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Possibilities of surgical treatment of pancreatic head neuroendocrine neoplasms with major venous invasion

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Abstract

Aim – to demonstrate the feasibility and relative safety of resection of the portal and/or superior mesenteric veins invaded by tumor during surgical treatment of the neuroendocrine neoplasm of the pancreatic head, as well as the feasibility of simultaneous resection of the liver for resectable metastases in patients with stage IV disease during primary surgery and at disease progression of any stage following surgical treatment.

Material and methods. Surgical treatment of 16 patients with neuroendocrine neoplasm of the pancreatic head with invasion of the superior mesenteric and/or portal veins of stages III-IV of high and moderate differentiation (G1 and G2) included a standard gastropancreoduodenal resection in 87.5% cases, extended gastropancreoduodenal resection with aortocaval lymph node dissection in 6.25% cases, and pancreatectomy in 6.25% cases. During the standard operation, in one female patient (6.25%) segmental resection of the liver was performed to remove the metastasis. The rate of portal vein resection was 6.25%, superior mesenteric vein, 50%, both major veins, 43.8%. Neoadjuvant treatment was not administered, while adjuvant XELOX treatment was administered to 3 (18.8%) patients. The statistic processing of the study results was performed in Statistica for Windows v.10 and SPSS v21. The obtained differences were deemed statistically significant at $p \leq 0.05$ ($\geq 95\%$ accuracy). In order to calculate the survival rate, the Kaplan-Meier method was used with log-rank test evaluation of significance of differences.

Results. The rate of R0 surgical treatment was 93.8%, the rate of complications of surgical treatment of Clavien-Dindo class III and above was 43.8% with the total rate of all complications of 75%. The main complications included gastric stasis (50.1%), arrosive hemorrhage (18.8%), acute gastrointestinal ulcer hemorrhage (18.8%), pneumonia (18.8%). The rate of postoperative thrombosis of the portal and/or superior mesenteric vein was 12.5%, leakage of

the pancreato-digestive anastomosis was 12.5%, leakage of the bilio-digestive anastomosis, 6.3%, pancreatic fistula, 12.5%. Relaparotomy was performed in 2 (12.5%) patients who later died due to complications of surgical treatment (leakage of the pancreato-digestive anastomosis with arrosive hemorrhage). Disease progression was seen in 10 (62.5%) of the patients within 3 to 69.3 months, the median time before identification of progression being 39.7 [7.1; 52.8] months, and mortality from progression being 50%. Local recurrence developed in 12.5% patients, metastases in the retroperitoneal lymph nodes in 6.25%, metastases in the liver in 43.75%, in two cases, liver resection due to metastases was performed. In cases of progression, all patients received antineoplastic therapy with analogs of prolonged somatostatin. The median overall survival was 70.1 months, progression-free survival, 49.2 months, one-year survival was 81.2% and 78.6%, respectively, three-year survival, 68.2% and 63.5%, five-year, 68.2% and 36.3%, ten-year, 20.55% and 18.1%.

Conclusion. The outcomes of surgical treatment of patients with neuroendocrine neoplasm of the pancreatic head with invasion of the portal and/or superior mesenteric vein show the feasibility, relative safety and efficiency of resection of these major veins. In the majority of patients surgical treatment may be performed in the radical volume and extended by liver resection in the event of resectable metastases. Considering the relatively favorable prognosis of the disease, liver resection for resectable metastases and disease progression may be performed: it is safe, it improves quality of life of patients, and extends the period without tumor manifestations.

Keywords: neuroendocrine neoplasm of the pancreas, gastropancreoduodenal resection, resection of the portal vein, resection of the superior mesenteric vein, resection of the liver.

Conflict of interest: nothing to disclose.

