

Evaluation of clinical factors and treatment results in patients with advanced pancreatic cancer

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Key words: *pancreatic cancer, chemoradiotherapy, chemotherapy, performance status, survival analysis.*

Summary. *Objective. The aim of the study was to assess the benefit of treatment modalities on the survival in patients with advanced pancreatic cancer and clinical factors affecting treatment efficacy and survival.*

Material and methods. One hundred eleven patients with advanced pancreatic cancer were analyzed retrospectively. Patients were grouped by treatment method, clinical stage, and Karnofsky Performance Index. Fifty-three patients were diagnosed with locally advanced disease and 58 with metastatic pancreatic cancer. Thirty-three patients at the time of diagnosis had Karnofsky Performance Index higher than 70, and in 78 patients it was 70 or lower. Fourteen patients were treated by concomitant chemoradiotherapy with gemcitabine or 5-fluorouracil, 25 – with gemcitabine only, and 72 patients underwent surgical palliation or observation alone.

Results. Patients treated with gemcitabine alone survived for 9.5 months, $p < 0.001$. Overall median survival of patients treated with concomitant chemoradiation was 8.5 months. Comparison of survival results between groups of patients treated with gemcitabine alone and the patients who have received radiation therapy with 5-fluorouracil (median survival 6.4 months) or gemcitabine (median survival – 8.8 months) revealed no difference. Median survival after surgical palliation or observation was 1.9 months.

Patients diagnosed with locally advanced pancreatic cancer and patients with Karnofsky Performance Index higher than 70 at diagnosis lived statistically longer than patients diagnosed with metastatic disease or Karnofsky Performance Index of 70 or lower.

Conclusions. Patients diagnosed with locally advanced pancreatic cancer, better performance status at diagnosis and treated with monotherapy with gemcitabine or combination of gemcitabine or 5-fluorouracil with radiation survived longer, than patients diagnosed with metastatic disease, patients of worse functional status and treated by palliative methods only.

Introduction

According to the Lithuanian Cancer Registry, four hundred new cases of pancreatic cancer are diagnosed every year in Lithuania and this number is increasing. In 2001 there were 441, and in 2002 – 480 patients diagnosed with pancreatic cancer. The peak incidence is 13.8 per 100,000 population. More than a half of patients were diagnosed with stage IV disease.

Pancreatic carcinoma is the fourth most common cause of death worldwide, with over 40000 deaths per year in Europe. Five-year survival of patients with pancreatic cancer is 4–5% (1). In many cases pancreatic cancer is diagnosed in advanced stages and definitive treatment is not applicable.

Radical surgery is a treatment of choice in local forms of pancreatic cancer. Most failures occur within

1–2 years of surgery, therefore there is a need for adjuvant therapy (2). Patients diagnosed with metastatic pancreatic cancer depending on their functional status are treated by palliative surgery, chemotherapy or radiotherapy.

The current standard of treatment in Lithuania for stage III and IV patients is definitive or palliative surgery followed by concomitant chemoradiation or monotherapy and is strongly dependent on such clinical factors as local or systemic spread of a tumor and patient's performance status at diagnosis. Radiation therapy is combined with such radiosensitization agents as 5-fluorouracil (5-Fu) or gemcitabine. Palliative radiotherapy is applied in cases of severe pain syndrome (3–5).

Significant factors in making decisions in pan-

creatic cancer patient management, predicting survival prognosis and treatment efficacy, currently, are the stage of the disease and functional status of patient (6).

The aim of this retrospective study was to assess the benefit of treatment modalities on the survival in patients with advanced pancreatic cancer and effect of clinical factors, such as stage of disease, patient's performance status, on treatment efficacy and patient survival.

