PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A proposed model for prediction of survival based on a follow up study in unresectable pancreatic cancer
AUTHORS	Forssell, Henrik; Wester, Michael; Åkesson, Katrin; Johansson, Sigrid

VERSION 1 - REVIEW

REVIEWER	Akihiro Tajima, MD, PhD, AGAF Assistant Professor Department of Gastroenterology Dokkyo Medical University Japan
REVIEW RETURNED	05-Oct-2013

GENERAL COMMENTS	The authors showed an easy-to-use model for prediction of survival time in patients with unresectable pancreatic cancer in order to individualize optimal patient care. This model is useful for patient-to-tailor therapy. Although the article has enough impact to clinical medicine, I have one suggestion to the authors. This article would be added to the field of pancreatic cancer. Major comments 1. In patients given gemcitabine treatment, would it be possible to use k-ras mutation status as a biomarker for the effectiveness of chemotherapy? If so, k-ras could be one of new marker for future study. Minor comments (although minor changes might be necessary at all): Method p4 l8 see.2 → see Forssell H et al.2 p4 l13 4.35 → 4.35 cm Results p5 l1 Figure 1. → Distribution of relative hazard in 132 patients with unresectable pancreatic cancer is shown in Figure 1.

REVIEWER	Falconi Massimo Prof. Massimo Falconi Clinica Chirurgia del Pancreas Università Politecnica delle Marche A.O.U. Ospedali Riuniti
REVIEW RETURNED	09-Oct-2013

GENERAL COMMENTS	Forssell et al. proposed a model for prediction of survival based on a follow up study in unresectable pancreatic cancer. Some major concerns can be arisen: 1) despite the elegant statistical model the Authors do not add anything to what already well known literature on the disease in this subset of patients; 2) moreover, despite likely for the observed survival, one of the essential criteria for the enrollment should be a cytological/histologically proven ductal adenocarcinoma; 3) in addition It can be supposed that a more easily retrievable parameter such as either Karnowsky Performance Status or ECOG could be a more precise proxy of the expected survival; 4) the enrolled population spans over a long period of time in which many alternative regimens than gemcitabine alone have been tested and approved for the treatment of the disease; some of the reported survival figures do not probably reflect the present expected survival; 5) to put together patients in whom the diameter was measured by CT with those in whom it has been measured by US do not seem appropriate.

REVIEWER	Hiroki Yamaue Wakayama Medical University Japan
REVIEW RETURNED	16-Oct-2013

GENERAL COMMENTS	Pancreatic cancer patients sometimes have suppressed performance stataus (PS). The authors shows the easy-to-model for prediction survival time in patients with unresectable pancreatic cancer by three factors; the maximum diameter, the presence of liver metastasis and the initiation of the gemcitabine treatment or not. This attempt may be contribute to optimize patients care. I think there are several points to be improved in this manuscript and please comments for my queries. Major comment 1. The authors demonstrate that the survival is different between three risk groups according to tumor size, liver metastasis and initiation of gemcitabine treatment or not. However, the poor PS patients with large tumor and liver metastasis cannot perform chemotherapy and those conditions are indicated the best supportive care, resulting that bad PS patients with large tumor and liver metastasis show the poorer survival. The authors describe that your trial contributes with optimize patient care for pancreatic cancer patients. I recommend to add treatment strategies distinguished by each risk group in discussion section. 2. The authors analyze univariable and multivariable Cox proportional hazards regression analysis using only five factors; tumor size, liver metastasis, the initiation of gemcitabine or not, age, and sex. Various prognostic factors have been reported in patients with unresectable pancreas cancer, such as Karnofsky performance

	scale, CA19-9 level, C-reactive protein level and more. Why the authors select the five factors for multivariate analysis? Please add the reason in the discussion section. 3. The authors use the 4.3cm of cut-off tumor diameter which means the median tumor diameter. Is the median level suitable for optimal cut-off point? I recommend the adding the grounds how to decide the cut-off in size. 4. The authors describe that 53 patients (29%) are excluded the measurement of tumor size. I think that pancreatic cancer is difficult to tumor border by the invasion into plexus. Please discuss the reason why 53 patients are difficult to evaluate tumor size.

VERSION 1 – AUTHOR RESPONSE

Reviewer Akihiro Tajima

1. Unfortunately we have not used k-ras mutation status in this study. It would be interesting to use k-ras in a future study.
2. We have done the minor changes in the manuscript, as suggested.