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Возможности хирургического лечения нейроэндокринной неоплазии головки поджелудочной железы, инвазирующей магистральные вены

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Аннотация

Цель – показать возможность и относительную безопасность резекции инвазированных опухолью воротной и/или верхней брыжеечной вен во время хирургического лечения нейроэндокринной неоплазии головки поджелудочной железы, а также возможность симультанной резекции печени по поводу резектабельных метастазов у больных с IV стадией заболевания во время первичного оперативного вмешательства и при прогрессировании заболевания любой стадии после хирургического лечения. **Материал и методы.** Хирургическое лечение 16 пациентов с нейроэндокринной неоплазией головки поджелудочной железы с инвазией верхней брыжеечной и/или воротной вен III–IV стадии высокой и умеренной степени дифференцировки (G1 и G2) включало стандартную гастропанкреатодуоденальную резекцию в 87,5% случаев, расширенную гастропанкреатодуоденальную резекцию с аортोकавальной лимфодиссекцией – в 6,25% и панкреатэктомию – в 6,25%. Во время стандартной операции у одной больной (6,25%) провели сегментарную резекцию печени для удаления метастаза. Частота резекций воротной вены составила 6,25%, верхней брыжеечной вены – 50%, обеих магистральных вен – 43,8%. Неoadьювантную терапию не проводили, адьювантное лечение по схеме XELOX получили 3 (18,8%) человека. Статистическую обработку результатов исследования выполнили на основе статистического пакета программ Statistica for Windows v.10 и SPSS v21. Полученные различия считали статистически значимыми при уровне значимости $p \leq 0,05$ ($\geq 95\%$ точность). Для расчета выживаемости использовали метод Каплана – Мейера с оценкой достоверности различий по log-rank test.

Результаты. Частота хирургического лечения в объеме R0 составила 93,8%, частота осложненного оперативного вмешательства III и выше класса по шкале Clavien – Dindo – 43,8% при общей частоте всех осложнений – 75%. Основные осложнения – гастростаз (50,1%), аррозивное кровотечение (18,8%), кровотечение из острой язвы желудочно-кишечного тракта (18,8%), пневмония (18,8%). Частота послеоперационного тромбоза воротной и/или верхней брыжеечной вен – 12,5%, несостоятельности

панкреатодигестивного анастомоза – 12,5%, несостоятельности билиодигестивного анастомоза – 6,3%, панкреатического свища – 12,5%. Релапаротомию выполнили 2 (12,5%) пациентам, которые впоследствии умерли от осложнений хирургического лечения в виде несостоятельности панкреатодигестивного анастомоза с аррозивным кровотечением. Прогрессирование болезни выявили у 10 (62,5%) человек в сроки от 3 до 69,3 месяца (медиана времени до выявления прогрессирования 39,7 [7,1; 52,8] месяца, летальность от прогрессирования – 50%). Местный рецидив развился у 12,5% больных, метастазы в забрюшинные лимфатические узлы – у 6,25%, метастазы в печень – у 43,75%, в двух случаях выполнена резекция печени по поводу метастазов. При прогрессировании все больные получали противоопухолевое лечение аналогами прологированного соматостатина. Медиана общей выживаемости составила 70,1 месяца, медиана выживаемости без признаков прогрессирования заболевания – 49,2 месяца, однолетние показатели выживаемости – соответственно 81,2% и 78,6%, трехлетние – 68,2% и 63,5%, пятилетние – 68,2% и 36,3%, десятилетние – 20,55% и 18,1%.

Заключение. Результаты хирургического лечения пациентов с нейроэндокринной неоплазией головки поджелудочной железы с инвазией воротной и/или верхней брыжеечной вен свидетельствуют о допустимости, относительной безопасности и эффективности резекций этих магистральных вен. У большинства пациентов хирургическое лечение можно провести в радикальном объеме, а также дополнить резекцией печени по поводу резектабельных метастазов. Учитывая относительно благоприятный прогноз заболевания, можно проводить резекцию печени по поводу резектабельных метастазов и при прогрессировании болезни: это безопасно, улучшает качество жизни пациентов и продлевает период без проявлений опухоли.