Material and methods

One hundred eleven patients with advanced pancreatic cancer were analyzed retrospectively. There were 61 men (median age 65 years), and 50 women (median age 67 years). Patients were grouped according to stage of disease, performance status and applied treatment method (Fig. 1). Fifty-three patients were diagnosed with locally advanced disease and 58 were diagnosed with metastatic pancreatic cancer. Thirty-three patients at the time of diagnosis had Karnofsky Performance Index (KPI) higher than 70, and 78 – KPI of 70 or lower. Twenty-five patients received gemcitabine in standard doses and schedules. Gemcitabine was administered 1000 mg/m² i. v. (30 min inf.) d1; weekly $\times 7$, followed by 1 week of rest, than weekly $\times 3$ every four weeks. Treatment with gemcitabine was well tolerated. No toxicity of third or fourth grade according to World Health Organization (WHO) grading was observed. Mild thrombocytopenia was observed in few patients, and drug associated allergic reaction in one.

Fourteen patients received concomitant chemoradiotherapy. Radiotherapy (RT) was delivered to a

median dose of 50 Gy in 25 fractions. Eight patients were treated with radiotherapy and 5-Fu. 5-Fu was 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. Six patients were treated with radiotherapy and gemcitabine administered in doses 250–300 mg/m² once a week. Chemoradiotherapy, in general, was well tolerated. Two patients had mild nausea, 1 patient treated with gemcitabine and one patient treated with 5-Fu had diarrhea. No WHO grade 3 or 4 toxicity was observed. There were no toxic deaths. All patients receiving chemoradiotherapy as a treatment modality were included in one group.

Seventy-two patients underwent palliative bypass or endoscopic bile duct stenting or observation alone.

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

Main symptoms registered were pain (37%), jaundice (19%), weight loss (19%), nausea (13%), and general weakness (12%). Mean duration of symptoms before diagnosis was 3 months. The sites of metastases are indicated in Fig. 2. Adenocarcinoma of the pancreas was diagnosed in all patients at pathology examination of biopsy specimens. Evaluating functional status of patients KPI of 90 was in 4 patients, KPI of 80 – in 29 patients, KPI of 70 – in 54 patients, KPI of 60 – in 13 patients, and KPI of 50 or lower – in 11 patients (range 20 – 90). Median KPI for all groups was 70.

Median survival of patients treated with radiotherapy and gemcitabine was 8.8 months and of patients treated with radiotherapy and 5-Fu it was 6.4 months. Overall median survival of patients treated with che-

