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Research Article

The Role of Radiotherapy in Neoadjuvant Treatment of Patients with Operable Pancreatic Head Cancer

LI Korytova*, DA Sklyar, AV Pavlovsky, EV Vlasova, AA Polikarpov, OV Korytov and VE Moiseenko

Federal State Budgetary Institution "Russian Scientific Center of Radiology and Surgical Technologies Named After Academician A.M. Granov" of Ministry of Health of the Russian Federation, St. Petersburg, Russia

***Corresponding Author:** LI Korytova, Federal State Budgetary Institution "Russian Scientific Center of Radiology and Surgical Technologies Named After Academician A.M. Granov" of Ministry of Health of the Russian Federation, St. Petersburg, Russia.

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Abstract

In the article "The role of radiotherapy in neoadjuvant treatment of patients with operable pancreatic head cancer" results of the combined neoadjuvant treatment of operable pancreatic cancer were presented. Patients, suffering from pancreatic cancer (n = 40) were randomized into two arms and compared arm one: intra-arterial chemotherapy + radiation therapy + operation (n = 20) vs arm two: intra-arterial chemotherapy + operation (n = 20).

Neoadjuvant radiation therapy was performed with 2 fractions per day 2 Gy each with 4-6 hours between them 5 days a week up until summary dose of 50 Gy. Neoadjuvant radiation therapy with a double fractioning per day had proven to be safe and effective. Arm 1 had statistically verified lower postoperative pancreatitis frequency and chances to develop fistulas, higher number of second degree pathomorphosis outcomes, as well as life expectancy median.

Keywords: Radiation Therapy; Pancreatic Cancer; Double Day Fractioning

Introduction

Pancreatic cancer (PC) ranks 7th in the worldwide cancer mortality structure [1]. 15 312 new cases of the disease were detected in Russia in 2019. The proportion of patients with stage I-II pancreatic cancer was 20.6% in the same year [2]. The recommended standard of treatment for operable pancreatic cancer is surgical treatment with the use of neo- and adjuvant chemotherapy [3,4,5]. Modern neoadjuvant chemotherapy (CT) improves the long-term results of combined treatment of patients with PC and increases the overall survival median [6].

However, there have been publications on high efficiency of radiation factor inclusion into the neoadjuvant treatment algorithm in the past few years [7].

According to the meta-analysis carried out by Cloyd J. M., *et al.* (2020), neoadjuvant therapy showed a clear trend towards improved treatment outcomes, increasing the overall survival median to 25 months in comparison with the group of patients who underwent surgery alone [8]. The pancreatic cancer tissue is radiation resistant, therefore, to overcome the resistance effect, a combination of radiation and chemotherapeutic radiomodifying

factors was used. The use of radiation therapy (RT) in combination with chemotherapy (CT) as a neoadjuvant in the PREOPANC-1 study showed an increase in the R0 resection rate, an increase in the progression-free period, and a decrease in the rate of local recurrence. In combination with adjuvant treatment in the chemoradiotherapy group, overall survival median reached 35.2 months [9]. The applied regimens of neoadjuvant chemotherapy, such as FOLFIRINOX and gemcitabine and nab-paclitaxel are quite effective, however, they are toxic and are not always well-tolerated by patients, especially in combination with RT [10]. The emergence of adverse events during neoadjuvant chemotherapy makes it necessary to postpone the planned stage of surgical intervention. This, in combination with incomplete preoperative anticancer treatment, can worsen the results of treatment. To reduce the incidence of adverse events resulting from chemotherapy, several studies have used transcatheter arterial infusion of chemotherapy drugs as neoadjuvant modes. Changes in the method of administration of chemotherapy contributed to a decrease in overall toxicity, an increase in the median of the period before relapse (time to progression), and overall survival compared with surgery alone [11,12]. There are various approaches to reduce the toxicity of radiation therapy, one of which is the daytime crushing of the fractional dose of radiation [24,25].

Purpose of the Study

The purpose of this study is to assess the safety and efficiency of patients with operable pancreatic cancer after combined use of radiation with daily double dose fractionation with intra-arterial chemotherapy.

Materials and Methods

The study includes materials from medical histories of 40 patients diagnosed with pancreatic cancer T1-3N0M0, who received treatment in the FSBI "Russian Scientific Center of Radiology and Surgical Technologies named after Academician A.M. Granov" in 2018 - 2021.

The staging of the tumor process was carried out based on the TNM classification of pancreatic cancer (8th edition, 2017) [16].

