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A proposed model for prediction of survival based on a follow up study in unresectable pancreatic cancer

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Keywords

Pancreatic cancer, pancreatic neoplasm, unresectable, tumor size, biliary stricture, palliative, survival, prediction of survival

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Abstract

Objectives: To define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.
Design: An observational retrospective study on patients with unresectable pancreatic cancer. The initial radiographs at presentation of symptoms were reviewed and the maximum diameter of the primary tumor was determined. The occurrence of liver metastases and initiation of chemotherapy was also used in the regression analysis to identify prognostic subgroups.
Setting: County hospital in south-east of Sweden.
Population: Consecutive patients with unresectable pancreatic cancer who were diagnosed between January 2003 and May 2010 (n=132).
Main outcome measures: Statistical analyses were performed using Stata V13. Survival time was assessed with Kaplan-Meier analysis, log-tank test for equality of survivor functions and Cox regression for calculation of individual hazard based on tumor diameter, presence of liver metastases and initiation of gemcitabine treatment according to patient performance status.
Results: The individual hazard was log h = 0.357 tumor size + 1.181 liver metastases - 0.989 gemcitabine. Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with a median survival time of 1.2 (iqr 1.7) months.
Conclusion: The maximum diameter of the primary tumor and the presence of liver metastases found at the X-ray examination of patients with pancreatic cancer, in conjunction with whether or not chemotherapy is initiated, predict the survival time for patients who do not undergo surgical resection. The findings result in an easy-to-use model for predicting the survival time.

Article summary

Article focus

- The aim of this study was to define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.

Key messages

- An easy-to-use decision model can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor, the presence of liver metastases at the patient's initial radiologic examination and clinical information on fitness for initiation of cytotoxic drug treatment.
- Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with very poor survival, a median survival time of only 1.2 (iqr 1.7) months.

Strengths and limitations of the study

- The data covers every patient with unresectable pancreatic cancer at a single hospital between January 2003 to May 2010.

- With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival.
- The knowledge of expected survival may improve opportunities to individualize optimal patient care.
- One limitation is that the validation of the proposed model for prediction has to be done.

Background

Pancreatic adenocarcinoma is a highly fatal neoplasm and one of the leading causes of death in cancer in the Western world. The prognosis of patients with unresectable pancreatic carcinoma is extremely poor with no prospects of a five-year survival rate.[1] The disease is difficult to treat because clinical presentation often is late, and most of the patients have an advanced tumor burden with a high incidence of metastatic disease at diagnosis. In a recent Swedish study, tumor size - but not length of bile duct stricture - measured at the initial radiographic examination predicted the survival rate of patients with unresectable pancreatic cancer.[2] Identifying factors that can accurately predict the duration of disease survival is potentially helpful in the treatment of patients with unresectable pancreatic cancer. It may be unsuitable for patients with a bulky tumor to be exposed to cytotoxic chemotherapy or other advanced palliative therapies, as it may not prolong their survival but instead impair the quality of their short remaining lives. Could information that is readily available to clinicians at the time of diagnosis be used to predict survival time?

The purpose of this study is to examine whether tumor size and the presence of liver metastases at initial radiographic imaging, studied in conjunction with the decision to start chemotherapy can predict survival length in patients with unresectable pancreatic cancer, and identify prognostic subgroups among patients by calculating individual hazards after Cox regression.

Method

During the period January 2003 to May 2010, 185 consecutive patients were diagnosed with ductal pancreatic cancer and recruited into a single center study. Only patients with a diagnosis of cancer in the caput, corpus and cauda of the pancreas, or carcinoma growth outside the pancreas into adjacent organs were enrolled. Patients who had surgery for curative purposes, i.e. Whipple procedure or total pancreatectomy, were excluded from this survey. Initial radiographs following admittance to the hospital were retrieved and reexamined, all by the same radiologist, and tumor size was measured again. For a more detailed description of this procedure of tumor evaluation see.[2] In summary, most patients were examined with multislice computed tomography (CT) with a slice thickness of 2 mm. The maximum tumor diameter could be measured in 132 patients, in 114 with CT and the rest, 18 patients, with transabdominal ultrasound examination. In 53/185 (29 %) cases, the image of the tumor was far too diffuse to be measurable by standard radiological means and these patients were not accounted for in this study. The median tumor maximum diameter was 4.35 and therefore the study material was classified into two equal groups with the cut-off diameter at 4.3 cm. Secondly, occurrence of liver metastases at the time of diagnosis was noted and the patients were divided into two groups depending on whether or not liver metastases were present. Thirdly, patients were divided into two groups depending on whether or not they had been selected for gemcitabine treatment. The choice to offer gemcitabine was entirely based on

clinical judgment, taking into account the patient's general level of fitness, comorbidity, and overall likelihood of benefitting from such treatment. Patient characteristics are given in Table 1.

Table 1. Baseline characteristics of patients with primary unresectable pancreatic neoplasm.

Patients	132
Female/male	75/57
Age, median (iqr)	74 (64-81)
Age ≤ 65/ > 65 years (%)	40/92 (30/70)
Tumor diameter ≤ 4.3 cm (%)	66 (50)
Tumor diameter > 4.3 cm (%)	66 (50)
Liver metastasis (%)	60 (45)
Gemcitabine started (%)	57 (43)

Ethics

The study was approved by the Regional Ethical Review Board in Lund, Sweden (EPN Dnr 2012/92).

Statistical analysis

The statistical analysis was performed using Stata version 13 (StataCorp LP, College Station, Texas, USA). Continuous variables are expressed as median values (interquartile range, iqr.) and were compared with two-sample Wilcoxon rank-sum test. The comparison among groups for categorical variables was performed with Pearson chi2 test. Overall survival estimates were calculated by the Kaplan-Meier method, and the difference between groups was assessed by the log rank. Survival rates are gives as median and interquartile range (iqr). Survival curves were truncated at 24 months, since the number of patients at risk after that time was very small. Independent factors for overall survival were assessed with Cox proportional hazards regression analysis. The relative hazard for each patient was calculated from coefficients received by Cox regression.[3] $P < 0.050$ was considered statistically significant.

Results

A total of 132 of 185 patients had a measurable tumor and were included in the study with a median age of 74 (iqr 64-81) years. Of these, 75 were women and 57 were men. Liver metastases were found in 60 patients (45 %) at the initial radiological investigation and presentation of symptoms. Median survival times for patients with the different tumor sizes according to liver metastasis and given gemcitabine treatment are shown in Table 2. A Cox-regression was performed to identify prognostic subgroups of patients with unresectable pancreatic cancer (Table 3). The final form of the Cox model calculated from data from the 132 patients with ductal pancreatic neoplasm is shown in the lower part of Table 3. This corresponds to log h= 0.357 tumor size + 1.181 liver metastasis – 0.989 gemcitabine. Tumor size ≤ 4.3, no liver metastasis and no given gemcitabine were all coded = 0 and the other alternatives = 1. By using the formula, each individual relative hazard (h) was calculated. Three prognostic groups were defined according to the frequency distribution of the relative hazard: a low risk group h ≤ 1, a medium risk group h > 1 but ≤ 2, and a high risk group h > 2,

Figure 1. The corresponding survival rates are shown in Table 4. Log rank tests for equality of survivor functions between the three groups indicated significant differences in survival rate, $p < 0.001$, Figure 2.

Table 2. Median survival time for patients according to tumor size, presence of liver metastasis and started gemcitabine treatment, days.