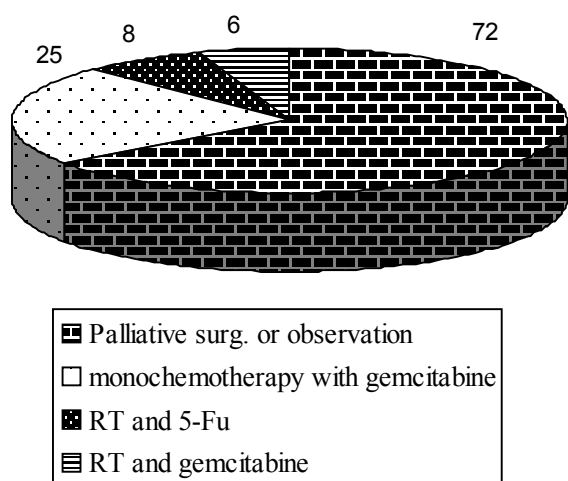


Fig. 1. Distribution of patients according the method of treatment

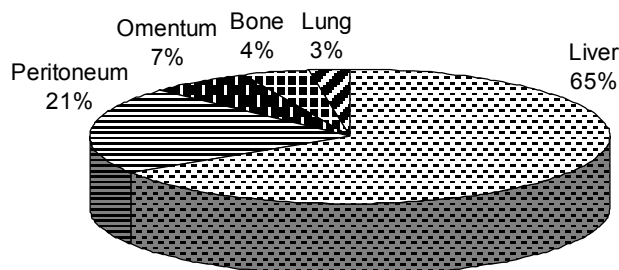


Fig. 2. Location of metastases

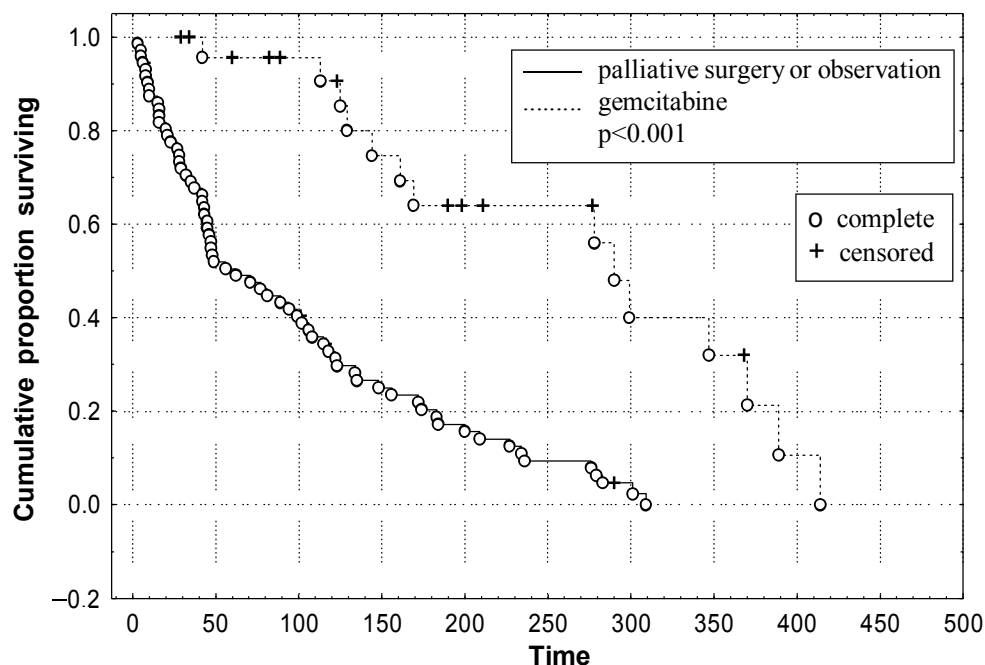


Fig. 3. Kaplan-Meier estimates of median survival time in patients with advanced pancreatic cancer treated by palliative surgery or observation only or by monochemotherapy with gemcitabine

moradiotherapy was 8.5 months. Comparison of survival results between groups of patients treated with gemcitabine alone and the patients who received radiation therapy with 5-Fu or gemcitabine revealed no difference.

Median survival in different groups of patients was calculated. Median survival of patients after surgical

palliation or observation was 1.9 months, whereas patients treated with gemcitabine alone survived for 9.5 months, $p < 0.001$ (Fig. 3).

Significant differences were also observed when comparing survival of patients after surgical bypass and those treated with concomitant chemoradiotherapy ($p < 0.00003$) (Fig. 4). Survival analysis of patients

