

INTRAOPERATIVE PHOTODYNAMIC THERAPY IN GASTRIC CANCER PATIENTS

Filonenko E.V., Kaprin A.D., Suleymanov E.A., Urlova A.N., Khomyakov V.M., Vashakmadze L.A., Sokolov V.V., Kirillov N.V.

National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russia

Abstract

Results of intraoperative photodynamic therapy (IOPDT) in patients with gastric cancer are represented in the article. The study included 240 patients with gastric cancer stage II-IV (T3-4N0-3M0-1) with evident or suspected peritoneal dissemination who underwent examination and treatment in P. Herzen Moscow Oncology Research Institute. The group 1, the study group, included 140 patients who underwent nominally curative or palliative surgery for locally advanced and disseminated gastric cancer with IOPDT as additional intraoperative intervention for antineoplastic and cancer treatment. The group 2, the control group, included 100 patients who also underwent nominally curative or palliative surgery (equal to extent of surgery in patients from the study group) for locally advanced and disseminated gastric cancer and no intraoperative implication of physical or chemical treatment methods. IOPDT did not worsen a course of early post-operative period, did not impact on severity of post-operative complications and was not associated with increase of post-operative mortality. IOPDT allowed for improvement of 1-year and 3-year disease-specific survival rates: by 16.1% and 16.7%, respectively. For nominally curative resections, median survival, 1-year and 3-year disease-specific survival rates were improved by 14 months, 17.8% and 31.3%, respectively. For R1, R2 resections, IOPDT improved 1-year disease-specific survival rates by 16.4%. Additionally, for nominally curative resections IOPDT did not increase the recurrence rate and improved median recurrence-free survival, 1-year and 3-year recurrence-free survival rates by 16 months, 27.2% and 25.4%, respectively.

Key words: gastric cancer, peritoneal carcinomatosis, intraoperative photodynamic therapy.

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Contacts: Filonenko E.V., e-mail: derkul23@yandex.ru

ИНТРАОПЕРАЦИОННАЯ ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ БОЛЬНЫХ РАКОМ ЖЕЛУДКА

Е.В. Филоненко, А.Д. Каприн, Е.А. Сулейманов, А.Н. Урлова, В.М. Хомяков, Л.А. Вашкамадзе, В.В. Соколов, Н.В. Кириллов

Национальный медицинский исследовательский радиологический центр Минздрава России, Москва, Россия

Резюме

В статье представлены результаты применения интраоперационной фотодинамической терапии (ИОФДТ) у больных раком желудка. В исследование включены 240 пациентов раком желудка II-IV стадии (T3-4N0-3M0-1) с наличием или подозрением на перитонеальную диссеминацию, которым в МНИОИ им. П.А. Герцена были проведены обследование и лечение. В первую, основную группу включено 140 больных, которым выполнены условно-радикальные или паллиативные операции по поводу местно-распространенного и диссеминированного рака желудка с применением в качестве метода дополнительного интраоперационного воздействия с целью интраоперационной антибластической и противоопухолевого воздействия – ИОФДТ. Вторую, контрольную группу составили 100 больных, которым были выполнены также условно-радикальные и паллиативные операции (по объему соответствующие хирургическим вмешательствам у больных основной группы) по поводу местно-распространенного и диссеминированного рака желудка без интраоперационного применения физических или химических методов воздействия. ИОФДТ не ухудшила течение раннего послеоперационного периода, не влияла на тяжесть послеоперационных осложнений и не ассоциирована с увеличением послеоперационной летальности. Проведение ИОФДТ позволило улучшить показатели 1-летней и 3-летней общей специфической выживаемости: на 16,1% и 16,7%, соответственно. При условно-радикальных операциях – медиану выживаемости на 14 мес, показатели 1-летней и 3-летней общей специфической выживаемости – на 17,8% и 31,3%, соответственно. При операциях в объеме R1, R2 проведение ИОФДТ улучшило 1-летнюю общую специфическую выживаемость на 16,4%. Кроме того, при условно-радикальных операциях проведение ИОФДТ не увеличило частоту рецидивов и улучшило

медиану безрецидивной выживаемости на 16 мес, показатели 1-летней и 3-летней безрецидивной выживаемости – на 27,2% и 25,4%, соответственно.

Ключевые слова: рак желудка, канцероматоз брюшины, интраоперационная фотодинамическая терапия.