	No liver metastasis			Liver metastasis		
	All	No gemcitabine	Gemcitabine	All	No gemcitabine	Gemcitabine
Tumor ≤ 4.3 cm	204	131	392	111	59	117
Tumor > 4.3 cm	157	107	196	58	35	139

Table 3. Univariable and multivariable Cox regression.

	Hazard ratio	95% Conf. Interval	P
Univariable regression			
Tumor size, ≤ 4.3 cm, > 4.3 cm	1.51	1.07-2.13	0.020
Liver metastases, no, yes	2.35	1.63-3.38	<0.001
Gemcitabine, no, yes	0.56	040-0.81	0.002
Age, ≤65 yrs, >65 yrs	0.93	0.67-1.30	0.690
Age groups,			
40	1		
50	2.29	0.53-9.91	0.269
60	1.66	0.40-6.87	0.481
70	1.41	0.34-5.79	0.638
80	1.55	0.38-6.38	0.541
90	3.69	0.77-17.5	0.102
Sex, male, female	0.93	0.70-1.25	0.689
Multivariable regression			
Tumor size, ≤ 4.3 cm, > 4.3 cm	1.43	1.01-2.04	0.048
Liver metastases, no, yes	3.26	2.16-4.92	<0.001
Gemcitabine, no, yes	0.37	0.25-0.55	<0.001

Table 4. Kaplan-Meier survival for prognostic subgroups.

Risk group	Relative hazard	Number of patients (%)	Median (iqr) survival, months	3-month survival rate, %	6-month survival rate, %	12-month survival rate, %	18-month survival rate, %
Low	≤ 1	57 (43)	6.7 (3.213.0)	81	58	32	12
Medium	>1 - ≤ 2	44 (33)	4.5 (2.7-7.2)	70	34	9	5
High	>2	31 (24)	1.2 (0.9-2.7)	13	0	0	0

iqr=interquartile range

Discussion

Our findings highlight three important factors that contribute to length of survival in patients with unresectable pancreatic cancer, i.e. tumor size defined as the tumor's maximum diameter, the presence of liver metastases, and the decision if gemcitabine is started or not according to clinically judgement of patient performance status. Earlier we have found that survival analysis using the Kaplan-Meier method showed a better survival rate in unresectable pancreatic cancer if the tumor size was below 4.3 cm.[2] By using Cox regression, adjusted for occurrence of liver metastases and gemcitabine treatment, the individual relative hazard was calculated. Age and gender were not included in this calculation since these variables had no

influence on the final multivariable Cox regression. Three different prognostic groups could be determined from the frequency distribution of individual hazard and the survival rate was clearly different between these groups ($p<0.001$), ranging from median 1.2 to 6.7 months (Figure 2). An easy-to-use model for prediction of survival in unresectable pancreatic neoplasm is therefore proposed, that discriminates survival better than predictions based on only tumor size, the presence of liver metastases or possible treatment with gemcitabine. The characteristics of the three groups are given in Table 5. The model is really a condensation of 8 (2^3) groups, i.e. 2 groups based on tumor size * 2 groups based on liver metastases * 2 groups based on gemcitabine treatment. The model also reveals a shift to a better risk group for patients with unresectable pancreatic cancer who start gemcitabine treatment. In the high risk group, tumor size has no influence on survival, which in their case is extremely short, about one month. The proposed model combines measurable hard data from initial radiographic examinations, in the form of tumor size and presence of liver metastases, with a somewhat weaker variable in the form of the physician-based decision to initiate gemcitabine or not, according to patient performance status. A clinical decision like this may be prone to individual bias in how the patient's general level of fitness, comorbidity and overall likelihood of benefitting from treatment is assessed. This may be seen as a potential limitation to the model's usefulness and reproducibility. However, it was necessary to give gemcitabine some form of consideration in the model, as the initiation of this drug clearly has a considerable impact on patient survival as shown in Table 2. Even if it is not an exact factor, excluding the gemcitabine variable would reduce the regression model too much. We therefore chose to deal with it in our calculations and to adjust for it in the regression analysis.

Table 5. Risk groups according to tumor size, liver metastases and initiation of gemcitabine treatment (i.e. clinically fit for cytotoxic drug treatment).

Liver metastases	Gemcitabine	Tumor size, cm	Risk group	Median survival
No	Yes	*Any*	Low	6.7 (iqr 3.2-13.0)
	No	≤ 4.3		
No	No	> 4.3	Medium	4.5 (iqr 2.7-7.2)
Yes	Yes	*Any*		
Yes	No	*Any*	High	1.2 (iqr 0.9-2.7)

The strengths of this study are that it includes consecutive patients from a single medical centre and that all initial X-rays following admittance to the hospital were re-examined, all by the same radiologist. For a comprehensive summary of the previous literature on prognostic factors in pancreatic cancer, see Stocken et al.[4] Factors implicated by more than one previous researcher can be broadly attributed to one of the five following groups: 1. Factors describing tumor burden, i.e. tumor size, TNM disease stage, and presence of metastases, not necessarily confined to the liver[5]; 2. Factors describing the patient's fitness level, i.e. performance status or nutritional status[6]; 3. Biochemical variables from blood, with varying degrees of disease specificity, with the non-specific inflammatory marker CRP most frequently mentioned, but including many others, like the tumor markers CA 19-9 and CA 242[4 7]; 4. Immunohistochemical analyses from pathological specimens, where more than 11 are identified as relevant in two or more studies, but none validated highly enough to be recommended for use in clinical practice as of now[8]; 5. Treatment factors, i.e. surgery and/or chemotherapy.[1 9 10] We find that our model fits these previous findings quite well. It may possibly require expansion to accommodate information from those groups that are not

represented at present, i.e. blood laboratory and immunohistochemistry. The gemcitabine variable in its current form is likely to reflect both the biological effect that the drug has on tumor cells and a selection bias in who receives treatment. It may in the future be modified to better reflect the difference between these two effects. The clinical implications of being able to give patients a more individualized prognosis are quite clear in order to improve optimal patient care. For example, as previously suggested by another research team, a more accurate individual prognosis may influence the choice between plastic and metal biliary stents for palliation of obstructive jaundice.[5] The initiation of gemcitabine treatment is correlated to survival advantages across all levels of tumor burden. It is not possible to determine which patients should have gemcitabine treatment based solely on the evaluation of initial patient X-rays. The survival advantages of gemcitabine treatment are least obvious in the low risk group, where we can only observe a non-significant tendency towards longer survival among those treated. In the future, we have plans to validate the findings of our model, using a new cohort of patients at our center who were diagnosed with unresectable pancreatic cancer from 2010 onwards. The model may also be expanded with new variables according to our previous line of discussion. Closer determination of what factors warrant the initiation of gemcitabine merits attention. Ideally, an effort should be made to adjust the survival times for quality of life during the disease.

Conclusion

We propose an easy-to-use decision model which can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor and the presence of liver metastases at the patient's initial radiologic examination, together with information on the initiation of chemotherapy. With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival. This knowledge may improve opportunities to individualize optimal patient care.

Competing interests

The authors declare that they have no competing interests.

All authors substantially contributed to the current manuscript as listed below:

HF drafted the manuscript, is the principal investigator of the study and designed this study. KÅ reviewed and measured tumor size of all X-rays. MW, KÅ, SJ revised the manuscript.