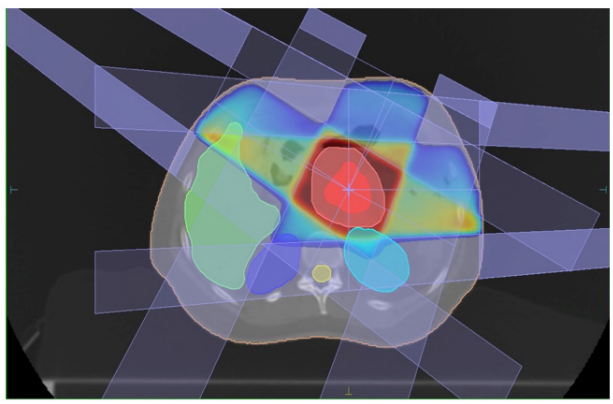
The method of blind randomization was used to compose 2 groups of 20 patients, differing in the algorithm of neoadjuvant treatment. Patients in both groups did not differ in age, stage, tumor histology, and concomitant pathology.

Neoadjuvant treatment in both groups was initiated with intra-arterial chemotherapy.

Intra-arterial chemotherapy in both groups was carried out according to the method accepted in the afore mentioned clinic. Chemoembolization of the pancreatic head tumor was performed by selective injection of oxaliplatin at 85 mg/m^2 with 4 ml of lipiodol into the gastro-duodenal artery after preliminary catheterization of the femoral artery, according to the Seldinger technique. Intra-arterial infusion of 1000 mg/m^2 with gemcitabine was being carried out into the celiac trunk for 3 hours. At the end of the procedure, the catheter was removed.

3 - 5 days after the end of chemotherapy, the control group underwent surgical treatment in pancreatoduodenal resection.

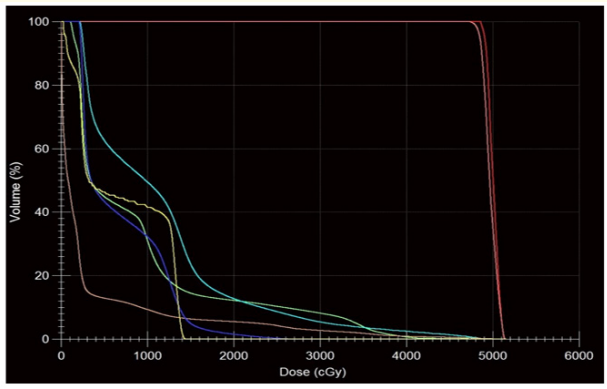
In the study group of the study, 3 - 5 days later, radiation therapy was started on the Axesse Linear accelerator with an energy of 6 MeV with a double irradiation of 2.0 Gy with a 4 - 6-hour break, 5 days a week, to a total dose of 50 Gy. Duration of therapy is 12 - 14 days. 3 - 5 days after the end of the RT, surgical treatment is performed in the volume of pancreatoduodenal resection.



Picture 1: Radiotherapy plan.

Evaluation of adverse events of preoperative anticancer treatment in the study groups was carried out based on the CTCAE version 5.0 criteria.

To assess the therapeutic pathomorphosis in the operational material, the classification of E.F. Lushnikov has been adapted. It



Picture 2: Dose-volume distribution. The histogram shows that the prescriptions were fully implemented.

includes 4 degrees and is characterized by the following features [13]:

- I (weak) - Dystrophic changes in individual tumor cells;
- II (moderate) - The appearance of foci of necrosis and dystrophic changes in tumor cells;
- III (pronounced) - Extensive fields of necrosis, pronounced dystrophic changes in tumor cells, few tumor cells retain their viability;
- IV (pronounced, complete) - The absence of tumor elements [13].

The study groups compared the median time to relapse (time to progression), and life expectancy.

Statistical processing of the material was carried out using Statistica for Windows version 17. The reliability of the results in the groups was determined by comparative analysis (Pearson's test), Fisher's exact method; the reliability of the mean values was determined using the Mann-Whitney U-test and the Student's test [14]. Life expectancy, survival median, time to progression and median time to progression were calculated using the Kaplan-Meier method [15].

Results

The study was dominated by patients with stage 2 of the tumor process in both the main and control groups, 18 people in each group, which is 90% of the total number (Table 1).

Stage	TNM	Study group (n = 20)		Control group (n = 20)		p
		Absolute number	%	Absolute number	%	
Ib	T2N0M0	2	10	2	10	1
IIa	T3N0M0	9	45	10	50	0.752
IIb	T1-3N1M0	9	45	8	40	0.75
Total		20	100	20	100	

Table 1: Distribution of patients by stage in the study and control groups.