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Контакты: Филоненко Е.В., e-mail: derkul23@yandex.ru

Introduction

Gastric cancer is one of the most common cancer digestive tract. In 2015 in Russia in structure of oncological diseases this pathological condition occupied 6th place (6.7%) after cancer of skin, breast and lung [1]. For gastric cancer peritoneal carcinomatosis is the most common type of metastasis [2,3,4] with incidence of 30–40% and median survival no more than 3.1 months without treatment [5].

The main method of treatment of resectable gastric cancer stage I–IV is curative surgery aimed at removal of primary tumor and all loco-regional metastases [6–9]. However, even for macroscopically complete cytoreduction the possibility of tumor cells diffusion over peritoneum cannot be excluded [10]; consequently surgical methods should be combined with additional antitumor methods. Considering disadvantages of systemic chemotherapy combined with cytoreductive resections for peritoneal carcinomatosis, there is necessity for development of new antitumor methods aimed at not only prevention of tumor cells from spreading over peritoneum but also at destruction of tumor cells. One of the promising directions is photodynamic therapy (PDT).

Results of IOPDT in patients with gastric cancer are represented in the article.

Materials and methods

The study included 240 patients with gastric cancer stage II–IV (T3–4N0–3M0–1) with evident or suspected peritoneal dissemination who underwent examination and treatment in P. Herzen Moscow Oncology Research Institute from 2005 to 2012. In all patients gastric tumor invaded to serosa and infiltrated adjacent organs and structures with no distant hematogenous and extraperitoneal lymphogenous metastases.

The group 1, the study group, included 140 patients who underwent nominally curative or palliative surgery for locally advanced and disseminated gastric cancer with IOPDT as additional intraoperative intervention for antitumor and cancer treatment. The group 2, the control group, included 100 patients who also underwent nominally curative or palliative surgery (equal to extent of surgery in patients from the study group) for locally advanced and disseminated gastric cancer and no intraoperative implication of physical or chemical treatment methods.

The study group included 83 (59.3%) men and 57 (40.7%) women, the control group – 61 (61%) men and 39 (39%) women. There were no differences in the gender

distribution between groups (F-test, $\chi^2=0.07$; $p=0.79$).

The age of patients accounted from 20 to 73 y.o. The minimal age in the study group and in the control group was 20 and 27 y.o., respectively; the maximal age – 72 and 73 y.o., respectively. The average age in the study group was 54.4 ± 11.1 y.o., in the control group – 57.1 ± 11.2 y.o. More than a half of patients (133 patients (55.5%)) were in socially active age group of 20–59 y.o. There were no differences by age between groups (t-test, $p=0.95$).

According to full examination data, 180 (75%) of 240 patients had different co-morbidity: 111 (79.3%) patients in the study group and 69 (69%) patients in the control group. There were no differences in the co-morbidity rate and structure between groups (F-test, $\chi^2=3.29$; $p=0.07$).

The clinical diagnosis according to international TNM staging system (6th ed.) was assigned in all patients after standard examination. For the study group, stage II (T3N0M0) was in 17 (12.1%) patients, stage IIIA (T3N1M0, T4N0M0) – in 21 (15%), stage IIIB (T3N2M0) – in 18 (12.9%) and stage IV (T3N0–3M0–1; T4N1–3M0–1) – in 84 (60%). For the control group, stage II (T3N0M0) was in 13 (13%) patients, stage IIIA (T3N1M0, T4N0M0) – in 18 (18%), stage IIIB (T3N2M0) – in 15 (15%) and stage IV (T3N0–3M0–1; T4N1–3M0–1) – in 54 (54%). In the study and control groups the majority of patients had gastric cancer stage IV – 60% и 54%, respectively. There was no difference in stage distribution between groups (F-test, for stage II – $p=0.49$; for stage IIIA – $p=0.32$; for stage IIIB – $p=0.39$; for stage IV – $p=0.21$).

According to full examination data in the study and control groups, involvement of one portion of stomach was diagnosed in 32 (22.9%) and 28 (28%) patients, subtotal involvement – in 77 (55%) and in 63 (63%), total involvement – in 31 (22.1%) and in 19 (19%), respectively. There was no difference in tumor location in stomach between groups (F-test, for lower third involvement (antral portion) – $p=0.25$, middle third (body of stomach) – $p=0.31$, upper third (cardiac portion) – $p=0.39$, for subtotal involvement – $p=0.43$, for total involvement – $p=0.34$).