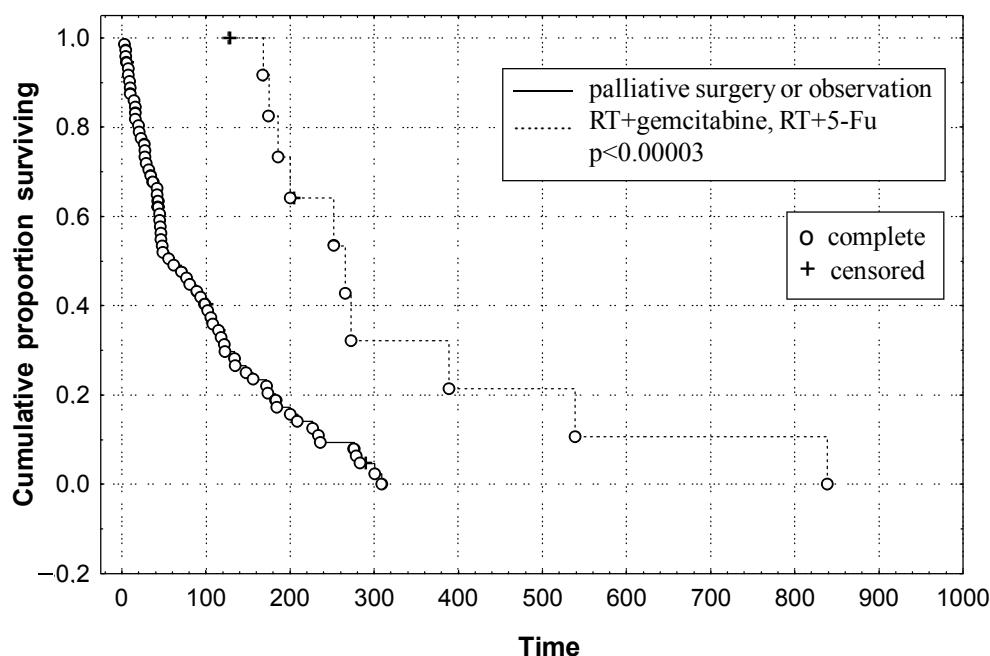


Fig. 4. Kaplan-Meier estimates of median survival time in patients with advanced pancreatic cancer treated by palliative surgery or observation only or by concomitant chemoradiotherapy with gemcitabine or 5-Fu

Table 1. Median survival of patients in groups treated by different treatment methods

Patient groups by treatment method	Median survival (month)	p value
Monochemotherapy with gemcitabine RT and gemcitabine, RT and 5-Fu	9.5 8.5	0.48
Monochemotherapy with gemcitabine RT and gemcitabine	9.5 8.8	0.629
Monochemotherapy with gemcitabine RT and 5-Fu	9.5 6.4	0.4
Palliative surgery or observation Monochemotherapy with gemcitabine	1.9 9.5	<0.001
Palliative surgery or observation RT and gemcitabine, RT and 5-Fu	1.9 8.5	0.00003

treated by different treatment methods is presented in Table 1.

Median survival of patients diagnosed with stages III and IVA was 5.7 months and of patients diagnosed with stage IVB disease it was 3.3 months (Fig. 5). Median survival of patients with KPI higher than 70 at diagnosis was 6 months and for patients with KPI of 70 or lower it was 3.6 months ($p=0.04$) (Fig. 6). Median survival of patients with KPI higher than 70 or equal or lower than 70 and treated by various treatment methods is presented in Table 2.

In our study median survival was 4.5 months for men and 3.8 months for women. The result was not statistically significant.

Discussion

Results of the treatment of pancreatic cancer are poor. Pancreatic cancer is a disease of elderly people. Men are more often diagnosed with pancreatic cancer than women, but in the last decade the incidence of pancreatic cancer in women has increased in Europe (7).

The mean age of patients was 66 years. Main symptoms were abdominal pain, jaundice, weight loss and general weakness. Most often jaundice or persistent severe pain were seen at admission, resulting in diagnosis of advanced stages of pancreatic cancer. Median duration of symptoms of gastrointestinal disorders was 3 months prior to diagnosis in our study.

