Predicting Survival After Irradiation of Metastases from Pancreatic Cancer

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Abstract. *Background/Aim: Patients with metastases from pancreas cancer benefit from individualized care, including radiotherapy for symptom control. To administer the optimal radiation therapy, it is important to understand a patient's prognosis. Patients and Methods: Seven variables were analyzed regarding their relationship with survival: age, gender, Karnofsky performance score (KPS), number of metastatic sites, interval from diagnosis of pancreatic cancer to irradiation of metastases, type of irradiated metastasis, and radiation dose. Results: On univariate analysis, survival was positively associated with age ≤67 years (p=0.045), KPS >70 (p<0.001), and involvement of only one metastatic site (p=0.013). A longer interval between diagnosis and irradiation of metastases showed a trend for better survival (p=0.077). On multivariate analysis, age [risk ratio (RR)=4.29; p=0.004], KPS (RR=1.95; p=0.020), number of metastatic sites (RR=2.20; p=0.009) and interval to irradiation (RR=4.41; p=0.005) achieved significance. Conclusion: The present study identified four independent predictors of survival in patients with pancreatic cancer irradiated for metastasis and thus contributes to treatment optimization.*

Patients with pancreatic cancer represent about 3% of all patients presenting with a malignant disease and are of great interest to cancer researchers who design treatment programs (1-6). If complete resection is not possible, the survival of patients with pancreatic cancer is poor. This applies particularly for patients with metastatic disease. In such a palliative situation, the patient's personal needs and wishes as well as the expected survival play important roles when designing individual treatment plans. Thus, the capability of predicting a patient's remaining lifetime as precisely as possible is of major importance for both the patient and treating physician. Such a prediction would be considerably facilitated by first identifying the significant and independent prognostic factors. Therefore, the present study was designed to focus on patients who were irradiated for metastatic pancreatic cancer with palliative intention. Several factors that may influence survival were analyzed in order to support both the patients and their physicians when selecting the treatment approach considered the best option for the patient's personal situation.

Patients and Methods

Thirty-nine patients irradiated for metastasis from pancreatic cancer were included in this retrospective study. For these patients, seven factors were analyzed for associations with survival following radiotherapy for metastases. These factors included age (≤67 years *vs.* ≥68 years, median age=67 years), gender, Karnofsky performance score (KPS <70 *vs.* KPS=70 *vs.* KPS>70), number of metastatic sites (affected organ systems) at the time of irradiation for metastasis (N=1 *vs.* N=2 *vs.* N=3), interval from first diagnosis of pancreatic cancer to irradiation of metastases (≤12 months *vs.* >12 months), site of irradiated metastases (bone *vs.* others *vs.* both), and the radiation dose given as equivalent dose in 2 Gy fractions (EQD2; α/β-value of 10 Gy for tumor-cell kill). The distribution of the factors that were analyzed is shown in Table I.

All seven factors were evaluated with respect to their potential influence on survival. Initially, the data were analyzed in an univariate manner using the Kaplan–Meier method and the Wilcoxon test (7). Those factors that achieved significance ($p<0.05$) or showed at least a trend for a relationship ($p<0.08$) in the univariate analysis were additionally evaluated in a multivariate manner with the Cox regression model.

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Table I. *Investigated factors*.

	Number of patients	Proportion (%)
Age		
≤67 years	20	51
≥68 years	19	49
Gender		
Female	16	41
Male	23	59
Karnofsky performance score		
<70	12	31
=70	7	18
>70	15	38
Unknown	5	13
Number of metastatic sites		
N=1	22	56
N=2	7	18
N=3	10	26
Interval from diagnosis of pancreatic cancer to irradiation of metastasis		
≤12 months	24	62
>12 months	15	38
Irradiated metastatic site		
Bone	30	77
Other	6	15
Both	3	8
Radiation dose		
<25 Gy	4	10
32.5 Gy	15	38
40 Gy	14	36
50 Gy	6	15

Table II. *Survival analysis (univariate)*.