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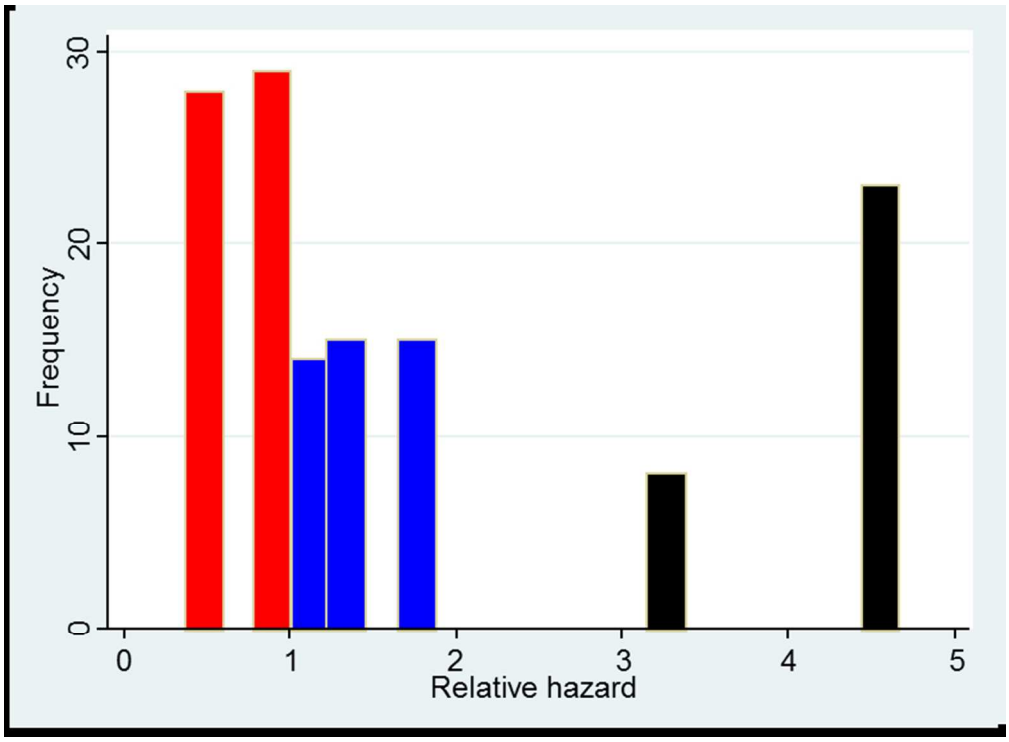
Figure legends:

Figure 1. Distribution of relative hazard in 132 patients with unresectable pancreatic cancer, red bar = low, blue bar = medium and black bar = high risk group, corresponding to the three subgroups shown in Table 3.

Figure 2. Survival analysis in patients divided into low (L), medium (M) and high risk (H) prognostic subgroups, N=132, $p<0.001$.



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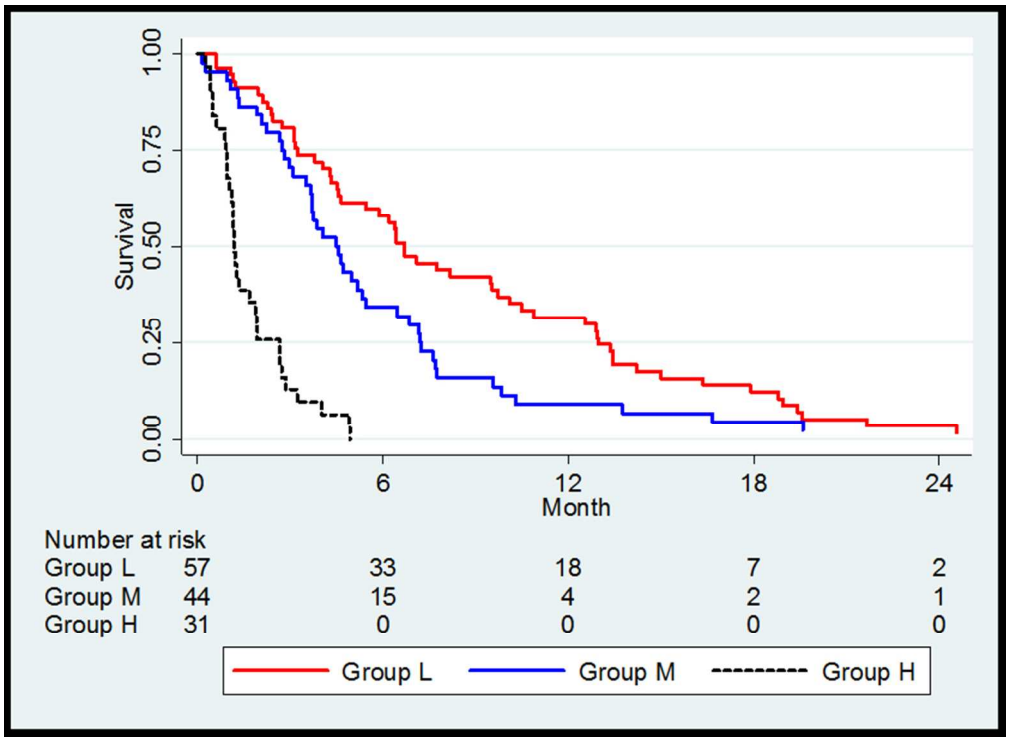

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Keywords

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Word counts: 19613000

Abstract

Objectives: To define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.
Design: An observational retrospective study on patients with unresectable pancreatic cancer. The initial radiographs at presentation of symptoms were reviewed and the maximum diameter of the primary tumor was determined. The occurrence of liver metastases and performance status that determines initiation of chemotherapy was also used in the regression analysis to identify prognostic subgroups.
Setting: County hospital in south-east of Sweden.
Population: Consecutive patients with unresectable pancreatic cancer who were diagnosed between January 2003 and May 2010 (n=132).
Main outcome measures: Statistical analyses were performed using Stata v13. Survival time was assessed with Kaplan-Meier analysis, log-rank test for equality of survivor functions and Cox regression for calculation of individual hazard based on tumor diameter, presence of liver metastases and initiation of chemotherapy treatment according to patient performance status.
Results: The individual hazard was log h = 0.357 tumor size + 1.181 liver metastases - 0.989 performance status/chemotherapy. Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with a median survival time of 1.2 (iqr 1.7) months.
Conclusion: The maximum diameter of the primary tumor and the presence of liver metastases found at the X-ray examination of patients with pancreatic cancer, in conjunction with whether or not chemotherapy is initiated according to performance status, predict the survival time for patients who do not undergo surgical resection. The findings result in an easy-to-use model for predicting the survival time.

Article summary

Article focus

- The aim of this study was to define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.

Key messages

- An easy-to-use decision model can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor, the presence of liver metastases at the patient's initial radiologic examination and clinical information on fitness for initiation of cytotoxic drug treatment.
- The prediction may be done immediately after radiologic investigations and assessment of patient performance status.
- Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with very poor survival, a median survival time of only 1.2 (iqr 1.7) months.

Strengths and limitations of the study

- The data covers every patient with unresectable pancreatic cancer at a single hospital between January 2003 to May 2010.

- With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival.
- The knowledge of expected survival may improve opportunities to individualize optimal patient care.
- One limitation is that the validation of the proposed model for prediction has to be done.