According to histological data in the study group, well differentiated adenocarcinoma was diagnosed in 2 (1.4%) patients, moderately differentiated adenocarcinoma – in 12 (8.6%), poorly differentiated adenocarcinoma – in 31 (22.1%), signet-ring cell carcinoma – in 40 (28.6%), combination of signet-ring cell carcinoma with adenocarcinoma – in 55 (39.3%). For the control group, well differen-

tiated adenocarcinoma was diagnosed in 2 (2%) patients, moderately differentiated adenocarcinoma – in 14 (14%), poorly differentiated adenocarcinoma – in 20 (20%), signet-ring cell carcinoma – in 22 (22%), combination of signet-ring cell carcinoma with adenocarcinoma – in 42 (42%). Thus, the study and control groups had predominately a combination of signet-ring cell carcinoma with adenocarcinoma (39.3% and 42%, respectively). There was no difference in morphological diagnosis between groups (F-test; well differentiated adenocarcinoma – $p=0.55$; moderately differentiated adenocarcinoma – $p=0.13$; poorly differentiated adenocarcinoma – $p=0.41$; signet-ring cell carcinoma – $p=0.16$; combination of signet-ring cell carcinoma with adenocarcinoma – $p=0.39$).

Intraoperative photodynamic therapy technique

For PDT we used photosensitizer fotogem (produced by “Fotogem”, Russia), a hematoporphyrin derivative. Fotogem was administered intravenously at a dose of 2.5 mg/kg body weight 48 h before surgery. Patients kept light regimen for 3-4 weeks after injection.

Surgical step was performed according to tumor distribution. If applicable, complete removal of primary tumor and all peritoneal metastases was done, where definitive treatment was impossible, palliative surgery with removal of primary tumor and maximal volume of peritoneal dissemination was carried out.

For both scenarios, IOPDT session was performed after completion of surgical step with sequential polypositional irradiation of all regions of parietal peritoneum at a dose of 6-10 J/cm² (Fig. 1). Exposure of visceral peritoneum was carried out by scattering irradiation and irradiation from a source of incoherent emission – operating lamp – for the duration of surgical procedure.

Results

Efficacy of IOPDT in patients with gastric cancer was analyzed by comparing results of treatment in the study and control groups. For this purpose completeness of cytoreduction, rate and profile of post-operative complications, mortality in early post-operative period and long-term results were assessed.

Characteristics of the surgical step

All patients had extended and combined surgery. The duration of surgical step accounted from 3 to 6.5 h.

The curative potential of gastric surgery was characterized using Japanese Classification of Gastric Carcinoma, JGCA (1998) [11]. According to this classification 3 types of resections are defined: A, B and C. Resection A implies curative surgery and appropriate for primary tumor T1 or T2 and for stage M0 (H0 – no liver metastases, P0 – no dissemination); N0 treated by D1, D2, D3 lymphadenectomy; N1 – D2, D3 lymphadenectomy; this type of resection is characterized by Cyt 0 – no tumor cells in peritoneal

