

Effect of different treatment methods on survival in patients with pancreatic cancer

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Abstract

Purpose: To assess the benefit of treatment modalities on the survival in patients with pancreatic cancer.

Material and methods: Eighty-five patients with pancreatic cancer were treated by surgery, radiotherapy, chemotherapy and combined therapy. The data was reviewed retrospectively and the benefit of various treatment methods to the median survival time of the patients was assessed.

Results: Median survival time of the patients diagnosed with local disease treated by radical resection and adjuvant treatment was 21.5 months; with radical resection only – 12.6 months ($p=0.6$). In patients with locally advanced disease and treated by radical resection and adjuvant therapies the median survival time was 12.1 months and by radical resection only 7.7 months ($p=0.6$). For patients treated by palliative surgery, chemotherapy and radiotherapy median survival was 8.8 months and by palliative surgery alone 1.8 month ($p=0.015$). 1-year actual survival of patients treated with radical resection and adjuvant therapies was 11.7%. For patients with radical resection only – 10.5%. 3-year actual survival for the same groups of patients was 3.5% and 2.3%, respectively. 1-year actual survival of patients treated by palliative methods was 2.3%.

Conclusions: Surgery with adjuvant treatment seems to be beneficial for pancreatic adenocarcinoma patients. In locally advanced and metastatic pancreatic cancer palliative chemotherapy or radiotherapy statistically significantly improved survival.

Key words: pancreatic cancer, radical surgery, palliative surgery, adjuvant treatment, median survival.

Introduction

Pancreatic carcinoma is the fourth commonest cause of death worldwide, with over 40000 deaths/year in Europe. In Lithuania about 400 new pancreatic cancer cases are diagnosed a year and more than 50% of cases are diagnosed in the advanced stages [1,2]. Median survival of patients with pancreatic carcinoma is in the range of 7-12 months. Less than 15% of patients are operable at the time of diagnosis. Although patients undergo potentially curative surgery, the median survival is only 10-18 months and 5-year survival is 17-24% [3].

The role of surgery, radiotherapy and chemotherapy in the treatment of local, locally advanced and metastatic pancreatic cancer was analyzed in many studies. Radical surgery is a treatment of choice in local forms of pancreatic cancer, but in locally advanced tumors does not substantially improve survival. Most failures occur within 1-2 years of surgery, therefore there is a need for adjuvant therapy [4]. Patients diagnosed with local and locally advanced tumors in addition to surgery are treated with chemotherapy and radiotherapy.

Many chemotherapeutic agents have been used in the treatment of advanced pancreatic cancer, but only older agents such as 5-fluorouracil (5-FU), mitomycin, and new agent such as gemcitabine have shown effect [5]. In most studies radiation therapy only slightly improved local control of pancreatic cancer. A more promising treatment in advanced operable and inoperable pancreatic cancer was shown to be chemoradiation [6]. Using various modes of radiotherapy and different chemotherapeutic agents there is an improvement in survival. Chemoradiotherapy is a toxic treatment and, therefore, patients with a better performance status do better.

We report the results of the study that aimed to address the results of the treatment of pancreatic cancer patients at our institution from years 1998 to 2000; and to estimate the survival comparing different modes of treatment of pancreatic cancer.

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Table 1. The survival of pancreatic cancer patients with local, locally advanced or metastatic disease treated by different treatment methods.

Treatment method	Stage	No of patients	Median survival (months)	p
Radical surgery and adjuvant treatment (Group 1)	I-II	8	21.5	0.6
Radical surgery and no adjuvant treatment (Group 2)		7	12.6	
Radical surgery and adjuvant treatment (Group 3)	III-IVA	9	12.1	0.6
Radical surgery and no adjuvant treatment (Group 4)		11	7.7	
Palliative surgery and radiotherapy, chemotherapy (Group 5)	III-IVB	5	8.8	0.015
Palliative surgery only (Group 6)		21	1.8	

The purpose of our work was to analyze median survival time, 1-year and 3-year actual survival rates of various groups of patients.

Material and methods

Eighty-five patients diagnosed with pancreatic cancer and treated between 1998 and 2000 at Kaunas Medical University Hospital were retrospectively analyzed.

