

Impact of different treatment methods on survival in advanced pancreatic cancer

Birutė Brasiūnienė, Elona Juozaitytė, Giedrius Barauskas¹

Department of Oncology, ¹Department of Surgery,
Kaunas University of Medicine, Lithuania

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Summary. The aim of the study was to evaluate the impact of different treatment methods on survival of patients treated for advanced pancreatic cancer at Kaunas University of Medicine Hospital from 1987 to 2003.

Materials and methods. Data on 262 patients with advanced pancreatic cancer treated from 1987 to 2003 were analyzed retrospectively. Four groups of patients were analyzed. One hundred eighty patients underwent palliative bypass or endoscopic bile duct stenting or observation alone. Forty three patients in addition to surgery were treated by radiotherapy. Twenty five patients received gemcitabine in standard doses and schedules. Fourteen patients received concomitant chemoradiotherapy (with gemcitabine or 5-fluorouracil).

All patients were grouped by treatment method and median survival was analyzed.

Results. Median survival of patients treated by palliative surgery only or observation alone was 1.9 month, and for patients treated by palliative surgery and radiotherapy was 6.1 months ($p=0.00007$). Median survival of patients treated with gemcitabine was 9.5 months ($p<0.001$), and median survival of patients treated with concomitant chemoradiotherapy was 8.5 months ($p=0.00003$).

Conclusion. Patients diagnosed with advanced pancreatic cancer in addition to surgical treatment should be treated by chemotherapy, concomitant chemoradiotherapy or radiotherapy.

Introduction

Five-year survival of patients with pancreatic cancer is very low, about 4–5% (1). When tumor is less than 2 cm, there are no metastases in regional lymph-nodes and if radical resection is performed, five-year survival is from 18 to 30%. Median survival of patients with pancreatic cancer is 6–20 months and it depends on a stage of the disease, treatment method and performance status of a patient. In most cases this cancer is diagnosed in advanced stages and definitive treatment is not applicable.

According to Lithuanian Cancer Registry every year 400 new cases of pancreatic cancer are diagnosed in Lithuania and this number is increasing. In the year 2002 there were 480 patients diagnosed with pancreatic cancer. The peak incidence is 13.8 cases per 10,000 population. More than a half of patients (62.1% men and 58.6% women) were diagnosed with stage IV disease. And every year 40,000 patients diagnosed with pancreatic cancer die in Europe.

The efficacy of adjuvant treatment after radical resection in stages I–III of a disease is questionable. In

Lithuania patients diagnosed in advanced stages are treated by definitive or palliative surgery and, depending on a performance status of a patient, by concomitant chemoradiotherapy or monochemotherapy, usually with gemcitabine. Radiation therapy (RT) is combined with such radiosensitizing agents as 5-fluorouracil (5-Fu) or gemcitabine. Palliative radiotherapy is also applied to patients with a severe pain syndrome (2, 3).

The aim of the study was to evaluate the impact of different treatment methods on survival of patients treated for advanced pancreatic cancer at Kaunas University of Medicine Hospital from 1987 to 2003.

Materials and methods

Results of various treatment methods of patients with advanced pancreatic cancer treated at Kaunas University of Medicine Hospital from 1987 to 2003 were compared retrospectively. Until 1997 patients with advanced pancreatic cancer were treated by palliative surgery and/or radiotherapy, and after 1997 some patient groups were treated by gemcitabine or

concomitant chemoradiotherapy.

Data on 262 patients with advanced pancreatic cancer treated from 1987 to 2003 were analyzed retrospectively. Four groups of patients were analyzed. 180 patients underwent palliative bypass or endoscopic bile duct stenting or observation alone. 43 patients in addition to surgery were treated by radiotherapy. The classical dose fractionation scheme was applied for the treatment of patients, total dose 40–60 Gy. 25 patients received gemcitabine in standard doses and schedules. Gemcitabine was administered 1000 mg/m² i. v. (30 min inf.) on day 1, repeated weekly $\times 7$, followed by 1 week of rest, than weekly $\times 3$ every four weeks. Fourteen patients received concomitant chemoradiotherapy. Radiotherapy was delivered to a median dose of 50 Gy in 25 fractions. 6 patients were treated with radiotherapy with gemcitabine administered in doses 250–300 mg/m² once a week. 8 patients were treated with radiotherapy and with 5-Fu administered in doses 350 mg/m² from day 1 to 5, on weeks 1 and 5, or in doses 500 mg/m² from day 1 to 3, on weeks 1 and 5.

The primary endpoint for analysis was calculated from the date of surgery or biopsy until the date of death or censored at the latest follow-up. Survival curves were obtained by Kaplan-Meier method and Cox Mantel test was applied to assess differences between the groups.