Ключевые слова: нейроэндокринная неоплазия поджелудочной железы, гастропанкреатодуоденальная резекция, резекция воротной вены, резекция верхней брыжеечной вены, резекция печени.

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НЭН – нейроэндокринная неоплазия; ПЖ – поджелудочная железа; ЖКТ – желудочно-кишечный тракт; ВВ – воротная вена; ВБВ – верхняя брыжеечная вена; ГПДР – гастропанкреатодуоденальная резекция.

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INTRODUCTION

Currently, there are relatively few publications in the literature addressing the frequency, characteristics, and outcomes of major venous resections in patients with locally advanced pancreatic neuroendocrine neoplasms (NENs) invading the portal and superior mesenteric veins. This may be explained by the low incidence of NENs (ca. 2% among oncological diseases of the pancreas and the gastrointestinal (GI) tract) [1, 2]; however, in the opinion of L.R. McKenna, B.H. Edil (2014) [3], one in every ten tumors of the pancreas is a neuroendocrine neoplasm. The Practical recommendations for drug treatment of neuroendocrine neoplasias of the

gastrointestinal tract and pancreas”, published in 2023, recommend that surgical treatment be recommended for resectable processes, still, there is no unified solution on neo- and adjuvant therapy, and personalized approach and discussion by a multidisciplinary team are required [4].

According to the publications of the last 10–15 years, the frequency of resection of major vessels in the course of surgical treatment of patients with locally advanced pancreatic NENs of high and moderate differentiation (G1 and G2) is multiple-values ranging from 5% to 25% [5]. Thus, S.-P. Haugvik et al. (2013) performed resection and reconstruction of vessels during resection of the pancreas in 7 (9.3%) out of 75 patients

with invasion into the portal vein (PV), splenic vein, or the common hepatic artery and the celiac trunk [6], whereas A.L. Titan et al. (2020), in 25.3% [7].

As far as the complications of vascular resections are concerned, they are comparable with the complications of similar surgical treatment of neoplasias of the pancreatic head without vascular resections. The study of S.-P. Haugvik et al. had no complications of grade III–IV on the Clavien – Dindo scale or lethal outcomes after the resection of major veins and arteries in 7 patients [6]. A.L. Titan et al. report that 30-day mortality after resections of NENs involving resection and reconstruction of invaded major veins was 2% [7]. In 2024, A. Nießen et al. published results of surgical treatment of NENs with resection of the portal vein and/or superior mesenteric vein (SMV) in 54 patients [8]. The incidence of complications of grade IIIb and above on the Clavien – Dindo scale was 27.8% and was similar to the outcomes surgeries without vascular resection (13%, $p=0.071$). The incidence rate of portal vein thrombosis was 19%, relaparotomy, 33%, 90-day mortality, 2%.

■ AIM

To demonstrate the feasibility and relative safety of resection of the portal and/or superior mesenteric veins invaded by tumor during surgical treatment of the neuroendocrine neoplasm of the pancreatic head, as well as the feasibility of simultaneous resection of the liver for resectable metastases in patients with stage IV disease during primary surgery and at disease progression of any stage following surgical treatment.

