.

As for the effect of treatment (Table 4), it was most often observed in the group of patients receiving CT according to the EP scheme (6 patients). Three (50%) of them had microcellular subtype cancer, 1 (17%) had macrocellular cancer, 2 (33%) had no data. Partial response was noted in 4 (40%) patients, of whom 2 (50%) — had microcellular cancer, 1 (25%) — microcellular cancer, 1 (25%) — undifferentiated; stabilization was noted in 2 (20%) patients, of whom 1 (50%) — macrocellular, 1 (50%) — unspecified; progression was noted in 4 (40%) patients, of whom 2 (50%) — macrocellular, 1 (25%) — microcellular, 1 (25%) — unspecified.

Table 5 shows the responses to treatment with the I-line therapy scheme in patients with NEC, depending on the histological type.

In 2 patients, a complete clinical response to CT was noted, but in 1 (microcellular cancer) of them, CT (IP) was prescribed for an unresectable local

Table 4. *Response to treatment depending on the scheme of the first line therapy in patients with NEC*

Treatment regimen	Response to treatment			
	FR	PR	DS	DP
EP	–	4 (40%)	2 (20%)	4 (40%)
XELOX	1 (25%)	–	–	3 (75%)
FOLFIRI	–	–	1 (50%)	1 (50%)
IP	1 (50%)	–	–	1 (50%)
Samarium	–	–	–	1 (100%)
Nivolumab	–	–	–	1 (100%)
5-FU-LV	–	–	–	1 (100%)
The regimen is unknown			1 (100%)	

Note: FR — full response, PR — partial response, DS — disease stabilization, DP — disease progression, EP — etoposide and cisplatin, XELOX — capecitabine and oxaliplatin, FOLFIRI — 5-fluorouracil, leucovorin and irinotecan, IP — irinotecan and cisplatin.

Table 5. *Response to treatment with the first-line therapy regimen in patients with NEC depending on histological type*

Histological structure	Response to treatment			
	FR	PR	DS	DP
Macrocellular	1 (12.5%)	2 (25%)	2 (25%)	3 (37.5%)
Microcellular	1 (14.3%)	1 (14.3%)	–	5 (71.4%)
No data	-	1 (14.3%)	1 (14.3%)	5 (71.4%)

Note: FR — full response, PR — partial response, DS — disease stabilization, DP –disease progression, EP — etoposide and cisplatin

relapse and was performed immediately after the course of RT.

The effect was evaluated only after the completion of RT and CT, which does not allow us to assess the contribution of these components of treatment separately. In another patient (macrocellular subtype), CT (XELOX) was performed for metastatic lesion of pelvic lymph nodes, established according to pelvic MRI data. Metastases were not histologically verified. However, their size and MR signs of metastatic lesion completely regressed after the treatment. One patient received nivolumab therapy in the 1st line, because the progression developed immediately after the completion of adjuvant CT according to the EP scheme. The effect of the treatment was not registered. In two patients in the first line of CT, only fluoropyrimidine or samarium monotherapy was prescribed (it was prescribed in a patient with metastatic bone lesion), in both cases due to low initial functional status. In both cases, no response to the treatment was registered.

The median follow-up was 43.6 months. The 2-year overall survival (OS) of patients with metastatic NEC was 11.3%, the median OS was 6.0 months (95% CI, 2.4–9.7 months) (Fig. 2).

The 2-year PFS was 4.3%. The median survival of patients with metastatic NEC was 2.9 months (95% CI, 0.6–5.3 months) (Fig. 3).

In the study, two patients with high survival rates were also revealed, despite the aggressive nature of the tumor.