Background

Pancreatic adenocarcinoma is a highly fatal neoplasm and one of the leading causes of death in cancer in the Western world. The prognosis of patients with unresectable pancreatic carcinoma is extremely poor with no prospects of a five-year survival rate.[1] The disease is difficult to treat because clinical presentation is often late, and most of the patients have an advanced tumor burden with a high incidence of metastatic disease at diagnosis. In a recent Swedish study, tumor size - but not length of bile duct stricture - measured at the initial radiographic examination predicted the survival rate of patients with unresectable pancreatic cancer.[2] Identifying factors that can accurately predict the duration of disease survival is potentially helpful in the treatment of patients with unresectable pancreatic cancer. It may be unsuitable for patients with a bulky tumor to be exposed to cytotoxic chemotherapy or other advanced palliative therapies, as it may not prolong their survival but instead impair the quality of their short remaining lives. Could information that is readily available to clinicians at the time of diagnosis be used to predict survival time?

The purpose of this study is to examine whether tumor size and the presence of liver metastases at initial radiographic imaging, studied in conjunction with the decision to start chemotherapy based on patient performance status can predict survival length in patients with unresectable pancreatic cancer, and identify prognostic subgroups among patients by calculating individual hazards after Cox regression.

Method

During the period January 2003 to May 2010, 185 consecutive patients were diagnosed with ductal pancreatic cancer and recruited into a single center study. Only patients with a diagnosis of cancer in the caput, corpus and cauda of the pancreas, or carcinoma growth outside the pancreas into adjacent organs were enrolled. Patients who had undergone surgery for curative purposes, i.e. Whipple procedure or total pancreatectomy, were excluded from this survey. The diagnosis of pancreatic cancer was based on radiographic examinations but cytological specimens were also performed. Initial radiographs following admittance to the hospital were retrieved and reexamined, all by the same radiologist, and tumor size was measured again. For a more detailed description of this procedure of tumor evaluation see Forssell et al.[2] In summary, most patients were examined with multislice computed tomography (CT) with a slice thickness of 2 mm. The maximum tumor diameter could be measured in 132 patients, in 114 with CT and the rest, 18 (14 %) patients, with transabdominal ultrasound examination. In 53/185 (29 %) cases, the image of the tumor was far too diffuse to be measured by standard radiological means and these patients were not accounted for in this study. When the tumor was measurable the median tumor maximum diameter was 4.35 cm and therefore the study material was classified into two equal groups with the cut-off diameter at 4.3 cm. Secondly, occurrence of liver metastases at the time of

diagnosis was noted and the patients were divided into two groups depending on whether or not liver metastases were present. Thirdly, patients were divided into two groups of performance status, good or bad, corresponding to a Karnofsky scoring index above or below 50 %. The decision to offer chemotherapy was entirely based on if patient performance status was good, i.e. clinical judgment, taking into account the patient's general level of fitness, comorbidity, and overall likelihood of benefitting from such treatment. If patients were offered chemotherapy it always started with gemcitabine. A second-line of chemotherapy consisted of 5-fluorouracile/calcium folinate (5 patients), capecitabine (6 patients) or oxaliplatin (1 patient). Patient characteristics are given in Table 1.

Table 1. Baseline characteristics of patients with primary unresectable pancreatic neoplasm.

Patients	132
Female/male	75/57
Age, median (iqr)	74 (64-81)
Age ≤ 65/ > 65 years (%)	40/92 (30/70)
Tumor diameter ≤ 4.3 cm (%)	66 (50)
Tumor diameter > 4.3 cm (%)	66 (50)
Liver metastases (%)	60 (45)
Performance status, corresponding to Karnofsky index > 50 %	57 (43)
Chemotherapy started with gemcitabine (%)	57 (43)
Second-line chemotherapy after gemcitabine treatment (%)	12 (9)

Ethics

The study was approved by the Regional Ethical Review Board in Lund, Sweden (EPN Dnr 2012/92).

Statistical analysis

The statistical analysis was performed using Stata version 13 (Stata Corp LP, College Station, Texas, USA). Continuous variables are expressed as median values (interquartile range, iqr.) and were compared with two-sample Wilcoxon rank-sum test. The comparison among groups for categorical variables was performed with Pearson chi2 test. Overall survival estimates were calculated by the Kaplan-Meier method, and the difference between groups was assessed by the log rank. Survival rates are given as median and interquartile range (iqr). Survival curves were truncated at 24 months, since the number of patients at risk after that time was very small. Independent factors for overall survival were assessed with Cox proportional hazards regression analysis. The relative hazard for each patient was calculated from coefficients received by Cox regression.[3] $P < 0.050$ was considered statistically significant.

Results

A total of 132 of 185 patients had a measurable tumor and were included in the study with a median age of 74 (iqr 64-81) years. Of these, 75 were women and 57 were men. Liver metastases were found in 60 patients (45 %) at the initial radiological investigation and presentation of symptoms. Median survival times for patients with the different tumor sizes according to liver metastases and given chemotherapy treatment are shown in Table 2. In the

group with failed cytological proven ductal adenocarcinoma (about half of the enrolled patients) the overall survival time was the same as in those patients with proven cancer. There were no difference in overall survival rate between patients included 2003-2006 and 2007-2010 (p=0.629). In the 53 patients with no measurable tumor the median overall survival time was 3.3 months and not significantly different from 4.9 months in those patients with a tumor size ≤ 4.3 cm or 3.1 months if tumor was > 4.3 cm. A Cox-regression was performed to identify prognostic subgroups of patients with unresectable pancreatic cancer (Table 3). The final form of the Cox model calculated from data from the 132 patients with ductal pancreatic neoplasm is shown in the lower part of Table 3. This corresponds to log h= 0.357 tumor size + 1.181 liver metastases – 0.989 performance status/chemotherapy. Tumor size ≤ 4.3 cm, no liver metastases and performance status bad/no given chemotherapy were all coded = 0 and the other alternatives = 1. By using the formula, each individual relative hazard (h) was calculated. Three prognostic groups were defined according to the frequency distribution of the relative hazard: a low risk group h ≤ 1, a medium risk group h > 1 but ≤ 2, and a high risk group h > 2. Distribution of relative hazard in 132 patients with advanced pancreatic cancer is shown in Figure 1. The corresponding survival rates are shown in Table 4. Log rank tests for equality of survivor functions between the three groups indicated significant differences in survival rate, p< 0.001, Figure 2.

Table 2. Median survival time for patients according to tumor size, presence of liver metastases and started chemotherapy, days.

	No liver metastases			Liver metastases		
	All	No chemotherapy	Chemotherapy	All	No chemotherapy	Chemotherapy
Tumor ≤ 4.3 cm	204	131	392	111	59	117
Tumor > 4.3 cm	157	107	196	58	35	139

Table 3. Univariable and multivariable Cox regression.

	Hazard ratio	95% Conf. Interval	P
Univariable regression			
Tumor size, ≤ 4.3 cm, > 4.3 cm	1.51	1.07-2.13	0.020
Liver metastases, no, yes	2.35	1.63-3.38	<0.001
Performance status, bad (no chemotherapy), good (chemotherapy started)	0.56	040-0.81	0.002
Age, ≤65 yrs, >65 yrs	0.93	0.67-1.30	0.690
Age groups, 40	1		
50	2.29	0.53-9.91	0.269
60	1.66	0.40-6.87	0.481
70	1.41	0.34-5.79	0.638
80	1.55	0.38-6.38	0.541
90	3.69	0.77-17.5	0.102
Sex, male, female	0.93	0.70-1.25	0.689
CRP	1.001	0.99-1.00	0.176
Multivariable regression			
Tumor size, ≤ 4.3 cm, > 4.3 cm	1.43	1.01-2.04	0.048
Liver metastases, no, yes	3.26	2.16-4.92	<0.001
Performance status, bad (no chemotherapy), good (chemotherapy started)	0.37	0.25-0.55	<0.001

Table 4. Kaplan-Meier survival for prognostic subgroups.