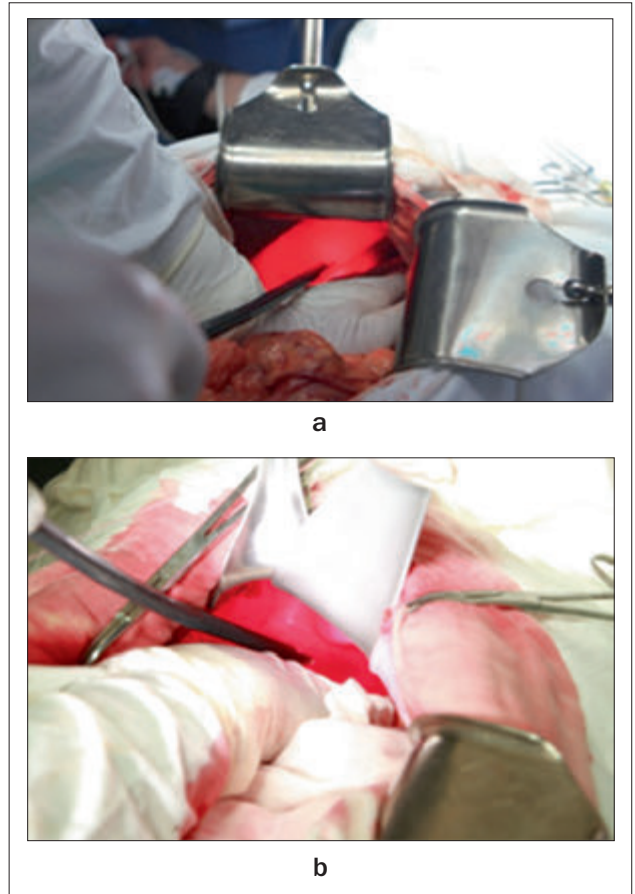


Fig. 1. IOPDT session:
 a – irradiation of upper region peritoneum;
 b – irradiation of pelvic peritoneum
Рис. 1. Сеанс ИОФДТ:
 а – облучение брюшины верхних отделов брюшной полости;
 б – облучение брюшины малого таза

lavage, and also by proximal and distal margins clearance more than 10 mm. Resection B implies resections with no residual disease (R0) but not fulfilling criteria for “Resection A”. This type of resection was defined as nominally curative surgery. For resection C, there is micro (R1) or macro (R2) residual tumor, this type is equivalent to palliative surgery. If unresectable tumor is detected during the surgery and surgery is terminated on this step this surgical intervention is defined as exploratory surgery. There were no resections A and no exploratory surgeries in our study. Distribution of patients according to curative potential of gastric surgery is represented in table 1.

For the study group, 78 (55.7%) patients underwent nominally curative resections (R0), 62 (44.3%) patients had palliative surgery (R1 – in 17 (12.2%), R2 – in 45 (32.1%) patients). For the control group, 58 (58%) patients underwent nominally curative resections (R0), 42 (42%) patients had palliative surgery (R1 – in 7 (7%), R2 – in 35 (35%) patients).

Thus, in the study and control groups rates of resections R0 and R1, R2 were approximately equal (rates of

Table 1
 Distribution of patients according to curative potential of gastric surgery

Таблица 1
 Распределение больных в зависимости от радикальности выполненной операции

Group of patients Группа больных	Type of resection Тип операции			Total, abs. (%) Итого, абс. (%)
	B	C		
		R0	R1	
Study group, abs. (%) Основная, абс. (%)	78 (55.7%)	17 (12.2%)	45 (32.1%)	140 (100%)
Control group, abs. (%) Контрольная, абс. (%)	58 (58%)	7 (7%)	35 (35%)	100 (100%)
Total, abs. (%) Всего, абс. (%)	136 (56.7%)	24 (10%)	80 (33.3%)	240 (100%)

resection R0 accounted for 55.7% and 58%, resection R1, R2 – 44.3% and 42%, respectively). There was no difference in curative potential of gastric surgery between groups (F-test, for R0 p=0.41; for R1 p=0.14; for R2 p=0.37).

Distribution of patients according to the extent of surgery is represented in table 2. Distal subtotal gastric resection was performed in 17 (12.2%) patients from the study group and in 12 (12%) patients from the control group, gastrectomy – in 37 (26.4%) and 27 (27%), combined resections – in 86 (61.4%) and 61 (61%), respectively.

In the study and control groups the majority of surgical procedures were combined resections (61.4% and 61%, respectively) due to extent of tumor. Gastrectomy was combined with resection of transverse colon, pancreas, liver, diaphragm, spleen. D2, D3 lymphadenectomy was performed. There was no difference in extent of surgery between groups (F-test, for distal subtotal gastric resection – p=0.57; for gastrectomy – p=0.52; for combined resection – p=0.53).

Early post-operative period

To compare the study group with the control group for course of post-operative period we used follow-

ing criteria: rate of acute post-operative complications, profile of acute post-operative complications, grade of acute post-operative complications, necessity for surgical treatment of complications and mortality. Chosen criteria allow assessing feasibility of IOPDT with no risk of worsening of early results of treatment.

Acute post-operative complications were in 32 (22.9%) of 140 patients in the study group and in 26 (26%) of 100 patients in the control group. Statistical analysis of rates of post-operative complications in the study and control groups with F-test showed no differences (p=0.32).