Sixty-five of the patients were operated. In thirty nine cases radical pancreatoduodenectomy was performed. Remaining twenty six patients have undergone biliary bypass procedure.

Seventeen patients were treated with radiation. Radiation therapy was administered either after operation, after operation with adjuvant chemotherapy, or for palliative purposes. Radiation therapy was given primarily to patients with advanced adenocarcinoma of the pancreas in order to palliate symptoms. Positive tumor margins, residual tumor, involved nodes, perineural infiltration or direct extension of tumor were the main indication for radiotherapeutic management. External beam radiation therapy – 15 MV photons from linear accelerator, was used in the dose range from 40 (20 fractions) to 60 (30 fractions) Gy. The classical dose fractionation scheme was applied for the treatment of the patients. The four-field (anteroposterior – posteroanterior, right and left lateral) or three-field (anterior and wedged right and left lateral) techniques were used to irradiate pancreatic tumor or tumor bed and adjacent lymph nodes. The radiation fields and treatment volume were established with information from computed tomography (CT), surgical description and clips. If the tumor was in the head of the pancreas treatment volume was 2-3 cm larger than the tumor volume, including the primary tumor, adjacent pancreatic tissue, the superior head, the pancreaticoduodenal celiac axis, portal hepatic lymph nodes. CT based treatment planning was performed on 3D computerized treatment planning system.

According to the stage nineteen patients were treated with either 5-FU or gemcitabine in standard doses and schedules. Four to six courses of 5-FU were administered depending on the performance status of the patients. No WHO grade 3 or 4 toxicity was observed while giving 5-FU regimens. Patients treated with gemcitabine, usually, because of their performance status, received three to four courses of treatment. Chemo-

therapy was generally well tolerated. Toxicity was mild and mostly thrombocytopenia. There were no toxic deaths.

The patients were grouped according to the stage of the disease and type of operation; either radical surgery or palliative surgical procedure. There were six groups. In Group 1 patients were diagnosed with local disease (stage I-II) and treated by radical surgery and adjuvant treatment (radiotherapy and/or chemotherapy). Group 2 – patients were diagnosed with local disease and treated by radical surgery only. Group 3 – patients with locally advanced disease (stage III-IVA) and treated with radical surgery and adjuvant treatment (radiotherapy and/or chemotherapy). Group 4 – patients with locally advanced disease and treated by radical surgery only. Patients in Group 5 – were diagnosed with locally advanced or metastatic disease (III-IVB) and treated by palliative surgery, radiotherapy or chemotherapy. Group 6 patients were diagnosed with locally advanced or metastatic disease and treated by palliative surgery only (Tab. 1).

The primary endpoint for analysis was death. Survival was calculated from the date of resection until the date of death or censored at the latest follow up. Kaplan-Meier survival curves were drawn and Cox-Mantel test was used to assess differences between the groups.

Results

Mean age was 60 years. The main tumor location was the head of the pancreas; histology for all cases – ductal adenocarcinoma. The mean duration of symptoms until the diagnosis was 2.5 months. The main symptoms were pain and jaundice. 90 percent of patients indicated pain as the main symptom.

In patients who underwent radical resection node positive disease was diagnosed in 20 patients. Distant metastases were diagnosed in 18 patients treated by palliative operation.

The median survival time of patients in Group 1 was 21.5 months. The median survival time of patients in Group 2 was 12.6 months. The result was not statistically significant ($p=0.6$) (Fig. 1 A).

For patients in Group 3 the median survival time was 12.1 months. The median survival time for Group 4 was 7.7 months. No significant difference in survival curves was observed ($p=0.6$) (Fig. 1 B).

In Groups 5 and 6 the median survival time was 8.8 months

Figure 1 A. Kaplan-Meier estimates of median survival time in patients with local disease treated with radical surgery and adjuvant therapy (Group 1) and patients with local disease treated with radical resection only (Group 2) ($p=0.6$).

