Author's response to reviews

Title: Survivin expression and its clinical significance in pancreatic cancer

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Author's response to reviews: see over
Author’s response to reviewers’ comment

Reviewer 1: Kennichi Satoh

General
This is an immunohistochemical study which examined survivin expression in pancreatic cancer and assessed the correlation of its expression with p53 and Bax expression and clinicopathological parameters. Although the authors found that survivin expression was not associated with p53 or Bax expression and clinical outcome, the author found that perineural invasion is significantly more common in the survivin-positive and venous invasion was significantly more common in the survivin-negative group. Survivin expression in pancreatic cancer has been shown to correlate with their aggressive phenotype such as poor survival, decreased apoptotic index or radioresistancy, etc. Thus it is difficult to understand that negative survivin expression correlated with venous invasion.

Reply:
Survivin expression is known to be associated with aggressive clinical course and poor outcome in many solid tumor, but it is not certain in pancreatic cancer. Venous invasion is another prognostic factor for liver metastasis in pancreatic cancer(Ref. 15). In the present study, we could not conclude that survivin expression may have a role as a prognostic factor for survival or other clinical outcome. So, we thought venous invasion is an independent prognostic factor irrelevant to survivin expression in aspect of liver metastasis. We expected that survivin expression in pancreatic cancer may be the predictive factor for anti-cancer therapy, such as radioresistancy.
As described in discussion, further study is required to determine the significance between survivin expression and venous invasion. According to recent reports, survivin expression has different clinical significance according to expression pattern. It may be another reason for this discrepancy, but we did not distinguish that in this study.
We added comment about this point in discussion.
Major revision
In figure B, intense survivin expression is seen in cancer cells. Although the authors state that normal glandular structures are negative, it is very difficult to find any normal glandular structure in this figure. The authors should show the picture with lower power of view or indicated arrows.

Reply:
In the present study, we performed immunohistochemical staining using tissue array. So no normal glandular structure was seen in slides. It was our mistake in description the figure. We deleted the explanation of figure 1(B).
Reviewer 2: Yoshinori nio

Major revision
The authors analyzed the effects of survivin expression on survival by classifying the 3 groups, score 0, 1, 2. However, judging from the figure 3 and tables, they can be classified into 2 groups, low expression (score 0 and 1) and high expression (score 2). The same things can be applied for Bax or p53 expression: For Bax, low(score 0 and 1 and high(score 2); and for p53, negative(score 0) and positive(score 1 and 2).

Survivin is thought to be associated with apoptosis, therefore the implication of survivin expression in relevance with Bax expression is interesting and should be analyzed in regard with the efficacy of chemotherapy.

Reply:
At first, we analyzed the results by classifying 2 group, low and high expression as comment, but we could not find any significance. As described in method, scoring systems is defined as follows: score 0= less than 10% of cells positive; 1= 10 - 49% positive; score 2= ≥50% positive. Score 0 means negative and score 1 means weakly positive including 40% positivity, so score 0 is very different from score 1. We decided that we’d better analyze by 3 scoring system.

We analyzed correlation between survivin expression and p53, Bax expression. We also investigate Bax expression and the efficacy of chemotherapy, but all patients who received chemotherapy showed 2 + in Bax protein expression. This result is commented in result part.
Reviewer 3: Naoki N Watanabe

Major revision

1. Although these authors explained that no correlation was found between survivin expression and p53 protein expression in result section, they did not show any figure or table to show this result. It is very important point because Lu et al. found a correlation between accumulation of mutant p53 protein and survivin expression in gastric cancer tissues (Cancer Res 1998;58:1808-12). In addition, Hoffman et al demonstrated that introduction of wild-type p53 gene into p53-null human lung cancer cells resulted in a significant decrease in expression of the survivin gene (J Biol Chem 2002;277:3247-57). Therefore authors should discuss the discrepancy between their observation and results shown in these previous reports.

2. Authors explained that some authors suggest that survivin may be independent prognostic marker not associated with p53 or Bax expression (Ref. 20 and 21). However, in Ref 20, Knuts et al. showed that survivin positivity was related to p53 expression (p=0.02) in rectal cancer. Authors explained that no correlation between survivin expression and survival. This explanation was too strong. Because survivin-negative group tended to show higher survival rate than in survivin-positive group by 50 months after operation.

Reply:
1. We described the association between p53 expression and survivin in Table 4. In some type of cancers, survivin expression has correlation with p53 expression. However, in other many reports, survivin expression is not associated with p53 by immunohistochemical staining in rectal, breast, ovarian cancer (Ref 21, 22. Int J Gynecol Pathol 2005;24:247-253).

So we added several comment about this discrepancy on discussion part

2. In Ref. 20 by Knuts et al, neither the intensity nor the percentage of survivin expression was related to p53 expression in the entire group or in the subgroup(p>0.05). (Table 5) They described in their abstract like this; Survivin positivity was related to worse survival, independent of Duke stage, local and distant recurrence, differentiation, gender, age, apoptosis, and p53 expression(p=0.02). It means survivin is related to worse survival (p=0.02), not associated with other factors.

Only 3 patients showed survivin negative, so it is not determine the correlation. We agree that it is too strong to make a conclusion about correlation. Therefore, we revised this sentence in
result, and explained the reason.

Minor revision

1. In table 2, although they examined 49 cases of pancreatic cancer, total numbers in lymphatic invasion, vein invasion and perineural invasion were 46.
2. Legend for figure 3 is missing.

Reply:

1. We obtained only tumor tissue from 3 patients. We could not find any pathological characteristics from these patients.
   We added explanation for this in the result part.
2. We added legend for Fig. 3