Reviewer Falconi Massimo

1. We think we add much of new knowledge especially with those patients with extremely poor survival rate – about 1 month in the worst group in our study – this has not been published before since the exact survival time is not published in the literature. We are of course aware of the bad prognosis in unresectable pancreatic cancer. For instance we made a thorough search in PubMed (MeSH terms survival, time, unresectable, advanced, pancreatic, cancer, neoplasm life expectancy and predictor [Title] AND survival [Title] AND advanced [Title] AND pancreatic [Title] AND cancer[Title]) and found many articles but non with the survival data as in our study. Most of the reported articles in PubMed were concerning different modalities of treatment regiments and survival. For instance Choi et al in Cancer Res Treat. 2012;44(2):127-132. And even back to more historical data by Moertel el al, Cancer. 1981 Oct 15;48(8):1705-10 they described a survival rate of about 5 months giving radiation therapy.
2. We have performed cytological/histological testing of our cancer patients and we had a positive PAD in 59/120 (49.2 %), i.e. proven cancer. In those patients with failed cytological proof the survival time for these patients were the same as in those patients with proven cancer. This highlights the clinical problem that we have in handling pancreatic neoplasm; it is not easy to get a conclusive specimen with fine needle aspiration of a tumor. So we have to rely on other diagnostic modalities, in most cases CT. In addition, the good thing with our proposed model for prediction is that we can have the prediction results already after admission to the hospital i.e. after X-ray investigations of the patient without to wait for sophisticated biochemical evaluations. By using our proposed prediction model it is possible to start immediately with best supported care in the group of patients that only have a survival of about 1 month.
3. We have not used the ordinary Karnofsky Performance Status or ECOG in this study and we used only the simple numeric binary variable (0 or 1) to describe fitness to receive chemotherapy or not corresponding to Karnofsky value below or above 50 %. If we have used Karnofsky Performance Status or ECOG in our final model after Cox regression we had come to difficulties in interpreting the results because we had to use several dummy variables.
4. We agree that the enrolled patients spans over several years. It is a single center study and it took time to receive a material as large as we reported and that the number of patients was large enough to perform good statistics on. For instance a study just published by Golden et al. Radiation Oncology 2012, 7:156 on chemoradiotherapy on 46 patients started 1997 and ended 2009. This highlights some of the problem performing studies in this field.

We are aware of new treatments and added in our manuscript those patients who actually received a second-line of chemotherapy (12 of 57 patients: 5 patients had some 5-fluorouracile/calcium folinate therapy, 6 patients were on capecitabine and 1 patient had oxaliplatin).

In our study there were no difference in survival rate between patients included between 2003 to 2006 and those included between 2007-2010 (p=0.6286). Three patients had second line chemotherapy in the first year cohort and 9 had second line chemotherapy in the second year cohort. New approved treatment did in fact not affect the survival time at all in our study.

We did not use in our calculations any dose of chemotherapy or how long time the chemotherapy was given. The aim of our study was to get a simple rule for prediction in unresectable pancreatic cancer.

5. We agree that we had to use ultrasound (US) in some patients (14 %) for measuring the tumor size but in those US there were a good and a clear-cut measure and therefore we did not exclude these patients. Furthermore, there were no difference in survival (p=0.459) according to if US or CT were the main diagnostic tool.

Reviewer Hiroki Yamaue
1. We have added in the discussion example of treatment strategies by the different risk groups. But the intention of our article was not to focus on different treatment strategies in unresectable pancreatic cancer but merely to identify those patients with extreme bad survival. These patients that only live about 1 month should have optimized patient care at home with analgesics, treatment against nausea and nutritional support.
2. We have added CRP in the Cox univariate regression analysis. It was not significant so it was not suitable to add CRP in the final model. We have added this in the discussion. We have not used Ca19-9 or ordinary Karnofsky Performance Index due to this would add to our model several dummy variables (for Karnofsky Performance Index 9 dummy variables) and then it would be difficult to interpret the Cox model.
3. About the 4.3 cm cut-off it was proposed and discussed in our article from 2012 (Forssell et al 2012, see reference 2)
4. We have added the reason why 29 % of the patients were excluded and added in the result section of our paper the median survival time for those with no measurable and diffuse cancers in comparison with those patient that had a measurable tumor