Patients in the study group had following acute post-operative complications: necrotizing pancreatitis – 19 (13.6%), esophago-intestinal anastomotic leakage – 4 (2.9%), colon anastomotic leakage – 1 (0.7%), acute intestinal obstruction – 4 (2.9%), postoperative wound infection – 3 (2.1%), pleuritis – 9 (6.4%), pneumonia – 5 (3.6%), pulmonary thromboembolism – 2 (1.4%). For the control group necrotizing pancreatitis was in 14 (14%) patients, esophago-intestinal anastomotic leakage – 1 (1%), acute intestinal obstruction – 2 (2%), postoperative wound infection – 2 (2%), pleuritis – 5 (5%), pneumonia – 3 (3%), pulmonary thromboembolism – 2 (2%), acute myocardial

Table 2
 Distribution of patients according to the extent of surgery

Таблица 2
 Распределение больных в зависимости от объема операции

Group of patients Группа больных	Type of operative procedure			Total, abs. (%) Итого, абс. (%)
	Distal subtotal gastric resection Дистальная субтотальная резекция желудка	Gastrectomy Гастрэктомия	Combined resection Комбинированная гастрэктомия	
Study group, abs. (%) Основная, абс. (%)	17 (12.2%)	37 (26.4%)	86 (61.4%)	140 (100%)
Control group, abs. (%) Контрольная, абс. (%)	12 (12%)	27 (27%)	61 (61%)	100 (100%)
Total, abs. (%) Всего, абс. (%)	29 (12.1%)	64 (26.7%)	147 (61.3%)	240 (100%)

infarction – 1 (1%), intra-abdominal hemorrhage – 1 (1%).

Thus, patients in the study and control groups most commonly had necrotizing pancreatitis and inflammation in lungs and pleura (13.8% and 9.1%, respectively) (table 3). Such profile of post-operative complications is due to the fact, that the majority of surgical procedures in the study and control groups were combined resections (61.4% and 61%, respectively). Additionally, pleuritis and pneumonia was associated with other types of complications (necrotizing pancreatitis, esophago-intestinal anastomotic leakage etc.) in the study and control groups.

In the profile of acute post-operative complications there was no colon anastomotic leakage in the control group ($p=0.58$) comparing with the study group, but there were acute myocardial infarction ($p=0.42$) and intra-abdominal hemorrhage ($p=0.42$). Statistic analysis using F-test showed no significant differences in the profile of acute post-operative complications. The p-values for necrotizing pancreatitis, anastomotic leakage, acute intestinal

obstruction, inflammation in lungs and pleura, thrombosis, wound infection when compared control group vs. IOPDT were 0.53, 0.21, 0.51, 0.39, 0.46, 0.65, respectively.

Surgical treatment for early post-operative complications was performed in 9 (28.1%) of 32 patients of the study group and in 8 (30.8%) of 26 patients of the control group. Statistic analysis of rates of surgeries for early post-operative complications using F-test showed no significant differences between the study and control groups ($p=0.52$).

There were 3 (2.1%) deaths in the study group and 3 (3%) patients died in the control group. Causes of death were pulmonary thromboembolism and necrotizing pancreatitis. Statistic analysis of mortality using F-test showed no significant differences between the study and control groups ($p=0.32$).

Long-term results

To evaluate efficiency of IOPDT long-term results in the study and control group were analyzed. For disease-

Table 3

Profile of acute post-operative complications

Таблица 3

Структура ранних послеоперационных осложнений

Type of complication Вид осложнений	Study group, abs. (% of total number of patients in the group) Основная группа, абс. (% от общего количества пациентов в группе)	Control group, abs. (% of total number of patients in the group) Контрольная группа, абс. (% от общего количества пациентов в группе)	Total, abs. (% of total number of patients) Итого, абс. (% от общего количества пациентов)
Necrotizing pancreatitis Панкреонекроз	19 (13.6%)	14 (14%)	33 (13.8%)
Esophago-intestinal anastomotic leakage Несостоятельность пищеводно-кишечного анастомоза	4 (2.9%)	1 (1%)	5 (2.1%)
Colon anastomotic leakage Несостоятельность толстокишечного анастомоза	1 (0.7%)	0	1 (0.4%)
Acute intestinal obstruction Острая кишечная непроходимость	4 (2.9%)	2 (2%)	6 (2.5%)
Postoperative wound infection Нагноение послеоперационной раны	3 (2.1%)	2 (2%)	5 (2.1%)
Pleuritis Плеврит	9 (6.4%)	5 (5%)	14 (5.8%)
Pneumonia Пневмония	5 (3.6%)	3 (3%)	8 (3.3%)
Pulmonary thromboembolism Тромбоз легочной артерии	2 (1.4%)	2 (2%)	4 (1.7%)
Acute myocardial infarction Острый инфаркт миокарда	0	1 (1%)	1 (0.4%)
Intra-abdominal hemorrhage Внутрибрюшное кровотечение	0	1 (1%)	1 (0.4%)
Total number of patients with complications, abs. (% of total number of patients in the group) Всего пациентов с осложнениями, абс. (% от общего количества пациентов в группе)	32 (22.9%)	26 (26%)	58 (24.2%)