Risk group	Relative hazard	Number of patients (%)	Median (iqr) survival, months	3-month survival rate, %	6-month survival rate, %	12-month survival rate, %	18-month survival rate, %
Low	≤ 1	57 (43)	6.7 (3.213.0)	81	58	32	12
Medium	>1 - ≤ 2	44 (33)	4.5 (2.7-7.2)	70	34	9	5
High	>2	31 (24)	1.2 (0.9-2.7)	13	0	0	0

iqr=interquartile range

Discussion

Our findings highlight three important factors that contribute to overall survival in patients with unresectable pancreatic cancer, i.e. tumor size defined as the tumor's maximum diameter, the presence of liver metastases, and patient performance status allowing starting chemotherapy. Those patients with good performance status corresponding to a Karnofsky index above 50 % received chemotherapy. We have previously found that survival analysis using the Kaplan-Meier method showed a better survival rate in unresectable pancreatic cancer if the tumor size was below 4.3 cm.[2] By using Cox regression, adjusted for occurrence of liver metastases and performance status to decide if chemotherapy should start or not, the individual relative hazard was calculated. Age, gender and CRP were not included in this calculation since these variables had no influence on the final multivariable Cox regression. Three different prognostic groups could be determined from the frequency distribution of individual hazard and the survival rate was clearly different between these groups ($p<0.001$), ranging from median 1.2 to 6.7 months (Figure 2). An easy-to-use model for prediction of survival in unresectable pancreatic neoplasm is therefore proposed, that discriminates survival better than predictions based on only tumor size, the presence of liver metastases or performance status to decide treatment with chemotherapy. The characteristics of the three groups are given in Table 5. The model is really a condensation of 8 (2^3) groups, i.e. 2 groups based on tumor size * 2 groups based on liver metastases * 2 groups based on performance status and initiation of chemotherapy treatment. The model also reveals a shift to a better risk group for patients with unresectable pancreatic cancer who start chemotherapy treatment. In the high risk group, tumor size has no influence on survival, which in their case is extremely short, about one month. The proposed model combines measurable hard data from initial radiographic examinations, in the form of tumor size and presence of liver metastases, with a somewhat weaker variable in the form of patient performance status and the physician-based decision to initiate chemotherapy or not. A clinical decision like this may be prone to individual bias in how the patient's general level of fitness, comorbidity and overall likelihood of benefitting from treatment is assessed. This may be seen as a potential limitation to the model's usefulness and reproducibility. However, it was necessary to give performance status/chemotherapy some form of consideration in the model, as the initiation of cytotoxic drug clearly has a considerable impact on patient survival as shown in Table 2. Even if it is not an exact factor, excluding the performance status/chemotherapy variable would reduce the regression model too much. We therefore chose to deal with it in our calculations and to adjust for it in the regression analysis.

Table 5. Risk groups according to liver metastases, performance status/initiation of chemotherapy and tumor size.

Liver metastases	Performance status	Tumor size, cm	Risk group	Median survival
No	Good, chemotherapy	Any	Low	6.7 (iqr 3.2-13.0)
	Bad, no chemotherapy	≤ 4.3		
No	Bad, no chemotherapy	> 4.3	Medium	4.5 (iqr 2.7-7.2)
Yes	Good, chemotherapy	Any		
Yes	Bad, no chemotherapy	Any	High	1.2 (iqr 0.9-2.7)

Another limitation of our study is that only half of the patients had cytological verified ductal adenocarcinoma and this highlights the clinical problems in managing pancreatic neoplasm and that in many cases the diagnose needs to rely on radiological examinations. However, in our study there was no difference in survival whether cytological diagnosis could be obtained or not. Nor were there any difference in overall survival with respect to enrolment periods and possible changes in second-line chemotherapy.

The strengths of this study are that it includes consecutive patients from a single medical centre and that all initial X-rays following admittance to the hospital were re-examined, all by the same radiologist. The prediction may be done immediately after radiologic investigations and assessment of patient performance status thereby not losing time while waiting for additional examinations. For a comprehensive summary of the previous literature on prognostic factors in pancreatic cancer, see Stocken et al.[4] Factors implicated by more than one previous researcher can be broadly attributed to one of the five following groups: 1. Factors describing tumor burden, i.e. tumor size, TNM disease stage, and presence of metastases, not necessarily confined to the liver[5]; 2. Factors describing the patient's fitness level, i.e. performance status or nutritional status[6]; 3. Biochemical variables from blood, with varying degrees of disease specificity, with the non-specific inflammatory marker CRP most frequently mentioned, but including many others, like the tumor markers CA 19-9 and CA 242[4 7]; 4. Immunohistochemical analyses from pathological specimens, where more than 11 are identified as relevant in two or more studies, but none validated highly enough to be recommended for use in clinical practice as of now[8]; 5. Treatment factors, i.e. surgery and/or chemotherapy.[1 9 10] We find that our model fits these previous findings quite well. In our study CRP had no impact on the final model for prediction of overall survival. However, it may require expansion to accommodate information from those groups that are not represented at present, i.e. blood laboratory and immunohistochemistry. The variable performance status/initiation of chemotherapy in its current form is likely to reflect both the biological effect that the drug has on tumor cells and a selection bias in who receives treatment. It may in the future be modified to better reflect the difference between these two effects. The clinical implications of being able to give patients a more individualized prognosis are quite clear in order to improve optimal patient care. Patients with an extremely short survival should have best supported care and those with a better predicted survival may be selected to radiochemotherapy. Also, as previously suggested by another research team, a more accurate individual prognosis may influence the choice between plastic and metal biliary stents for palliation of obstructive jaundice.[5] The initiation of chemotherapy treatment is correlated to survival advantages across all levels of tumor burden. It is not possible to determine which patients should have chemotherapy treatment based solely on the evaluation of initial patient X-rays. The survival advantages of chemotherapy are at least obvious in the low risk group, where we can observe a non-significant tendency towards longer survival among those treated. In the future, we have plans to validate the findings of our model, using a new cohort of patients at our center who were diagnosed with unresectable pancreatic cancer from 2010 onwards. The model may also be expanded with new variables according to our previous line of discussion. Closer determination of what factors warrant the initiation of chemotherapy merits attention. Ideally, an effort should be made to adjust the survival times for quality of life during the disease.

Conclusion

We propose an easy-to-use decision model which can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor and the presence of liver metastases at the patient's initial radiologic examination, together with performance status information to initiate chemotherapy. With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival. This knowledge may improve opportunities to individualize optimal patient care.

Competing interests

The authors declare that they have no competing interests.

All authors substantially contributed to the current manuscript as listed below:

HF drafted the manuscript, is the principal investigator of the study and designed this study. KÅ reviewed and measured tumor size of all X-rays. MW, KÅ, SJ revised the manuscript.

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Data sharing

No additional data available.

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Figure legends:

Figure 1. Distribution of relative hazard in 132 patients with unresectable pancreatic cancer, red bar = low, blue bar = medium and black bar = high risk group, corresponding to the three subgroups shown in Table 3.

Figure 2. Survival analysis in patients divided into low (L), medium (M) and high risk (H) prognostic subgroups, N=132, $p<0.001$.