Results

Median survival of patients treated by palliative surgery only or observation alone was 1.9 month, and for patients treated by palliative surgery and radiotherapy – 6.1 months ($p=0.00007$). Median survival of patients treated with gemcitabine was 9.5 months

($p<0.001$), and median survival of patients treated with concomitant chemoradiotherapy was 8.5 months ($p=0.00003$) (4).

The median survivals of different patients' groups are compared in Fig.

Discussion

Survival of patients with pancreatic cancer is poor. Pancreatic cancer is a disease of the elderly people. Incidence of pancreatic cancer is similar in women and men. Age and sex are not considered as statistically significant prognostic factors (5).

Pancreatic cancer, usually, is diagnosed in advanced stages. In our retrospective studies patients mostly presented with symptoms three months before diagnosis.

Patients with advanced pancreatic cancer are usually treated with chemotherapy or chemoradiotherapy. According to study of the European Organisation for Research and Treatment of Cancer (EORTC) where 9044 patients after radical surgical resection were treated by various methods, in patients treated by radiotherapy only 5 year survival was 13%, and for patients treated by chemotherapy or chemoradiotherapy, 17.7 and 17% respectively (6, 7). Median survival of patients treated at our institution by radiotherapy was 6.1 months, and median survival of patients treated by palliative surgery only was 1.9 months. There are few studies analyzing the efficacy of radiotherapy treating patients with pancreatic cancer. Most recent study analyzing effect of brachytherapy for patients treated with RT and 5-Fu is CMM-95079 phase II study (8).

For many years pancreatic cancer patients were treated with 5-Fu. Until 1997 only few patients at our

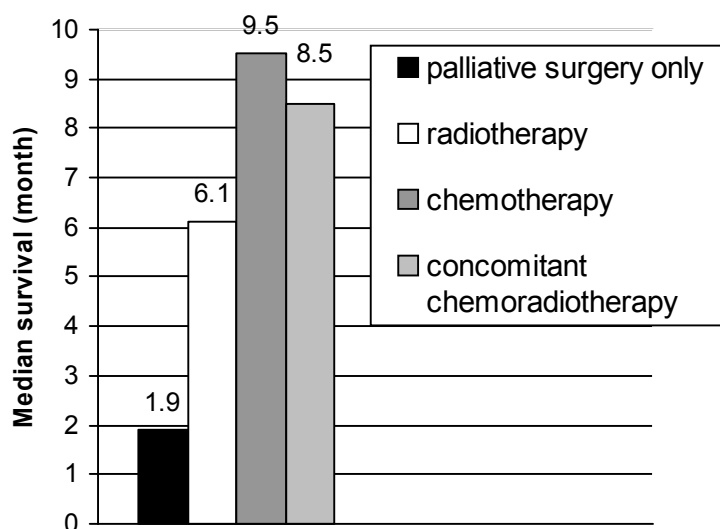


Fig. Survival of patients treated by different methods

institution were treated by 5-Fu and were not analyzed in the study. Currently, patients with pancreatic cancer are mostly treated with gemcitabine. Gemcitabine is a pyrimidine analogue, active through its metabolites, which affect tumor cell DNA (9). In one study Burris *et al.* treated 126 patients with advanced pancreatic cancer with 5-Fu or gemcitabine. For patients receiving gemcitabine response was 23.8% and in the group of patients treated with 5-Fu – 4.8% ($p=0.0022$); median survival – 5.65 and 4.4 months ($p=0.0025$) and one year survival – 18 and 2%, respectively (10).

In the study of Rothenberg *et al.* 63 patients were treated with 5-Fu and upon the progression of the disease these patients were treated with gemcitabine. 87.3% of patients with progressive disease were diagnosed with distant metastases. 27% of those patients responded to the treatment. Median survival of patients treated with gemcitabine was 3.9 months and stable disease was in 29.8% of patients. Median time to progression was 2.5 months (11).

In literature, response to treatment with gemcitabine is described from 4.3 to 18.2%, median survival 5–9.8 months and one-year survival 14.3–39.0% (12–14). Median survival of patients treated with gemcitabine at our institution was 9.5 months and one-year survival was 32%. Treatment results in our patients were comparable with data reported by others. European Study Group for Pancreatic Cancer Trial 3 (ESPAC-3) is the most recent study, where observation after surgical resection is compared to treatment with gemcitabine or 5-Fu (15).