Adverse events of preoperative therapy are presented in the table below. In the study group, 1 - 2 grade anemia was observed in two patients (10%), in the control group in three (15%). In the study group 1 - 2 grade neutropenia was observed in three (15%) cases, and in two (10%) cases in the control group. 1 - 2 grade thrombocytopenia was observed in two patients (10%) in the study group. There were no significant differences in the manifestation of hematological toxicity in the groups. Among the manifestations of non-hematological toxicity, 6 patients (30%) of the study group had 1 - 2 grade diarrhea (p = 0.038), while it was registered with only one patient (5%) in the control group. In the study group, nausea 1 - 2 degree observed in 5 patients (25%), in the control group - in 3 patients (15%). 1 - 2-degree vomiting was registered with two (10%) patients from the study group and three patients (15%) from the control group (Table 2).

Immediate results of surgical treatment

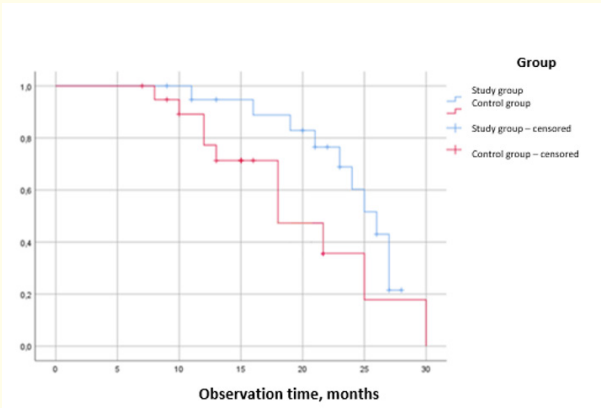
All patients (n = 40) included in the study underwent routine surgical treatment 3 - 5 days after the end of neoadjuvant therapy. Comparison of indicators of patients' condition was carried out. Significant differences in the study and control groups were found in the frequency of complications. The frequency of pancreatic fistulas of type B and C in the study group of diagnosis in 1 (5%) patient versus 6 (30%) patients (p < 0.038); postoperative pancreatitis diagnosis in 3 patients (5%) versus 11 (55%) (p < 0.09), the level of pancreatic amylase after surgery was 7.4 ± 6.09 U/ml versus 139.4 ± 95,8 U/ml in the study group (p = 0.033).

The average life expectancy was 24.1 ± 1.1 months in the study group, and 19.5 ± 2.1 months in the control group. The survival

Type and Degree of Adverse Effects	Study Group (N = 20)	Control Group (N = 20)	P
I Haematological			
Anemia (1-2)	2 (10)	3 (15)	0,633
Neutropenia (1-2)	3 (15)	2 (10)	0,633
Thrombocytopenia (1-2)	2 (10)	0 (0)	0,147
II Non-haematological			
Amylase level increase (1-2)	2 (10)	3 (15)	0,633
AST\ALT level increase (1-2)	5 (25)	3 (15)	0,430
Raise in GGTP level (1-2)	3 (15)	2 (10)	0,633
Nausea (1-2)	5 (25)	3 (15)	0,430
Vomiting (1-2)	2 (10)	3 (15)	0,633
Diarrhea (1-2)	6 (30)	1 (5)	0,038

Table 2: Adverse events after preoperative therapy in the study groups.

median in the study group was 26 ± 1.6 months, and in the control group, 22 ± 1.2 months (p = 0.044) (Picture 3).



Picture 3: Life expectancy.

Based on the results of the assessment of the pathomorphological study of the removed tissues, the diagnosis of pancreatic cancer was confirmed in all patients. In the study group, 19 (95%) patients had a therapeutic pathomorphosis, while in 6 patients (30%) it corresponded to the 2nd degree, in 13 cases (65%) it corresponded to the 1st degree. Signs of medical pathomorphosis of the 1st degree were registered in the control group in 5 people (25%). In the study group, there was a significant increase in the frequency of grade II therapeutic pathomorphosis (p = 0.008).

During further observation of the study group, disease progression was registered in 10 (50%) patients. One patient (5%) had local recurrence, 7 (35%) had liver metastases, one (5%) had lung metastases, and one (5%) had peritoneal carcinomatosis. In the control group, progression was observed in 11 patients: in 4 patients (20%) local recurrence, in 6 (30%) liver metastases and in one (5%) peritoneal carcinomatosis (Table 3).