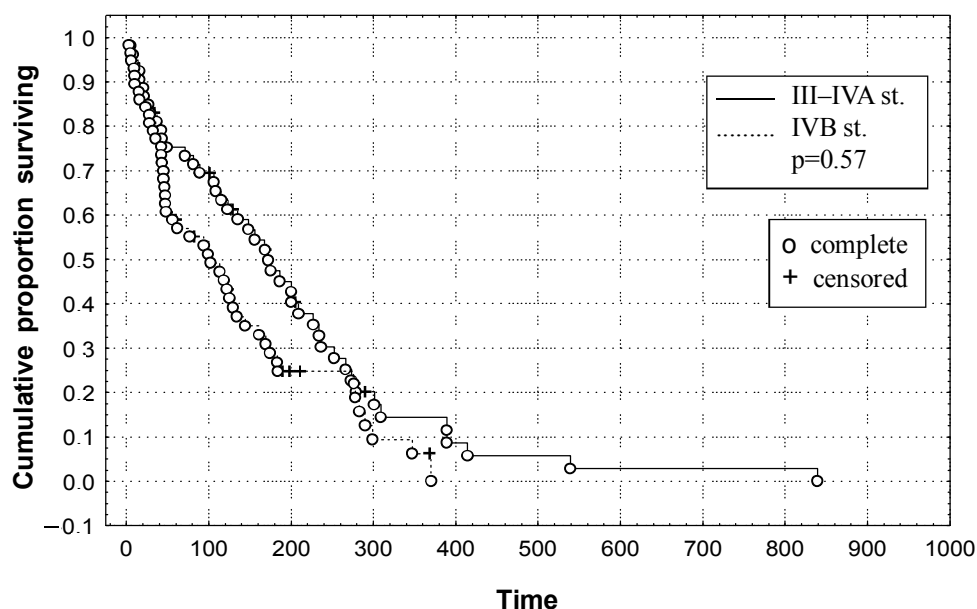


Fig. 5. Kaplan-Meier estimates of median survival time in patients diagnosed with stage III-IVA and stage IVB pancreatic cancer

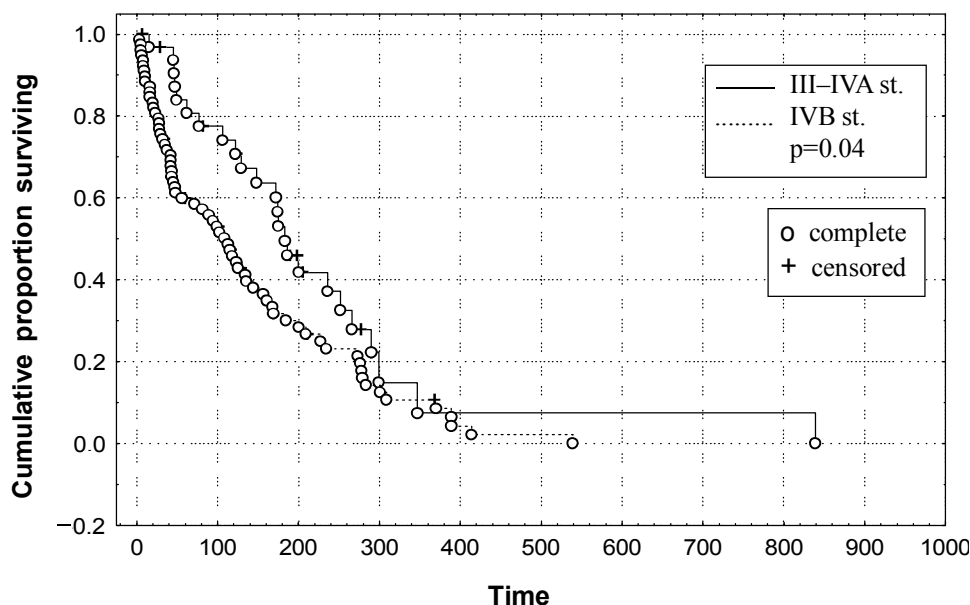


Fig. 6. Kaplan-Meier estimates of median survival time in patients with advanced pancreatic cancer with KPI \leq 70 and KPI >70

Table 2. Median survival of patients in groups treated by various treatment methods according to Karnofsky Performance Index

Characteristics	Chemoradiotherapy		Monochemotherapy with gemcitabine		Palliative surgery or observation		All patients	
KPI	>70	\leq 70	>70	\leq 70	>70	\leq 70	>70	\leq 70
N. of patients	6	8	10	15	17	55	33	78
Median survival (months)	7.8	8.1	9.7	5.8	3.5	1.5	6	3.6
Mean KPI	70		70		70		70	
p	0.439		0.85		0.25		0.04	

Majority of distant metastases were revealed in liver and other sites within the peritoneal cavity. Karnofsky Performance Index in most cases was from 60 to 80 (median – 70), what indicated the possibility to treat patients by chemotherapy or concomitant chemoradiotherapy.