specific survival the end-point was a death of a patient from cancer disease. For recurrence-free survival the end-point was a recurrence or progression of cancer in patients who underwent nominally curative surgery. Patients who died in early post-operative period from complications (n=6) were excluded from the analysis. Long-term results were obtained in 97.5% of patients.

For the study group, maximal follow-up period was

72 months with median survival of 20 months. One-year disease-specific survival accounted for $70.6 \pm 3.9\%$, 3-year – $39.6 \pm 4.3\%$. For the control group, maximal follow-up period was 58 months with median survival of 13 months. One-year disease-specific survival accounted for $54.5 \pm 5.1\%$, 3-year – $22.9 \pm 4.4\%$. Statistic analysis using Log-Rang Test showed no significant difference between groups but data tended toward significance ($p=0.07$) (Fig. 2).

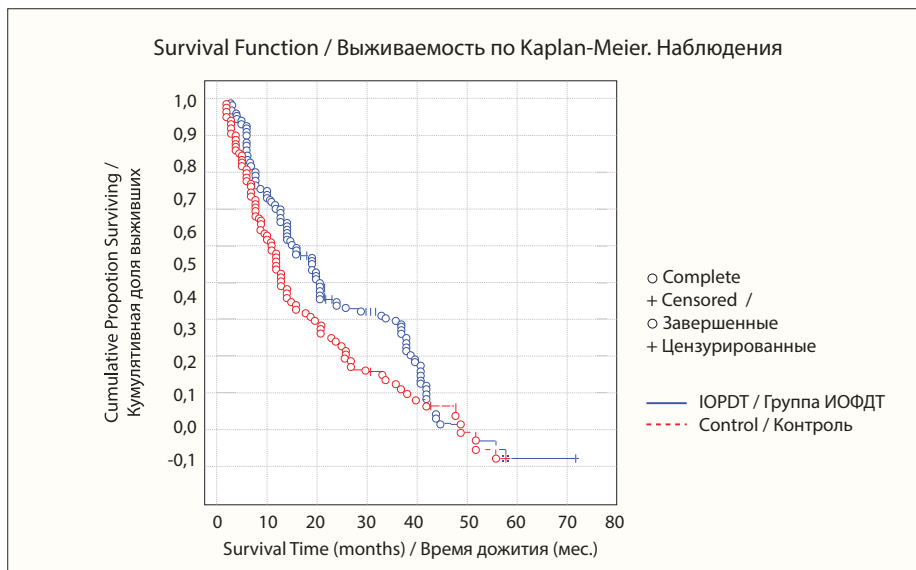


Fig. 2. Disease-specific survival in the study and control groups
Рис. 2. Общая специфическая выживаемость в основной и контрольной группах

For the study group, in patients with nominally curative resections maximal follow-up period was 72 months with median survival of 41 months. One-year disease-specific survival accounted for $96.1 \pm 2.2\%$, 3-year – $71.4 \pm 5.5\%$. For the control group, maximal fol-

low-up period was 58 months with median survival of 27 months. One-year disease-specific survival accounted for $78.3 \pm 5.5\%$, 3-year – $40.1 \pm 6.8\%$. Statistic analysis using Log-Rang Test showed significant difference between groups ($p=0.05$) (Fig. 3).