Indicator	Study Group	Control Group	P
Local recurrence	1	4	0,152
Liver metastases	7	6	0,736
Lung metastases	1	-	0.312
Peritoneal carcinomatoses	1	1	1

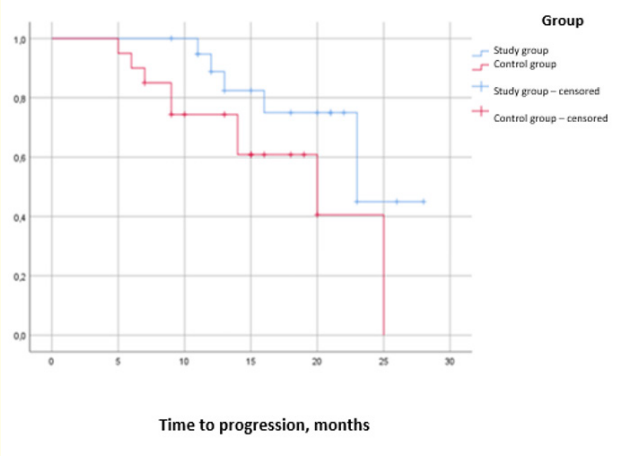
Table 3: Relapse profile in study groups.

The average time to progression was 22.8 ± 1.6 months in the control group, and 17.9 ± 1.9 (p = 0.043) months in the control group. The median time to progression in the study group was 23 ± 4.1 months, and in the control group - 20 ± 1.9 months (p = 0.049) (Picture 4).

Discussion

The generally accepted treatment standard for operable pancreatic cancer involves surgery followed by adjuvant chemotherapy.

However, the radicalism of such treatment depends on the presence of microscopic metastases in the lymph nodes and surrounding tissues [17]. Adjuvant chemotherapy is recommended after surgical treatment for patients to reduce the frequency of early relapses and improve long-term results. However, not all patients manage to undergo CT in time due to the complicated postoperative period.



Picture 4: Time period before progression.

Theoretically, the goal of preoperative chemoradiation therapy for pancreatic cancer is to reduce the area of contact between the tumor and the vessels, increase the likelihood of a negative resection margin, and prolong survival by affecting micrometastases [19]. The use of intra-arterial chemotherapy allows the delivery of chemotherapy drugs selectively to the tumor vessels. Increasing the concentration of chemotherapy drugs in the tumor and regional lymph nodes with superfluid lipiodol allows achieving a pronounced symptomatic effect and potentiating the effect of radiation therapy [20,21].

The use of intra-arterial therapy can reduce the incidence of adverse events. In our study, the frequency of adverse events was comparable to previous studies [11]. There was a significant difference in the increase in the incidence of grade 1 - 2 diarrhea in patients of the study group ($p = 0.038$). The use of double fractionation of the radiation dose makes it possible to reduce the number of adverse events in the early postoperative period, which does not affect the surgical treatment initiation timing. In the work of Peng JS., *et al*. (2019), out of 71 patients who underwent preoperative chemoradiation therapy based on gemcitabine, 38.1% had a moderate response to treatment, which is comparable to our data on 30% of patients in the study group with grade II therapeutic pathomorphosis. ($p = 0.008$) [22].

According to the data of an early study on the incidence of relapses after the use of intra-arterial chemotherapy, the frequency of local relapses was comparable and was at the level of 20% of all patients [23].

The use of conventional radiation therapy in operable pancreatic cancer patients can improve the results [19].

However, the increase of frequency of toxic effects that negatively affect the patients' condition with resectable pancreatic cancer drew attention to possible options of changing the radiation regime. Thus, we focused on publications concerning the effectiveness of the results of using a daily fractionated dose of radiation in combination with chemotherapy in the treatment of other tumor localizations.

Radiation therapy with double daily dose splitting with CT is the "gold standard of radiation" for limited stages of small cell lung cancer [25].

Double day fractionation by Coen Y., *et al.* 2021 was successfully used to preserve the bladder to reduce toxicity when combined with radiation with a highly toxic chemotherapy regimen of CT 5 FU + cisplatin [24].

In our study, a significant difference in pathomorphosis of the 2^{nd} degree was obtained in the study group compared to the control group. There was also an improvement in the survival median of the median time to progression. However, this significantly increased the frequency of diarrhea during RT.

Conclusion

1. Neoadjuvant use of a combination of radiation therapy in the multifractionation mode and intra-arterial selective administration of the drugs gemcitabine and oxaliplatin is safe and is not accompanied by a significant deterioration in the quality of patients' life. Adverse events after the use of radiation therapy did not exceed grade-2, but the differences were not significant ($p > 0.05$).
2. Radiation therapy provides in the postoperative period a significant reduction in the number of significant pancreatic fistulas (type B and C) and manifestations of pancreatitis ($p = 0.008$).

3. In the study group, an increase in the frequency of second-degree therapeutic pathomorphosis was proved (p = 0.043).
4. The combination of radiation therapy and intra-arterial chemotherapy increases life expectancy and median survival (p = 0.049).

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