Treatment of patients with locally advanced or metastatic pancreatic cancer with gemcitabine is a reasonable option. Treatment of this particular subset of patients with standard doses of gemcitabine results in response rate of 4.3–18.2%, disease stabilization in 18.8–50.0% with following median survival from 5 to 9.8 months, and 1-year survival ranging from 14.3% to 39.0% (8–10). H. Burris et al reported significant advantage of gemcitabine in comparison with 5-Fu in patients with advanced pancreatic cancer in terms of response rate and survival (11). In recent ESPAC-1 study the median survival time in patients treated with chemotherapy was also significantly improved when compared to observation alone (12, 13).

Monotherapy with gemcitabine in our patients was comparable with the data reported by others, resulting in median survival of 9.5 months and 1-year survival of 32%.

Concomitant treatment with chemotherapy and radiotherapy is also reported to be advantageous in pancreatic cancer. In a study from Mayo Clinic median survival of patients treated by external beam radiation 40–60 Gy in 6 weeks and chemotherapy was 12.6 months (14). Median survival of patients who were given RT in doses of 63–67 Gy in 7–9 weeks and chemotherapy at Thomas Jefferson Hospital was 7.3 months (14).

Few studies have analyzed results of chemoradiotherapy with gemcitabine in advanced pancreatic cancer. Treatment regimens differed in dose, time period of gemcitabine administration and in total RT dose as well as in number of fractions. Studies discussed reported median survival varying from 6 to 12 months, time to progression to be 7 months and 1-year

survival up to 66%. The treatment effect is assumed to be better when gemcitabine is administered before chemoradiotherapy and when the achieved cumulative dose of gemcitabine is higher, though doses of gemcitabine varied from 200 to 500 mg/m² (15–18).

In our study concomitant chemoradiotherapy with 5-Fu or gemcitabine showed to be more advantageous when compared to surgical bypass or observation. Treatment with radiotherapy and gemcitabine resulted in prolonged median survival when compared with patients treated with radiotherapy and 5-Fu (8.8 vs. 6.4 months, respectively), though significant difference was not achieved. Similarly a retrospective study from US also showed non-significant benefit of survival in patients treated with radiation and gemcitabine when compared to RT and 5-Fu regimen (19).

Chemoradiotherapy with 5-Fu is shown in numerous reports to achieve median survival of 7–12 months and 1-year survival of 32% to 48% (20, 21). In a Japanese study median survival of patients treated with radiotherapy and 5-Fu continuous infusion was 13.2 months and was significantly longer than in the patients without chemoradiation (22). By contrast phase III EORTC trial showed curative resection and radiation therapy with 5-Fu median survival was better when compared to curative resection and observation (24.5 vs. 19 months), but the difference was not significant (23).

Our results show median survival in patients treated with radiation and gemcitabine or radiation and 5-Fu to be 8.8 months and 6.4 months, respectively.

Importantly monochemotherapy with gemcitabine showed prolonged median survival when compared to RT with gemcitabine and RT with 5-Fu group, though the result did not reach statistical significance, which might be attributed to small sample size in the groups. This particular observation might be explained by observation that irradiation enhances invasive potential in some pancreatic cancer cells due to over-expression of matrix metalloproteinase-2 activity (24).

Recent data, discussing the rational of radiotherapy in pancreatic cancer treatment regimens and showing similar or even better (12) results obtained with chemotherapy alone advocate the need for further randomized prospective studies and novel standardized protocols for treatment of advanced pancreatic cancer.