In the first patient, the tumor was located in the upper rectum with the initial stage IIIB. The first stage was colorectal resection in 2017. Histologically, microcellular neuroendocrine cancer was verified. After 5.5 months, progression to mesenteric and paraaortic lymph nodes was detected. Histological verification was not carried out. It was decided to do 7 courses of CT according to the XELOX scheme, against which a complete regression of metastases and normalization of the CEA from 60 to 6 were noted. The last checkup was 43 months after the progression. The patient died of unknown causes, the overall survival rate was 50 months. Another female patient had microcellular neuroendocrine cancer of the lower ampullary rectum, stage IIIB in 2009. She underwent preoperative chemoradiotherapy (CRT) with induction and consolidating CT according to the EP scheme (a total of 6 courses), then abdominal-anal resection (AAR) of the rectum was performed. Fourteen months after the initial radical surgery, a recurrence was detected along the posterior semicircle of the upper third of the vagina measuring 55x40 cm with the involvement of the cervix. It was decided to do three CT courses according to the IP scheme

of 1,8,15 days. A complete clinical response was received after 1 course of the therapy. With the third course of CT, RT ROD 2 Gr, SOD 24 Gr was carried out. On MRI, the tumor formation in the vaginal area was not determined. After another 24 months, repeated progression was revealed — solitary metastasis to the brain. In the area of a previously determined relapse — without signs of tumor growth. The removal of metastasis of the right occipital region of the brain was performed, followed by RT of ROD 2.5Gr, SOD 30 Gr on the area of the removed metastasis. In June 2014, a recurrence of the tumor in the area of the sacro-spinous ligament on the left was revealed. Six courses of chemotherapy were carried out according to the scheme: cisplatin 60mg/ m^2i/v in 1 day + irinotecan 60mg/ m^2i/v in 1, 8 days, against which positive dynamics was noted in the form of a decrease in the tumor size in the sacro-spinous ligament.

In June 2015, stereotactic radiation therapy of ROD 9Gr, SOD 27Gr was performed on the area of a recurrent tumor.

In January 2016, a metastasis to the left temporal lobe of the brain revealed and continued growth of a recurrent tumor in the sacroiliac ligament. Chemotherapy was performed according to the scheme: capecitabine 1500 mg/ m^2orally daily for 1–14 days + temozolomide 150 mg/m^2 orally daily for 1–14 days. In March 2016, a gamma knife SOD 44Gr was used to treat metastasis in the temporal lobe of the brain. Avastin was added to the therapy since October 2016. In August 2017, negative shift was noted due to an increase in the focus size in the sacrum. Next, CT Cyclophosphane + Doxorubicin was prescribed. The last checkup was carried out