A proposed model for prediction of survival based on a follow up study in unresectable pancreatic cancer

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Keywords

Pancreatic cancer, pancreatic neoplasm, unresectable, tumor size, biliary stricture, palliative, survival, prediction of survival

Word counts: 19613000

Abstract

Objectives: To define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.
Design: An observational retrospective study on patients with unresectable pancreatic cancer. The initial radiographs at presentation of symptoms were reviewed and the maximum diameter of the primary tumor was determined. The occurrence of liver metastases and performance status that determines initiation of chemotherapy was also used in the regression analysis to identify prognostic subgroups.
Setting: County hospital in south-east of Sweden.
Population: Consecutive patients with unresectable pancreatic cancer who were diagnosed between January 2003 and May 2010 (n=132).
Main outcome measures: Statistical analyses were performed using Stata ~~V13~~v13. Survival time was assessed with Kaplan-Meier analysis, log-~~tank~~ rank test for equality of survivor functions and Cox regression for calculation of individual hazard based on tumor diameter, presence of liver metastases and initiation of ~~gemcitabine~~ chemotherapy treatment according to patient performance status.
Results: The individual hazard was log h = 0.357 tumor size + 1.181 liver metastases - 0.989 ~~gemcitabine~~performance status/chemotherapy. Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with a median survival time of 1.2 (iqr 1.7) months.
Conclusion: The maximum diameter of the primary tumor and the presence of liver metastases found at the X-ray examination of patients with pancreatic cancer, in conjunction with whether or not chemotherapy is initiated according to performance status, predict the survival time for patients who do not undergo surgical resection. The findings result in an easy-to-use model for predicting the survival time.

Background

Pancreatic adenocarcinoma is a highly fatal neoplasm and one of the leading causes of death in cancer in the Western world. The prognosis of patients with unresectable pancreatic carcinoma is extremely poor with no prospects of a five-year survival rate.[1] The disease is difficult to treat because clinical presentation is often ~~is~~ late, and most of the patients have an advanced tumor burden with a high incidence of metastatic disease at diagnosis. In a recent Swedish study, tumor size - but not length of bile duct stricture - measured at the initial radiographic examination predicted the survival rate of patients with unresectable pancreatic cancer.[2] Identifying factors that can accurately predict the duration of disease survival is potentially helpful in the treatment of patients with unresectable pancreatic cancer. It may be unsuitable for patients with a bulky tumor to be exposed to cytotoxic chemotherapy or other advanced palliative therapies, as it may not prolong their survival but instead impair the quality of their short remaining lives. Could information that is readily available to clinicians at the time of diagnosis be used to predict survival time?

The purpose of this study is to examine whether tumor size and the presence of liver metastases at initial radiographic imaging, studied in conjunction with the decision to start chemotherapy based on patient performance status can predict survival length in patients with

unresectable pancreatic cancer, and identify prognostic subgroups among patients by calculating individual hazards after Cox regression.

Method

During the period January 2003 to May 2010, 185 consecutive patients were diagnosed with ductal pancreatic cancer and recruited into a single center study. Only patients with a diagnosis of cancer in the caput, corpus and cauda of the pancreas, or carcinoma growth outside the pancreas into adjacent organs were enrolled. Patients who had undergone surgery for curative purposes, i.e. Whipple procedure or total pancreatectomy, were excluded from this survey. The diagnosis of pancreatic cancer was based on radiographic examinations but cytological specimens were also performed. Initial radiographs following admittance to the hospital were retrieved and reexamined, all by the same radiologist, and tumor size was measured again. For a more detailed description of this procedure of tumor evaluation see Forssell et al.[2] In summary, most patients were examined with multislice computed tomography (CT) with a slice thickness of 2 mm. The maximum tumor diameter could be measured in 132 patients, in 114 with CT and the rest, 18 (14 %) patients, with transabdominal ultrasound examination. In 53/185 (29 %) cases, the image of the tumor was far too diffuse to be ~~measurable~~ measured by standard radiological means and these patients were not accounted for in this study. When the tumor was measurable ~~The~~ the median tumor maximum diameter was 4.35 cm and therefore the study material was classified into two equal groups with the cut-off diameter at 4.3 cm. Secondly, occurrence of liver metastases at the time of diagnosis was noted and the patients were divided into two groups depending on whether or not liver metastases were present. Thirdly, patients were divided into two groups of performance status, good or bad, corresponding to a Karnofsky scoring index above or below 50 %. ~~depending on whether or not they had been selected for gemcitabine treatment.~~ The ~~choice~~ decision to offer ~~gemcitabine~~ chemotherapy was entirely based on if patient performance status was good, i.e. clinical judgment, taking into account the patient's general level of fitness, comorbidity, and overall likelihood of benefitting from such treatment. If patients were offered chemotherapy it always started with gemcitabine. A second-line of chemotherapy consisted of 5-fluorouracile/calcium folinate (5 patients), capecitabine (6 patients) or oxaliplatin (1 patient). Patient characteristics are given in Table 1.

Table 1. Baseline characteristics of patients with primary unresectable pancreatic neoplasm.

Patients	132
Female/male	75/57
Age, median (iqr)	74 (64-81)
Age ≤ 65/ > 65 years (%)	40/92 (30/70)
Tumor diameter ≤ 4.3 cm (%)	66 (50)
Tumor diameter > 4.3 cm (%)	66 (50)
Liver ~~metastasis~~ metastases (%)	60 (45)
Performance status, corresponding to Karnofsky index > 50 %	57 (43)
~~Gemcitabine~~ Chemotherapy started with gemcitabine ~~started~~ (%)	57 (43)
Second-line chemotherapy after gemcitabine treatment (%)	12 (9)

Ethics

The study was approved by the Regional Ethical Review Board in Lund, Sweden (EPN Dnr 2012/92).

Statistical analysis

The statistical analysis was performed using Stata version 13 (Stata Corp LP, College Station, Texas, USA). Continuous variables are expressed as median values (interquartile range, iqr.) and were compared with two-sample Wilcoxon rank-sum test. The comparison among groups for categorical variables was performed with Pearson chi2 test. Overall survival estimates were calculated by the Kaplan-Meier method, and the difference between groups was assessed by the log rank. Survival rates are ~~gives~~ given as median and interquartile range (iqr). Survival curves were truncated at 24 months, since the number of patients at risk after that time was very small. Independent factors for overall survival were assessed with Cox proportional hazards regression analysis. The relative hazard for each patient was calculated from coefficients received by Cox regression.[3] $P < 0.050$ was considered statistically significant.

Results

A total of 132 of 185 patients had a measurable tumor and were included in the study with a median age of 74 (iqr 64-81) years. Of these, 75 were women and 57 were men. Liver metastases were found in 60 patients (45 %) at the initial radiological investigation and presentation of symptoms. Median survival times for patients with the different tumor sizes according to liver ~~metastasis~~ metastases and given ~~gemcitabine~~ chemotherapy treatment are shown in Table 2. In the group with failed cytological proven ductal adenocarcinoma (about half of the enrolled patients) the overall survival time was the same as in those patients with proven cancer. There were no difference in overall survival rate between patients included 2003-2006 and 2007-2010 (p=0.629). In the 53 patients with no measurable tumor the median overall survival time was 3.3 months and not significantly different from 4.9 months in those patients with a tumor size ≤ 4.3 cm or 3.1 months if tumor was > 4.3 cm. A Cox-regression was performed to identify prognostic subgroups of patients with unresectable pancreatic cancer (Table 3). The final form of the Cox model calculated from data from the 132 patients with ductal pancreatic neoplasm is shown in the lower part of Table 3. This corresponds to log h= 0.357 tumor size + 1.181 liver ~~metastasis~~ metastases – 0.989 ~~gemcitabine~~performance status/chemotherapy. Tumor size ≤ 4.3 cm, no liver ~~metastasis~~ metastases and performance status bad/no given ~~gemcitabine~~ chemotherapy were all coded = 0 and the other alternatives = 1. By using the formula, each individual relative hazard (h) was calculated. Three prognostic groups were defined according to the frequency distribution of the relative hazard: a low risk group h ≤ 1, a medium risk group h > 1 but ≤ 2, and a high risk group h > 2. ~~,~~Distribution of relative hazard in 132 patients with advanced pancreatic cancer is shown in Figure 1. The corresponding survival rates are shown in Table 4. Log rank tests for equality of survivor functions between the three groups indicated significant differences in survival rate, p< 0.001, Figure 2.