	At 6 months (%)	At 12 months (%)	*p*-Value
Age			
≤67 years	60	40	
≥68 years	21	0	0.045
Gender			
Female	44	17	
Male	39	20	0.88
Karnofsky performance score			
<70	0	0	
=70	57	14	
>70	73	45	<0.001
Number of metastatic sites			
N=1	59	26	
N=2	29	0	
N=3	10	10	0.013
Interval from diagnosis of pancreatic cancer to irradiation of metastasis			
≤12 months	33	11	
>12 months	53	33	0.077
Irradiated metastatic site			
Bone	37	13	
Other	50	33	
Both	67	33	0.49
Radiation dose			
<25 Gy	25	n.a.	
32.5 Gy	47	25	
40 Gy	36	10	
50 Gy	50	25	0.09

n.a., Not available.

Results

The median follow-up period was 5 months (range=1-53 months) for the entire cohort and 9 months (range=6-18 months) in those patients alive at the last follow-up.

The univariate analysis revealed a significant positive association with age ≤67 years (p=0.045, Figure 1), a KPS >70 (p<0.001, Figure 2), and involvement of only one metastatic site (p=0.013, Figure 3). In addition, a longer interval from diagnosis of pancreatic cancer to irradiation of metastases showed a trend for improving survival (p=0.077, Figure 4). The data of the univariate analysis are summarized in Table II. In the subsequent multivariate analysis, age [risk ratio (RR)=4.29; 95% confidence interval (CI)=1.58-12.41; p=0.004], KPS (RR=1.95; 96% CI=1.10-3.64; p=0.020), number of metastatic sites (RR=2.20; 95% CI=1.22-4.04; p=0.009) and interval to irradiation (RR=4.41; 95% CI=1.55-14.49; p=0.005) achieved significance.

Discussion

About 40% of patients with pancreatic cancer present with metastatic disease at diagnosis, and most of these receive systemic treatment with chemotherapy or novel targeted-therapies alone (1-6). However, radiotherapy can be very useful to palliate symptoms such as pain, dyspnea and neurological deficits and to prevent complications such as pathological fractures of osteolytic bone, intracranial pressure, vena cava superior syndrome and compression of the spinal cord or peripheral nerves (8, 9).

If radiotherapy is indicated, several dose-fractionation regimens are available. These include single-fraction programs, short-course multi-fraction programs (overall treatment time of about one week) and longer-course programs (overall treatment time of two to five weeks) (10). In order to be able to select the most suitable dose-fractionation regimen for each patient, the patient's individual situation plays an important role. The patient's individual situation includes personal preferences, social situation (family, friends, job situation), medical condition (age, performance status, co-morbidity) and survival prognosis. Patients with a short expected survival time would ideally be treated with a short course of radiotherapy to minimize the time spent receiving treatment. In contrast, patients with a more favorable survival prognosis would likely benefit from longer-course radiotherapy programs with

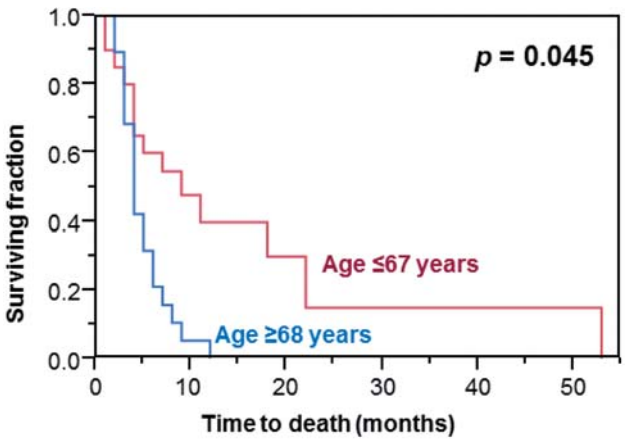

Figure 1. *Univariate analysis of survival with respect to age (≤67 years vs. ≥68 years).*

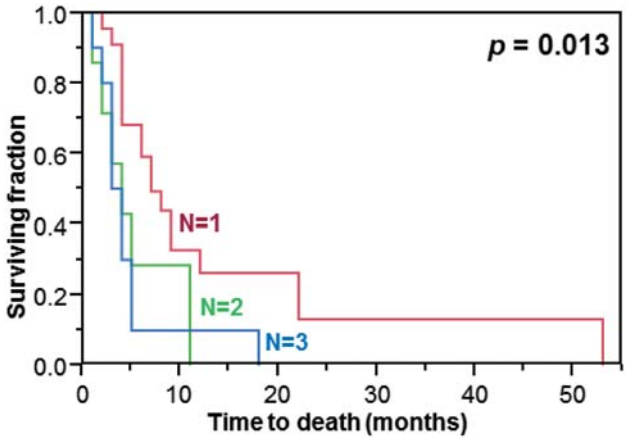

Figure 3. *Univariate analysis of survival with respect to the number of involved metastatic sites (N=1 vs. N=2 vs. N=3).*