Important factor in deciding how to manage patients with advanced pancreatic cancer is evaluation of functional status of a patient. Patients who had KPI higher than 70 at diagnosis had a better prognosis, confirming the results of other studies, that functional status is an important clinical prognostic factor in pancreatic cancer (6, 25).

Conclusion

Patients diagnosed with locally advanced pancreatic cancer, with a better performance status at diagnosis and treated by monochemotherapy with gemcitabine or combination of gemcitabine or 5-Fu with radiation had a longer median survival, than patients diagnosed with metastatic disease, patients of worse functional status and treated by palliative methods only.

Ligoniu, kuriems diagnozuotas išplitęs kasos vėžys, klinikinių veiksnių ir gydymo rezultatų įvertinimas

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Raktažodžiai: kasos vėžys, chemospindulinis gydymas, chemoterapija, funkcinė būklė, išgyvenimas.

Santrauka. *Tikslas.* Įvertinti įvairių gydymo metodų įtaką ligonių, sergančių išplitusiu kasos vėžiu, išgyvenimui, taip pat klinikinius veiksniai, kurie turi įtakos gydymo veiksmingumui ir ligonių išgyvenimui.

Medžiaga ir metodai. Retrospektyviai tirta 111 ligonių, sergančių užleistu kasos vėžiu. Ligoniai suskirstyti į grupes pagal gydymo metodus, klinikinę ligos stadiją ir Karnovskio indeksą. 53 ligoniams diagnozuota lokaliai išplitusi liga, 58 – metastazavęs kasos vėžys. 33 ligoniams ligos diagnozavimo metu Karnovskio indeksas nustatytas didenis kaip 70, ir 78 ligoniams – 70 arba mažesnis. 14 ligonių gydyti suderintu chemospinduliniu gydymu (spinduliniu gydymu ir gemcitabinu arba spinduliniu gydymu ir 5-fluorouracilu), 25 ligoniai gydyti vien tik gemcitabinu, 72 ligoniams atlikta tik paliatyvi operacija arba visai negydyti.

Rezultatai. Ligoniu, gydytų vien tik gemcitabinu, išgyvenimas buvo 9,5 mėn., $p < 0,001$. Ligoniu, gydytų chemospinduliniu gydymu, išgyvenimas – 8,5 mėn. Palyginus grupę ligonių, gydytų vien tik gemcitabinu, ir grupes ligonių, gydytų chemospinduliniu gydymu (spinduliniu gydymu ir gemcitabinu, išgyvenimo mediana – 8,8 mėn.), bei chemospinduliniu gydymu (spinduliniu gydymu ir 5-fluorouracilu, išgyvenimo mediana – 6,4 mėn.), reikšmingo išgyvenimo prailgėjimo nenustatyta.

Ligoniai, kuriems buvo diagnozuotas vietiskai išplitęs kasos vėžys, ir ligoniai, kuriems ligos diagnozavimo metu Karnovskio indeksas nustatytas didesnis nei 70, statistiškai reikšmingai gyveno ilgiau už ligonius, kuriems buvo diagnozuota metastatinė liga arba Karnovskio indeksas nustatytas 70 arba mažesnis.

Išvados. Ligoniai, sergantys vietiskai pažengusiu kasos vėžiu, taip pat ligoniai, kurie diagnozės nustatymo metu buvo geresnės funkcinės būklės ir buvo gydyti vien tik gemcitabinu arba chemospinduliniu gydymu (spinduliniu gydymu ir gemcitabinu arba spinduliniu gydymu ir 5-fluorouracilu) išgyveno ilgiau už ligonius, kuriems diagnozuota metastatinė liga, buvo blogesnės funkcinės būklės ir buvo gydyti palatyviais gydymo metodais.

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Received 25 June 2004, accepted 30 September 2004
Straipsnis gautas 2004 06 25, priimtas 2004 09 30