Table 2. Median survival time for patients according to tumor size, presence of liver ~~metastasis~~ metastases and started chemotherapy~~gemcitabine treatment~~, days.

No liver metastas~~e~~is	Liver ~~metastasis~~metastases

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	All	No ~~gemcitabine~~chemotherapy	~~Gemcitabine~~Chemotherapy	All	No ~~gemcitabine~~chemotherapy	~~Gemcitabine~~Chemotherapy
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Performance status, bad (no chemotherapy), good (chemotherapy started)~~Gemcitabine, no, yes~~	0.37	0.25-0.55	<0.001

Table 4. Kaplan-Meier survival for prognostic subgroups.

Risk group	Relative hazard	Number of patients (%)	Median (iqr) survival, months	3-month survival rate, %	6-month survival rate, %	12-month survival rate, %	18-month survival rate, %
Low	≤ 1	57 (43)	6.7 (3.213.0)	81	58	32	12
Medium	>1 - ≤ 2	44 (33)	4.5 (2.7-7.2)	70	34	9	5
High	>2	31 (24)	1.2 (0.9-2.7)	13	0	0	0

iqr=interquartile range

Discussion

Our findings highlight three important factors that contribute to ~~length of~~overall survival in patients with unresectable pancreatic cancer, i.e. tumor size defined as the tumor's maximum diameter, the presence of liver metastases, and patient performance status allowing starting chemotherapy. Those patients with good performance status corresponding to a Karnofsky index above 50 % received chemotherapy~~the decision if gemcitabine is started or not according to clinically judgement of patient performance status~~. ~~Earlier~~ W~~w~~e have previously found that survival analysis using the Kaplan-Meier method showed a better survival rate in unresectable pancreatic cancer if the tumor size was below 4.3 cm.[2] By using Cox regression, adjusted for occurrence of liver metastases and performance status to decide if chemotherapy should start or not~~gemcitabine treatment~~, the individual relative hazard was calculated. Age~~, and~~ gender and CRP were not included in this calculation since these variables had no influence on the final multivariable Cox regression. Three different prognostic groups could be determined from the frequency distribution of individual hazard and the survival rate was clearly different between these groups ($p<0.001$), ranging from median 1.2 to 6.7 months (Figure 2). An easy-to-use model for prediction of survival in unresectable pancreatic neoplasm is therefore proposed, that discriminates survival better than predictions based on only tumor size, the presence of liver metastases or performance status to decide~~possible~~ treatment with ~~gemcitabine~~chemotherapy. The characteristics of the three groups are given in Table 5. The model is really a condensation of 8 (2^3) groups, i.e. 2 groups based on tumor size * 2 groups based on liver metastases * 2 groups based on performance status and initiation of chemotherapy~~gemcitabine~~ treatment. The model also reveals a shift to a better risk group for patients with unresectable pancreatic cancer who start ~~gemcitabine~~ chemotherapy treatment. In the high risk group, tumor size has no influence on survival, which in their case is extremely short, about one month. The proposed model combines measurable hard data from initial radiographic examinations, in the form of tumor size and presence of liver metastases, with a somewhat weaker variable in the form of patient performance status and the physician-based decision to initiate ~~gemcitabine~~ chemotherapy or not~~, according to patient performance status~~. A clinical decision like this may be prone to individual bias in how the patient's general level of fitness, comorbidity and overall likelihood of benefitting from treatment is assessed. This may be seen as a potential limitation to the model's usefulness and reproducibility. However, it was necessary to give ~~gemcitabine~~ performance status/chemotherapy some form of consideration in the model, as the initiation of ~~this~~ cytotoxic drug clearly has a considerable impact on patient survival as shown in Table 2. Even if it is not an exact factor, excluding the ~~gemcitabine~~ performance status/chemotherapy variable would reduce the regression model too much. We therefore chose to deal with it in our calculations and to adjust for it in the regression analysis.

Table 5. Risk groups according to liver metastases, performance status/initiation of chemotherapy and tumor size~~, liver metastases and initiation of gemcitabine treatment (i.e. clinically fit for cytotoxic drug treatment)~~.

Liver metastases	~~Gemcitabine~~Performance status	Tumor size, cm	Risk group	Median survival
No	~~Yes~~Good, chemotherapy	Any	Low	6.7 (iqr 3.2-13.0)
	~~No~~Bad, no chemotherapy	≤ 4.3		
No	~~No~~Bad, no chemotherapy	> 4.3	Medium	4.5 (iqr 2.7-7.2)
Yes	~~Yes~~Good, chemotherapy	Any		
Yes	~~No~~Bad, no chemotherapy	Any	High	1.2 (iqr 0.9-2.7)

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The strengths of this study are that it includes consecutive patients from a single medical centre and that all initial X-rays following admittance to the hospital were re-examined, all by the same radiologist. The prediction may be done immediately after radiologic investigations and assessment of patient performance status thereby not losing time while waiting for additional examinations. For a comprehensive summary of the previous literature on prognostic factors in pancreatic cancer, see Stocken et al.[4] Factors implicated by more than one previous researcher can be broadly attributed to one of the five following groups: 1. Factors describing tumor burden, i.e. tumor size, TNM disease stage, and presence of metastases, not necessarily confined to the liver[5]; 2. Factors describing the patient's fitness level, i.e. performance status or nutritional status[6]; 3. Biochemical variables from blood, with varying degrees of disease specificity, with the non-specific inflammatory marker CRP most frequently mentioned, but including many others, like the tumor markers CA 19-9 and CA 242[4 7]; 4. Immunohistochemical analyses from pathological specimens, where more than 11 are identified as relevant in two or more studies, but none validated highly enough to be recommended for use in clinical practice as of now[8]; 5. Treatment factors, i.e. surgery and/or chemotherapy.[1 9 10] We find that our model fits these previous findings quite well. In our study CRP had no impact on the final model for prediction of overall survival. However, it may possibly require expansion to accommodate information from those groups that are not represented at present, i.e. blood laboratory and immunohistochemistry. The gemcitabine variable variable performance status/initiation of chemotherapy in its current form is likely to reflect both the biological effect that the drug has on tumor cells and a selection bias in who receives treatment. It may in the future be modified to better reflect the difference between these two effects. The clinical implications of being able to give patients a more individualized prognosis are quite clear in order to improve optimal patient care. Patients with an extremely short survival should have best supported care and those with a better predicted survival may be selected to radiochemotherapy. For exampleAlso, as previously suggested by another research team, a more accurate individual prognosis may influence the choice between plastic and metal biliary stents for palliation of obstructive jaundice.[5] The initiation of gemcitabine chemotherapy treatment is correlated to survival advantages across all levels of tumor burden. It is not possible to determine which patients should have gemcitabine chemotherapy treatment based solely on the evaluation of initial patient X-rays. The survival advantages of gemcitabine chemotherapy treatment are at least obvious in the low risk group, where we can only observe a non-significant tendency towards longer survival among those treated. In the future, we have plans to validate the findings of our model, using a new cohort of patients at our center who were diagnosed with unresectable pancreatic cancer from 2010 onwards. The model may also be expanded with new variables according to our previous line of discussion. Closer determination of what factors warrant the initiation of gemcitabine chemotherapy merits attention. Ideally, an effort should be made to adjust the survival times for quality of life during the disease.