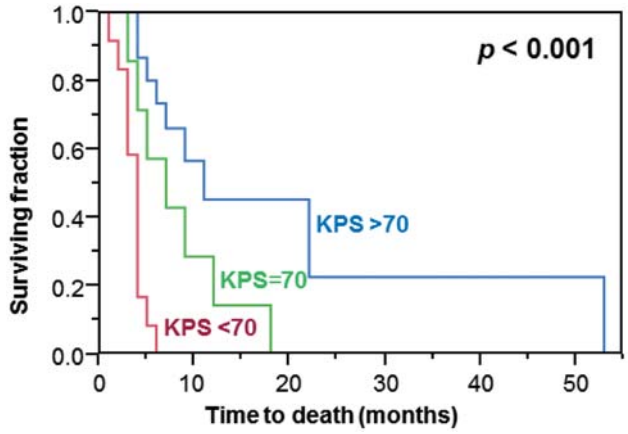

Figure 2. *Univariate analysis of survival with respect to the Karnofsky performance score (KPS <70 vs. KPS=70 vs. KPS >70).*

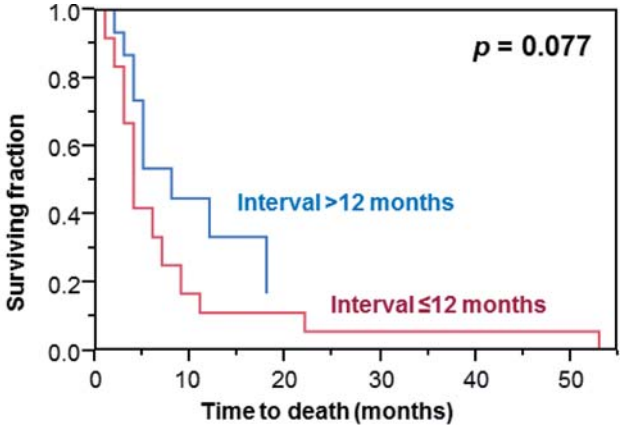

Figure 4. *Univariate analysis of survival with respect to the interval from first diagnosis of pancreatic cancer to irradiation of metastases (≤12 months vs. >12 months).*

higher doses to achieve longer control and to reduce the risk of experiencing some radiation-related late effects (11-13). Thus, predictive factors that allow estimating the survival prognosis of patients irradiated for metastatic pancreatic cancer would be of great value when physicians have to choose for the most appropriate dose-fractionation regimen for the individual patient.

Therefore, the present study was performed with the major goal of identifying such predictive factors. And indeed, the present analysis identified four independent predictors, *i.e.* age, performance status, number of metastatic sites and interval from first diagnosis of pancreatic cancer to irradiation for metastatic disease. According to the results of the study, older patients (age ≥68 years) with a poor performance status (KPS <70), involvement of more than one metastatic site and a shorter interval (≤12 months) from first diagnosis of pancreatic cancer to irradiation for metastatic disease have the shortest survival. These patients would likely be best irradiated with a single-fraction or a short-course program. In contrast, younger patients (age ≤67 years) with a better performance status (KPS ≥70), involvement of only one metastatic site and a longer interval (>12 months) from first diagnosis of pancreatic cancer to irradiation for metastatic disease are candidates for longer-course radiotherapy programs such as 40 Gy in 20 fractions over four weeks. These recommendations agree with those given for palliative radiotherapy of brain metastasis and metastatic spinal cord compression (11-15).

In conclusion, the present study identified four independent prognostic factors of survival in patients receiving radiotherapy for metastases from cancer of the pancreas. These prognostic factors can be of great value for the treating physicians when they need to design individualized treatment programs including choosing the most appropriate dose-fractionation regimen.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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