■ MATERIAL AND METHODS

In this retrospective analysis, we included the data of 16 with NEN of the pancreatic head invading into the PV and/or SMV, who were examined or treated at the N.N. Blokhin National Medical Research Center of Oncology in 2001–2023. The study included 5 (31.3%) men and 11 (68.7%) women, aged at the moment of hospitalization from 22 to 62 years (median age: 51 years). In all of the patients, the tumor had no clinical hormonal activity, the size varying from 2.5 to 7 cm (median size: 5.3 cm). Stage T2N1M0 was identified in 1 (6.25%) patient, T4N0M0 in 12 (75%), T4N1M0 in 2 (12.5%) and T4N1M1 in 1 (6.25%). In 3 (18.8%) cases, high degree of tumor differentiation (G1) was diagnosed, and in 13 (81.2%) cases, moderate degree (G2). The median level of Ki-67 was 8.5%, and in patients from the SMV+PV group the marker credibly was higher than in the SMV group (14% vs. 4.5%, $p=0.032$). In 4 (25%) patients, tumor invasion was identified into the duodenum, and in 3 (18.8%), into the duodenum and the choledochus. In 9 (56.3%) patients jaundice was identified at the time of hospitalization, and it required biliary drainage; its progression in the SMV+PV group was observed credibly more frequently than in the SMV group (100% vs. 25%, $p=0.006$). Standard pancreatoduodenectomy (PD) was performed in 14 (87.5%) patients; a mesenteric approach was used in 1 (6.25%) case; extended PD with aortocaval lymph node dissection was performed in 1 (6.25%) patient; and pancreatectomy was performed in 1 (6.25%). During standard PD, one female patient (6.25%) underwent a segmental liver resection to remove a metastasis. Resection of the PV was performed in 1 (6.2%) patients, SMV, in 8 (50%) patients;

resection of both major veins (SMV+PV), in 7 (43.8%) patients. In 14 (87.5%) patients, circular resection of major veins was performed with the length of 2 to 5 cm (median length: 3.5 cm). In 9 (56.3%) cases, end-to-end anastomosis was performed, and in 5 (31.3%) cases, reconstruction with synthetic Gore-Tex prosthesis was performed. Two patients (12.5%) underwent partial (wedge) venous wall resection of major veins with a length of 1 to 3 cm (median: 2.0 cm); the repair was performed using a running suture. The portal vein clamp time for constructing a direct end-to-end anastomosis was from 13 to 16 minutes, while in the case of using a synthetic graft, it ranged from 22 to 32 minutes. Temporary bypass shunts were not created. Neoadjuvant therapy was not administered; adjuvant XELOX chemotherapy was given to 3 (18.8%) patients.

Statistical processing of the study results was performed in Statistica for Windows v.10 and SPSS v21. The obtained differences were considered statistically significant at $p \leq 0,05$ ($\geq 95\%$ accuracy). In order to calculate survival, the Kaplan-Meier method was used with differences evaluated for reliability using the log-rank test.

■ RESULTS

Out of the 16 patients, 15 (93.8%) underwent R0 surgery, and 1 (6.2%) underwent R2 surgery due to NEN invasion of the superior mesenteric artery and surrounding adipose tissue. The median duration of surgeries was 305 [265; 360] minutes (from 210 to 600 min.), and median intraoperative blood loss was 3000 [2100; 4850] mL (from 600 to 6500 mL).

Complications of surgical treatment were observed in 12 (75%) out of 16 patients: 7 (43.8%) patients had complications of grade III and above on the Clavien – Dindo scale. The incidence of early complications was 62.5% (10/16), early and late, 12.5% (2/16). In 3 (18.8%) patients, one complication developed, in 2 (12.5%), two, in 4 (25%), three, and in 3 (18.7%), four and more. The most frequent complications included gastric stasis (50.1%), arrosive hemorrhage (18.8%), gastrointestinal ulcer hemorrhage (18.8%) and pneumonia (18.8%). The types and the incidence rate of complications depending on the volume of the venous resection follow in Table 1.

Two (12.5%) female patients underwent relaparotomy for leakage efrom pancreato-digestive anastomosis with arrosive hemorrhage; both patients died due to complications of surgery.

The histopathological study of surgical specimens in 13 (81.3%) out of 16 patients confirmed invasion of the NEN of the pancreatic head to the surrounding adipose tissue. Retroperitoneal extraorgan invasion was verified in 10 (62.5%) cases, and perineural invasion in 6 (37.5%); in 3 patients extrapancreatic lesion was identified, in 2, intrapancreatic, in one patient, extra- and intrapancreatic lesions. The frequency of histologic confirmation of deformation of PV and/or SMV as per Nakao classification was as follows: type A – 33.3%, type B – 87.5%, type C – 75%, type D – 100%.