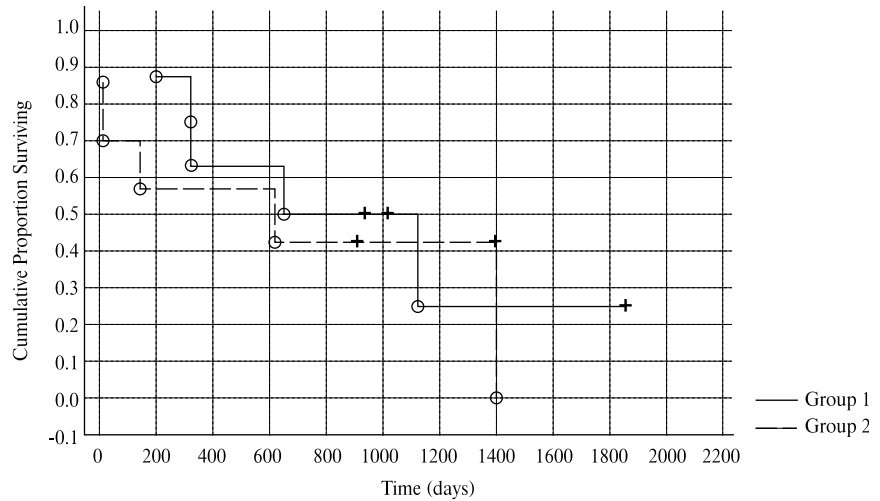


Figure 1 B. Kaplan-Meier estimates of median survival time in patients with locally advanced disease treated with radical surgery and adjuvant therapy (Group 3) and in patients with locally advanced disease treated by radical resection only (Group 4) ($p=0.6$).

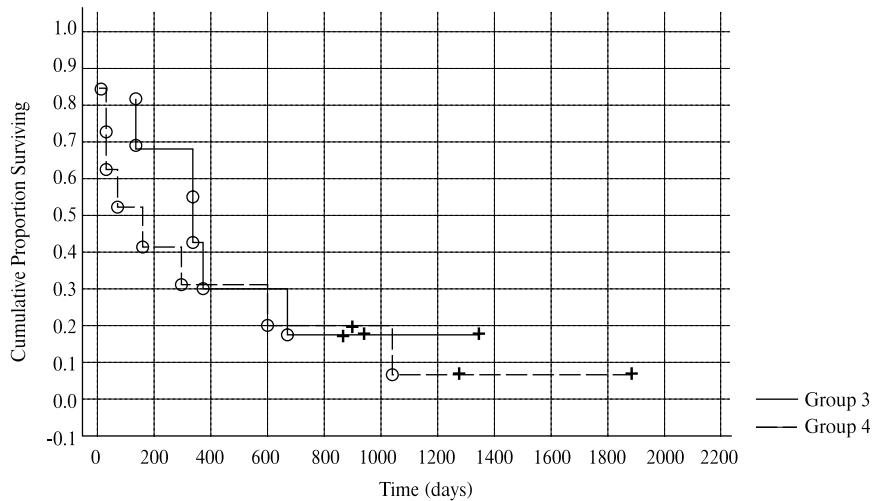
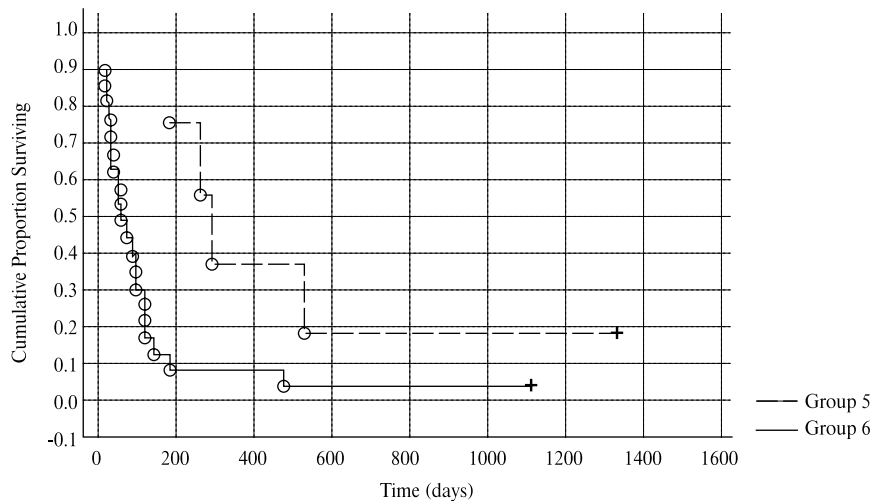