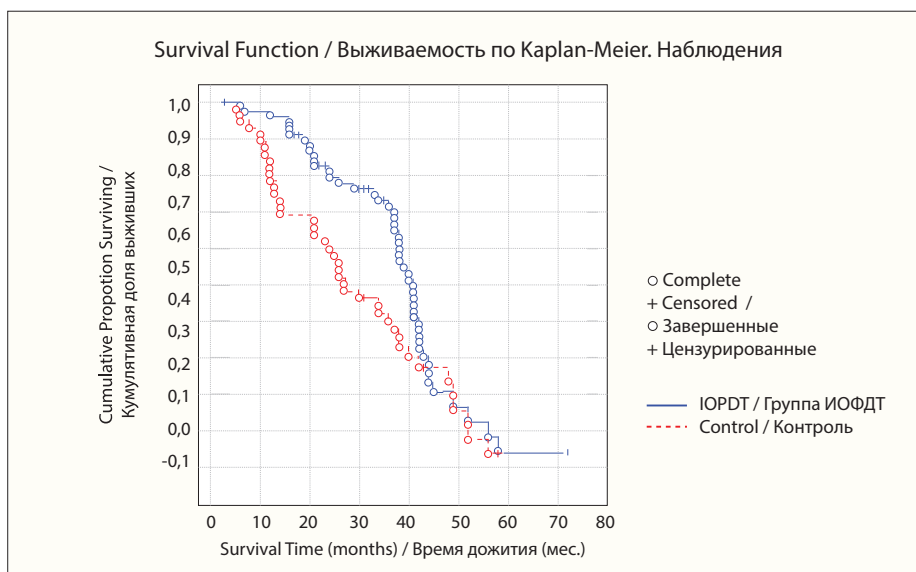


Fig. 3. Disease-specific survival in the study and control groups in patients with nominally curative resections
Рис. 3. Общая специфическая выживаемость в основной и контрольной группах при условно-радикальных операциях

For the study group, in patients with R1, R2 resections maximal follow-up period was 21 months with median survival of 8 months. One-year disease-specific survival accounted for $38.3 \pm 6.3\%$. For the control group, maximal

follow-up period was 20 months with median survival of 7 months. One-year disease-specific survival accounted for $21.9 \pm 6.4\%$. Statistic analysis using Log-Rang Test showed significant difference between groups ($p=0.04$) (Fig. 4).

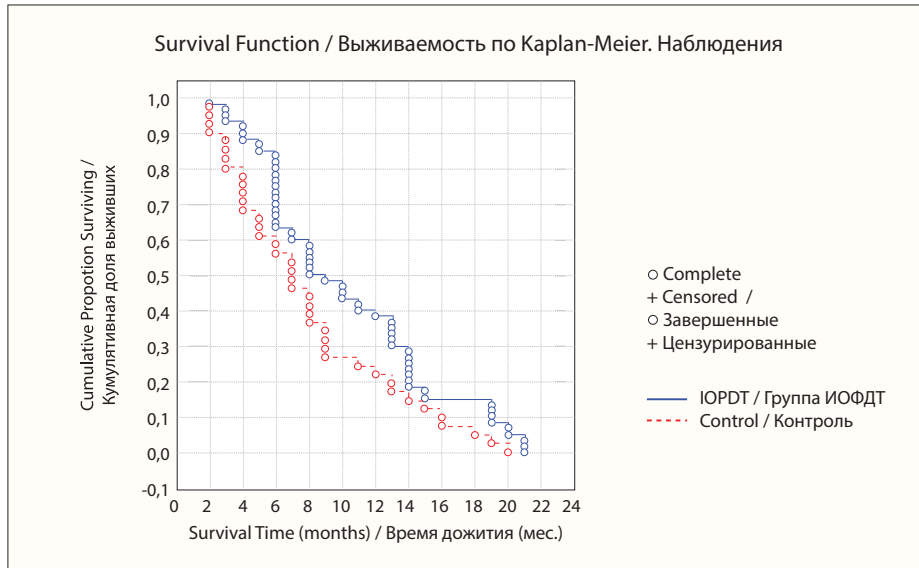


Fig. 4. Disease-specific survival in the study and control groups in patients with R1, R2 resections
Рис. 4. Общая специфическая выживаемость в основной и контрольной группах при операциях R1 и R2

For the study group, in patients with nominally curative resections the recurrence diagnosed in 52 (66.7%) of 78 patients, in the control group – in 43 (74.1%) of 58. Statistic analysis using Log-Rang Test showed no significant difference between groups (F-test, $p = 0.23$).