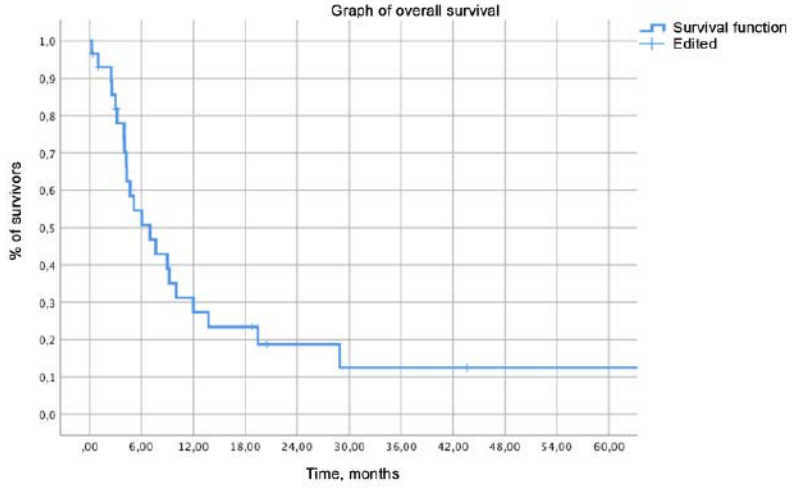

Figure 2. *OS of patients with NEC*

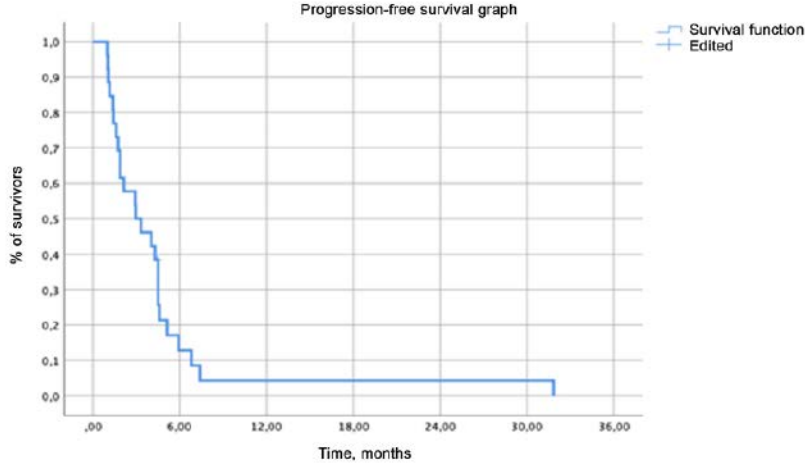

Figure 3. *PFS of patients with NEC*

on 06.12.2018. The patient died from the progression of the disease; the overall survival was 116 months.

DISCUSSION

The use of CT according to the EP scheme is the preferred of the existing treatment options for metastatic NEC. In our study we focused only on data on the effectiveness of this scheme due to the presence of only single cases of the use of alternative treatment regimens. The response rate to the treatment in our study was 60% compared to 56.4–87.5% according to other authors [1–5]. At the same time, the indicators were similar to ours in studies in which the results of treatment of patients with NEC site only in the large intestine were analyzed — 42–62.5% [1,2,4], the indicators in mixed groups with NEC of various gastrointestinal organs were higher — 74.5–87.5% [3,5]. Thus, a lower sensitivity of the colorectal NEC to chemotherapy according to the EP scheme is likely compared to the NEC of other gastrointestinal organs. Another possible explanation for the relatively low response rate to chemotherapy in our study may be the shortcomings of collecting material during retrospective analysis. Responses to treatment for NEC are often unstable [2]. During the retrospective analysis, some of the information about the interim effect assessment could have been lost (we took into account the data of the effect assessments at least once every 4 months, but the interim data during this interval could not be available). It should also be noted that the published data on the response rate to the first line CT in a mixed group of patients with gastrointestinal NEC [3] are usually higher than in studies where patients with colorectal NEC are presented in isolation [4].

In the study, the median OS of patients with metastatic NEC was7.0 months (95% CI, 3.4–10.6 months) and was similar to that obtained in other studies — in patients with colorectal NEC — 4.04–12.5 months. [1,2,4,13], and in mixed groups with NEC of various gastrointestinal organs — 11–14 months [3,5], despite the fact that 27.6% of patients in our study had such rapid progression of the disease that they could not even start the first line CT. The high proportion of patients who were unable to start treatment indicates the need for accelerated clinical decision-making when identifying patients with colorectal NEC. The disadvantages of this trial are directly related to the retrospective nature and the heterogeneity of the study group. There was no single standardized treatment plan. Some patients received CRT in parallel with the 1st line CT, which does not allow an objective assessment of the particular treatment regime. Also, there were no unified approaches to determining indications for surgical treatment, choosing a CT regimen. This led to the formation of small subgroups of patients receiving different types of treatment, comparison between which is difficult. Also, some of the information on the effect of chemotherapy could be lost in the retrospective study, and therefore the incidence of registered responses to treatment could be underestimated.

Despite these limitations, this is one of the few studies in which a group of colorectal NEC is collected, without combining all the NEC of the gastrointestinal tract. This allows us to study in more detail the individual features of the course and forecast of the NEC of this location.

CONCLUSION

Colorectal NEC is a disease with an extremely negative prognosis and a high risk of rapid progression. It is necessary to start treatment quickly, because the progression often prevents the beginning of a special therapy. The accumulated data speak in favor of using the EP scheme as the first line chemotherapy, which was confirmed in our series of cases. It is necessary to further study this disease and accumulate information within large multicenter registries.

AUTHORS CONTRIBUTION

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