The median follow-up period of 16 patients was 62.6 [17.7; 98.2] months, the follow-up terms varying from 0.5 to 172.0 months. Disease progression was found in 10 (62.5%) patients after 3 to 69.3 months (median time before progression was found was 39.7 [7.1; 52.8] months). Local relapse developed in 2 (12.5%) patients, metastases in the liver in 7 (43.75%)

Complication	Volume of major vein resection						Total (n=16)	
	PV (n=1)		SMV (n=8)		SMV+PV (n=7)		Abs.	%
	Abs.	%	Abs.	%	Abs.	%		
Bilio-digestive anastomosis leakage	-	-	1	12,5	-	-	1	6,3
Pancreato-digestive anastomosis leakage	-	-	1	12,5	1	14,3	2	12,5
Pancreatic fistula (type)	Total	-	1	12,5	1	14,3	2	12,5
	B	-	1	12,5	-	-	1	6,3
	C	-	-	-	-	1	14,3	1
Gastric stasis	-	-	5	62,5	3	42,9	8	50,1
Intestinal fistula	-	-	1	12,5	-	-	1	6,3
Peritoneal abscess	-	-	1	12,5	-	-	1	6,3
Cholangitis	-	-	-	-	1	14,3	1	6,3
Arrosive hemorrhage	-	-	1	12,5	2	28,6	3	18,8
Gastrointestinal ulcer hemorrhage	-	-	2	25,0	1	14,3	3	18,8
SMV and/or PV thrombosis	-	-	1	12,5	1	14,3	2	12,5
PATE								
Diarrhea	-	-	1	12,5	-	-	1	6,3
Pneumonia	-	-	1	12,5	2	28,6	3	18,8
Pleuritis								
Multi-organ failure	-	-	-	-	2	28,6	2	12,5
Sepsis	-	-	1	12,5	1	14,3	2	12,5

Table 1. Types and incidence rate of complications depending on venous resection during surgical treatment of patients with neuroendocrine neoplasm of the pancreatic head with invasion of major veins

Таблица 1. Виды и частота осложнений в зависимости от объема венозной резекции во время хирургического лечения пациентов с НЭН головки ПЖ с инвазией магистральных вен

patients, metastases in the retroperitoneal lymph nodes in one (6.25%) patients. In the event of progression all patients received antitumor therapy with analogs of slow-release somatostatin. As of the end of the study, eight patients were dead and two patients were alive.

It is to be mentioned that out of the 7 patients with metastases to the liver, two female patients underwent liver resection in the course of anti-tumor treatment with analogs of slow-release somatostatin, after which they lived without manifestations of disease for two years when secondary progression of the NEN (metastases to the liver) developed.

One of these female patients (age: 22) underwent surgical treatment of stage III NEN (T4N0M0G2) in the volume of standard radical pancreatoduodenectomy with wall resection of the SMV with repair performed using a running suture. The metastasis to the liver was diagnosed 53 months after the surgery. The patient received no additional antitumor therapy. The patient underwent resection of the metastasis to the liver and received anti-tumor treatment with analogs of slow-release somatostatin. 24 months later, recurrent progression of the NEN was diagnosed (metastases to the liver and retroperitoneal lymph nodes). The patient died 100.6 months after the surgery.

The second female patient (age: 51) underwent surgical treatment of stage III NEN (T4N0M0G2) in the volume of radical extended pancreatoduodenectomy with circular resection of the PV with end-to-end anastomosis formation. After 66 months, metastases to the liver were found. The metastases were resected, and anti-tumor treatment with analogs of slow-release somatostatin was administered. 23 months later, metastases in the liver developed recurrently. The death was certified 99.5 months after surgical treatment of the NEN.