Conclusion

We propose an easy-to-use decision model which can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor and the presence of liver metastases at the patient's initial radiologic examination, together with performance status information ~~on the~~to initiat~~ion of~~ chemotherapy. With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival. This knowledge may improve opportunities to individualize optimal patient care.

Competing interests

The authors declare that they have no competing interests.

All authors substantially contributed to the current manuscript as listed below:

HF drafted the manuscript, is the principal investigator of the study and designed this study. KÅ reviewed and measured tumor size of all X-rays. MW, KÅ, SJ revised the manuscript.

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Article summary

Article focus

- The aim of this study was to define an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to optimize patient care.

Key messages

- An easy-to-use decision model can predict survival time in patients with unresectable pancreatic cancer by determining the maximum diameter of the primary tumor, the presence of liver metastases at the patient's initial radiologic examination and clinical information on fitness for initiation of cytotoxic drug treatment.
- The prediction may be done immediately after radiologic investigations and assessment of patient performance status.
- Three prognostic groups could be defined: a low risk group with a median survival time of 6.7 (iqr 9.7) months, a medium risk group with a median survival time of 4.5 (iqr 4.5) months and a high risk group with very poor survival, a median survival time of only 1.2 (iqr 1.7) months.

Strengths and limitations of the study

- The data covers every patient with unresectable pancreatic cancer at a single hospital between January 2003 to May 2010.
- With the described model, it is possible to identify patients with a very short expected survival time, and those patients who are likely to have a somewhat longer duration of survival.
- The knowledge of expected survival may improve opportunities to individualize optimal patient care.
- One limitation is that the validation of the proposed model for prediction has to be done.

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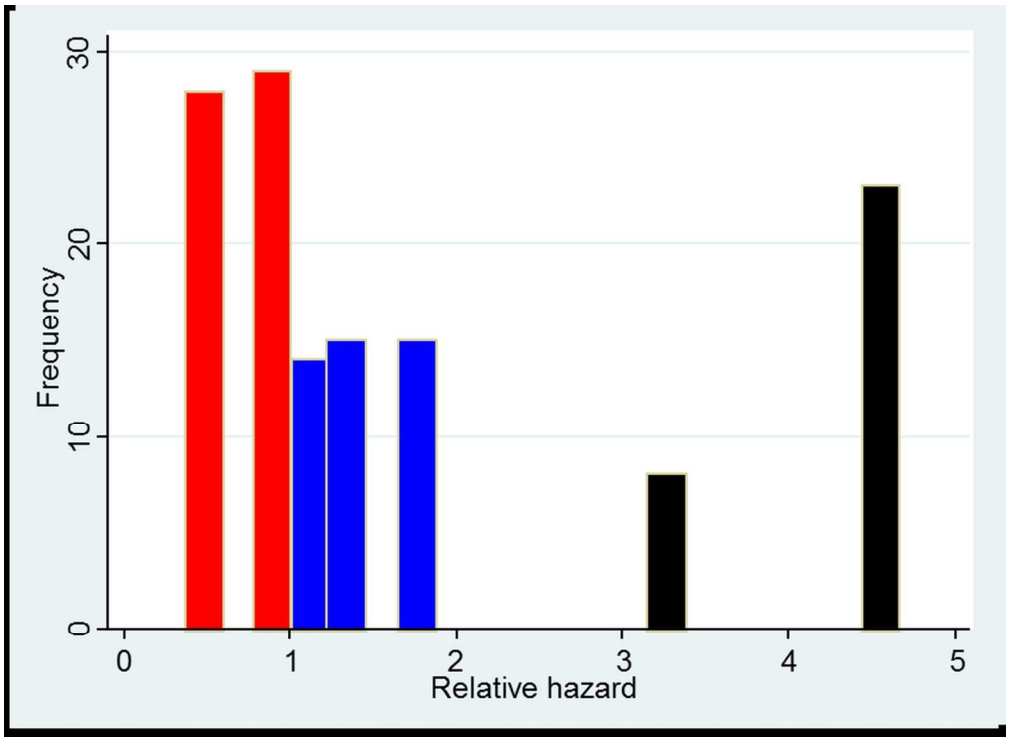
Figure legends:

Figure 1. Distribution of relative hazard in 132 patients with unresectable pancreatic cancer, red bar = low, blue bar = medium and black bar = high risk group, corresponding to the three subgroups shown in Table 3.

Figure 2. Survival analysis in patients divided into low (L), medium (M) and high risk (H) prognostic subgroups, N=132, $p<0.001$.



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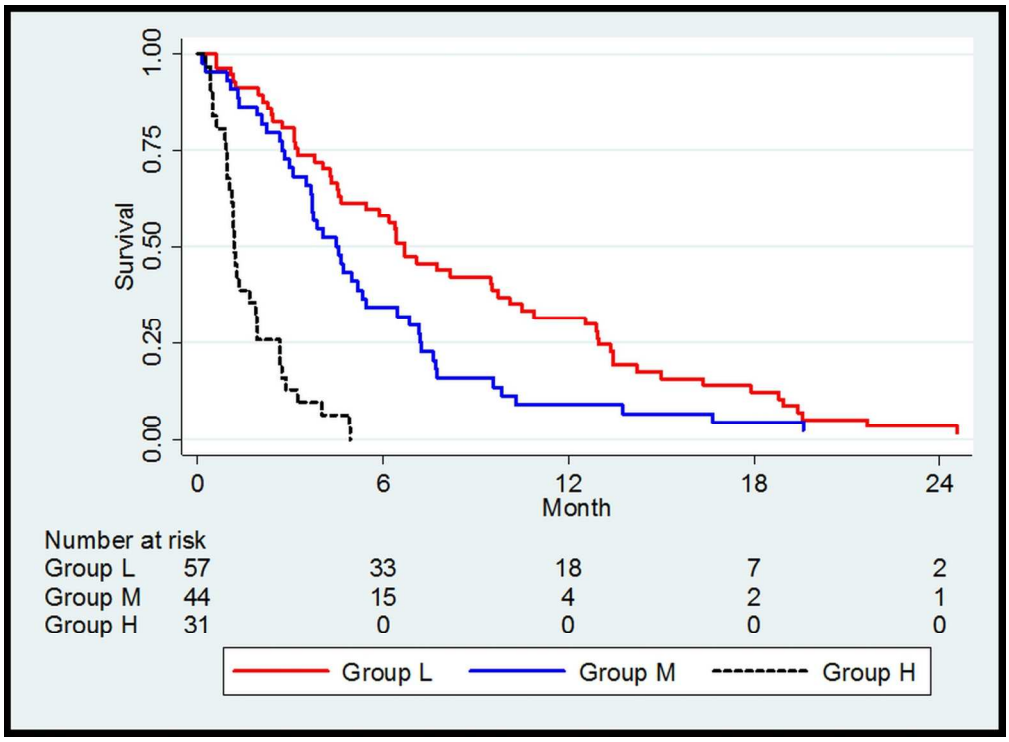

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