Figure 1 C. Kaplan-Meier estimates of median survival time in patients with locally advanced and metastatic disease treated by palliative surgery, radiation or chemotherapy methods (Group 5) and in patients with locally advanced and metastatic disease treated with palliative surgery only (Group 6) ($p=0.015$).



and 1.8 months respectively. The difference between the two groups was significant ($p=0.015$) (*Fig. 1 C*).

The 1-year actual survival of patients treated with radical resection and adjuvant therapy was 11.7%. For patients with radical resection only 1-year actual survival was 10.5%. A 3-year actual survival of the same groups of patients was 3.5% and 2.3% respectively.

The 1-year actual survival of patients treated by palliative methods (surgery, radiotherapy or chemotherapy) was 2.3%.

Discussion

The morbidity with pancreatic cancer is low but the results of the treatment are poor. We analyzed some demographic and clinical factors. Pancreatic cancer is a disease of elderly people. The mean age in our study was 60 years: 64 years for women and 59 years for men. In Lithuania there is a similar rate of pancreatic cancer diagnosis for men and women. In the world men are more often diagnosed with pancreatic cancer, but in

Europe the incidence of pancreatic cancer among women is increasing [7].

In our study tumor was mainly located in the head of the pancreas, and main symptoms were pain and jaundice. Symptoms, usually, appeared 2.5 months before the diagnosis.

The treatment of pancreatic cancer is problematic and results are poor. The disease is treated with combined treatment methods, but because of the advanced stage of the disease at diagnosis and poor performance status of the patients the treatment is complicated. The earlier the stage, the more radical treatment is possible and the results of treatment are better.

There are not many randomized multicenter studies on the effect of pancreatic cancer treatment modalities. The GITSG (Gastrointestinal Tumor Study Group) in 1983 proved the efficiency of the adjuvant treatment in pancreatic cancer. After surgery patients who were treated with radiotherapy and chemotherapy statistically significantly lived longer, comparing to the patients who were just operated. Median survival was 20 and 11 months respectively [8]. EORTC (The European Organization for Research and Treatment of Cancer) study 40891 analyzed also two groups of patients where one group of patients was operated only and the other group of patients was treated by operation and chemoradiotherapy. The median survival was 19 and 23.5 months, respectively [9]. In our study patients with local disease who were treated by radical surgery and adjuvant therapies lived 9 months longer, than patients with no adjuvant treatment. Patients diagnosed with locally advanced disease and treated by radical resection and adjuvant treatment lived 4 months longer than by radical resection only. The results are not statistically significant because of the small patient groups, but the addition of the adjuvant treatment in both cases improved survival.

Patients treated with palliative surgery, radiotherapy and/or chemotherapy survived longer (median survival 8.8 months), than patients who had undergone palliative surgical procedure only. The survival was 7 months longer and the difference was statistically significant. Similar results were described by the researchers from the Mayo Clinic (US). In the study patients with unresectable tumors were treated by external beam radiation therapy with or without chemotherapy and their median survival was 12.6 months [10]. The median survival time of patients treated by similar protocols at Tomas Jefferson Hospital (US) was 7.3 months [10].

In recent ESPAC-1 study the median survival time in patients treated with chemotherapy was significantly improved; 19.7 months, compared to 14 months in a group that did not received chemotherapy [11,12]. These and other studies show the need of new standardized protocols of pancreatic cancer treatment, especially for advanced pancreatic cancer.

In the world five year survival in different countries is about 3 to 5% [13,14]. In our study 1-year and 3-year actual survival rates in pancreatic carcinoma patients were low too. The best result was achieved when patients were treated with radical surgery and adjuvant treatment. 1-year survival was 10-11% of patients.

Conclusions

Surgery and adjuvant treatment seems to be beneficial for pancreatic adenocarcinoma patients.

In locally advanced and metastatic pancreatic cancer palliative chemotherapy or radiotherapy statistically significantly improved survival.

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