The overall survival median of the 16 patients with NEN of the pancreatic head with invasion in the major veins was 70.1 [11.4; 100.1] months, recurrence-free survival was 49.2 [14; 66.7] months; one-year survival was 81.2±9.8% and 78.6±11.0%, respectively; three-year survival was 68.2±11.8%

and 63.5±13.1%, five-year survival, 68.2±11.8% and 36.3±14.0%, ten-year survival, 20.5±12.5% and 18.1±11.5%.

No statistically significant differences of any of the represented indicators depending on the volume of vein resection were identified (p>0.05).

DISCUSSION

Our findings match the data of A. Nießen et al. [8]. It follows from literature that the complications after the vascular resections in patients with neuroendocrine neoplasias of the pancreas are characterized with an acceptable incidence rate and low level of mortality in comparison with similar surgeries without vascular resections [9–11].

In almost all studies, remote oncological outcomes of pancreatic head resection with vascular reconstruction in patients with highly and moderately differentiated neuroendocrine tumors confirm favorable prognosis, especially in R0 resections and lack of remote metastases [12–14]. E.g., D.J. Birnbaum et al. (2015) report that the median overall survival of patients with locally advanced forms of pancreatic NENs was 90 months, five-year overall survival was 66%, and five-year recurrence-free survival was 26% [15]. In the study of A. Nießen et al. [8], the overall five-year survival of patients with NEN who underwent PV resection was 66.7% for G1 tumors and 51.2% for G2 tumors (p=0.0008), with greater difference in the five-year recurrence-free survival, 66.7% and 22.8%, respectively. For the entire group of patients after vascular resection, three-year overall survival was 66.4%, five-year survival – 44.6%, and ten-year survival reached 41.2%.

The surgical treatment for patients with pancreatic head NENs involving the SMV and/or PV is feasible, relatively safe, and can be combined with liver resection for resectable metastases. The 5-year overall and recurrence-free survival rates reach high values, supporting the viability and efficacy of vascular resections in pancreatic head NENs, provided the tumors are well- to moderately differentiated and surgical treatment is radical.

CONCLUSION

The outcomes of surgical treatment for patients with highly differentiated to moderately differentiated (G1, G2) pancreatic head NENs invading the PV and/or SMV support the feasibility, relative safety and efficacy of resecting these major veins. For the majority of patients, surgeries can be performed radically

and appended with liver resection for resectable metastases. Considering the relatively favorable prognosis of the disease, resection of resectable liver metastases can be performed even upon disease progression at any stage. This approach is safe, it improves the patients' quality of life and prolongs the symptom-free period. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical Approval Statement. The article was performed as part of the dissertation "Angioplasty operations in abdominal oncology" for the degree of Doctor of Medical Sciences. The thesis topic was approved by the Scientific Council of the Scientific Research Institute of Clinical Oncology n.a. Academician of the Russian Academy of Sciences and the Russian Academy of Medical Sciences N.N. Trapeznikov, Blokhin National Research Medical Center of Oncology.	Этическая экспертиза. Статья выполнена в рамках диссертации «Ангиопластические операции в абдоминальной онкологии» на соискание ученой степени доктора медицинских наук. Тема диссертации утверждена на ученом совете НИИ Клинической онкологии имени академика РАН и РАМН Н.Н. Трапезникова ФГБУ НМИЦ онкологии имени Н.Н. Блохина Минздрава России.
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Abgaryan M.G., Berdnikov S.N., Avdyukhin I.G., Belozerskikh A.M.: data collection, analysis and interpretation, preparation of the text of the article. Abgaryan M.G., Kotelnikov A.G.: study concept and design. Peregorodiev I.N., Polyakov A.N.: editing of the article. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Абгарян М.Г., Бердников С.Н., Авдюхин И.Г., Белозерских А.М.: сбор, анализ и интерпретация данных, подготовка текста статьи. Абгарян М.Г., Котельников А.Г. – концепция и дизайн работы. Перегородиев И.Н., Поляков А.Н. – редактирование текста статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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