For the study group, in patients with nominally curative resections maximal follow-up recurrence-free period accounted for 72 months with median recurrence-free

survival of 37 months. One-year recurrence-free survival accounted for $89.4 \pm 3.5\%$, 3-year – $51.9 \pm 6.1\%$. For the control group, maximal follow-up recurrence-free period accounted for 58 months with median recurrence-free survival of 21 months. One-year recurrence-free survival accounted for $62.2 \pm 6.5\%$, 3-year – $26.5 \pm 6.2\%$. Statistic analysis using Log-Rang Test showed significant difference between groups ($p=0.03$) (Fig. 5).

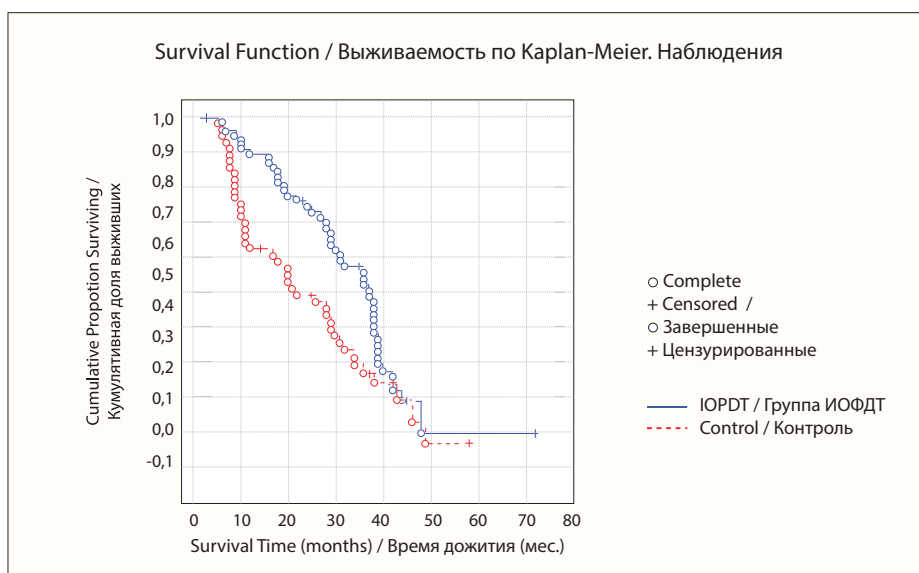


Fig. 5. Recurrence-free survival in the study and control groups in patients with nominally curative resections
Рис. 5. Безрецидивная выживаемость в основной и контрольной группах при условно-радикальных операциях

Discussion

Historically methods of additional antitumor methods developed from irrigation with solutions and instillation of radioactive substances to implication of photosensitizing agents for photodynamic destruction of tumor implants and also to implication chemotherapeutical agents injected to peritoneum at doses exceeding standard ones for systemic treatment [12]. Toxicity of intraperitoneal chemotherapy may be high and efficiency of disease control depends considerably on histological structure of the tumor [13,14]. Despite the active development of intraperitoneal chemotherapy treatment results in patients with gastric cancer with peritoneal carcinomatosis remain unsatisfactory: post-operative complications are up to 40%, post-operative mortality – 20%, median survival rates – 6–15.4 months, 1-year survival rates by Kaplan–Meier – up to 50.7% [15–17].

In our study, IOPDT did not worsen a course of early post-operative period, did not impact on severity of post-operative complications and was not associated with increase of post-operative mortality when comparing the study and control groups ($p=0.32$). IOPDT

allowed for improvement of median survival, 1-year and 3-year disease-specific survival rates: by 7 months, 16.1% and 16.7%, respectively ($p=0.07$). For nominally curative resections, median survival, 1-year and 3-year disease-specific survival rates were improved by 14 months, 17.8% and 31.3%, respectively ($p = 0.05$). For R1, R2 resections, IOPDT improved median survival and 1-year disease-specific survival rates by 1 month and 16.4% ($p=0.04$), respectively. Additionally, for nominally curative resections IOPDT did not increase the recurrence rate ($p=0.23$) and improved median recurrence-free survival, 1-year and 3-year recurrence-free survival rates by 16 months, 27.2% and 25.4%, respectively ($p = 0.03$).

Conclusion

Intraoperative photodynamic therapy is an efficient and safe method of intraoperative intervention in patients with gastric cancer with high risk or confirmed peritoneal dissemination. Widespread implementation of the method into clinical practice will promote improvement of oncological treatment results in this group of patients.

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