In our study we also evaluated another treatment modality for advanced pancreatic cancer – chemoradiotherapy. Historically, this treatment method was described by Moertel *et al.* in 1969, when 5-Fu was administered concomitantly with RT (16). In the study of the Gastrointestinal Tumor Study Group (GITSG) done in 1987, the median survival time and 5-year survival rates of patients was 20 months *vs.* 11 months ($p<0.005$) and 20% *vs.* 5%, respectively, and were significantly higher in the patient group receiving postoperative chemoradiotherapy (17). These and other studies proved the efficacy of chemoradiotherapy over surgical treatment alone. Retrospective studies in literature indicate similar results. In the retrospec-

tive study from UK where 24 patients with locally advanced pancreatic cancer were treated with chemoradiotherapy based on 5-Fu, median survival of the patients was 12 months, 1-year and 2-year survival was 48 and 29%, respectively (18). In the study from the Radiation Therapy Oncology Group (RTOG-9209) where patients were treated with RT, 5-Fu and leucovorin median survival was 7.4 months and one-year survival 28.6 % (19). In similar studies from Mayo clinic and Thomas Jefferson Hospital median survival for patients treated by chemoradiotherapy was 12–13 months, but in these studies patients with chemoradiotherapy also received intraoperative RT (20).

Gemcitabine is also a radiosensitizing agent. Gemcitabine with RT is not a treatment standard, but studies evaluating these treatment modalities are underway.

There are few studies comparing RT with gemcitabine and RT with 5-Fu. In one study where these treatments were compared, treatment results for a group of patients treated with gemcitabine were better, but not statistically significant (21). Median survival of patients treated at our institution and receiving RT with gemcitabine or RT with 5-Fu was 8.5 months and patients lived statistically significantly longer – 6.6 months, than patients who were not treated. Median survival of these patients was 1.9 months.

Results of new studies (EORTC-40013 II/III phase study evaluating RT with gemcitabine *vs.* observation alone; studies from the Eastern Cooperative Oncology Group (ECOG-4201 phase III) comparing gemcitabine *vs.* gemcitabine with RT and other studies) evaluating chemoradiotherapy in cases with unresectable pancreatic cancer, will determine the effect of this treatment modality in its place in the management of a patient with pancreatic cancer (8).

The results of treatment of pancreatic cancer are poor and there is a need to improve efficacy of currently available methods in patients with this aggressive form of cancer.

Conclusions

Patients diagnosed with advanced pancreatic cancer in addition to surgical treatment should be treated by chemotherapy, concomitant chemoradiotherapy or radiotherapy.

Įvairių gydymo metodų įtaka ligonių, sergančių išplitusiu kasos vėžiu, išgyvenimui

Birutė Brasiūnienė, Elona Juozaitytė, Giedrius Barauskas¹

Kauno medicinos universiteto Onkologijos klinika, ¹Chirurgijos klinika,

Raktažodžiai: kasos vėžys, spindulinė terapija, chemoterapija, kompleksinis gydymas.

Santrauka. Tyrimo tikslas. Įvertinti įvairių gydymo metodų, skirtų ligonių, sergančių išplitusiu kasos vėžiu, įtaka išgyvenimui.

Medžiaga ir metodai. Atlikta retrospektyvioji 262 ligonių, sergančių išplitusiu kasos vėžiu, gydymo duomenų analizė. Analizuotos keturios ligonių grupės. 180 ligonių atlikta paliatyvioji operacija, arba jie buvo tik stebėti. 43 ligoniai papildomai gydyti spinduline terapija, 14 ligonių gydyti suderinta chemospinduline terapija su gemcitabinu arba 5-fluorouracilu, 25 ligoniai gydyti chemoterapija gemcitabinu. Visi ligoniai sugrupuoti pagal gydymo metodą ir analizuotos šių grupių išgyvenimo medianos.

Rezultatai. Ligonius, kurie buvo tik paliatyviai operuoti arba tik stebėti, išgyvenimo mediana – 1,9 mėn.; gydytų papildomai spinduline terapija išgyvenimo mediana – 6,1 mėn. ($p=0,00007$). Gemcitabinu gydytų ligonių išgyvenimo mediana buvo 9,5 mėn. ($p<0,001$), o ligonių, gydytų suderintu chemospinduliniu gydymu, išgyvenimo mediana – 8,5 mėn. ($p=0,00003$).

Išvados. Ligoniai, sergantys pažengusiu kasos vėžiu, turėtų būti papildomai gydomi chemoterapija, suderintu chemospinduliniu gydymu arba spinduline terapija.

Adresas susirašinėti: B. Brasiūnienė, KMU Onkologijos klinika, Eivenių 2, 50009 Kaunas
El. paštas: birutebras@yahoo.com

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