

Journal of Hepato-Biliary-Pancreatic Sciences

Long-term outcomes after revision of Kasai portoenterostomy for biliary atresia --Manuscript Draft--

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Abstract:	<p>Background: The indications for and efficacy of revision of portoenterostomy (PE) for biliary atresia (BA) needs to be reassessed in an era of liver transplantation. We therefore reviewed the long-term outcomes following revision of PE.</p> <p>Methods: This was a retrospective study of the medical records of patients with BA who underwent PE and revision of PE. We investigated the role of revision on outcomes of jaundice-free native liver survival. (approval number:2015-0094)</p> <p>Results: PE was performed in 76 patients, among whom 22 underwent revision. Revision for recurrent jaundice was performed for four of 51 patients, who were transiently jaundice free after initial PE, but only one achieved native liver survival. Revision for repeated cholangitis in two patients achieved native liver survival over ten years. Revision was performed in 16 of the 25 patients in whom initial PE failed; of these, four survived with their native liver (ages 3, 12, 12, and 14 years). The PE revision didn't significantly affect liver transplantation duration and survival outcome.</p> <p>Conclusions: Revision of PE was suitable for repeated cholangitis. Revision for recurrent jaundice, regardless of whether the initial PE was successful, could have a limited but positive effect in preventing long-term progressive liver failure.</p>
Response to Reviewers:	<p>Thank you very much for your useful comments.</p> <p>We have revised the manuscript according to your comments. The revision are highlighted in yellow in the revised manuscript and we have responded to the point as shown below</p> <p>Reviewers' comments:</p>

	<p>Kaplan-Meier survival curves might be compared using log-rank test or generalized Wilcoxon test. The statistical analytical method should be specified in "Statistical analysis".</p> <p>We have added the following statement in Statistical analysis section according to your suggestion.</p> <p>We look forward to hearing from you at your earliest convenience.</p>
<p>Author Comments:</p>	<p>Dear Prof. Takada, Re: Manuscript Reference No JHBP-D-16-00171R1 Please find attached a revised version of our manuscript entitled "Long-term outcomes after revision of Kasai portoenterostomy for biliary atresia," which we would like to resubmit for publication as an Original Article in Journal of Hepato-Biliary-Pancreatic Sciences. We would like to thank the reviewers for their insightful comments. The comments by the reviewers have been helpful in allowing us to revise and strengthen our manuscript. We have attempted to address the questions raised by the reviewers. The detailed review of the manuscript is appreciated. Please find our point by point responses to the reviewers' comments below. The revisions in the text are indicated in yellow. We hope that the revisions and our accompanying responses will be sufficient to make our manuscript suitable for publication in Journal of Hepato-Biliary-Pancreatic Sciences. We look forward to hearing from you at your earliest convenience.</p> <p>Sincerely yours, Hiroo Uchida, MD., Chiyoe Shirota, MD.</p>
<p>Additional Information:</p>	
<p>Question</p>	<p>Response</p>
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5 August, 2016

Prof. Tadahiro Takada

Editor-in-Chief

Journal of Hepato-Biliary-Pancreatic Sciences

Dear Prof. Takada,

Re: Manuscript Reference No JHBP-D-16-00171R1

Please find attached a revised version of our manuscript entitled “***Long-term outcomes after revision of Kasai portoenterostomy for biliary atresia,***” which we would like to resubmit for publication as an Original Article in *Journal of Hepato-Biliary-Pancreatic Sciences*.

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The revisions in the text are indicated in **yellow**. We hope that the revisions and our accompanying responses will be sufficient to make our manuscript suitable for publication in *Journal of Hepato-Biliary-Pancreatic Sciences*.

We look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Responses to the comments of Reviews

Thank you very much for your useful comments.

We have revised the manuscript according to your comments. The revision are highlighted in **yellow** in the revised manuscript and we have responded to the point as shown below

Reviewers' comments:

Kaplan-Meier survival curves might be compared using log-rank test or generalized Wilcoxon test. The statistical analytical method should be specified in "Statistical analysis".

⇒ We have added the following statement in Statistical analysis section according to your suggestion.

We compared the survival curves for the two groups with the log-rank test.

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4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abstract

Background: The indications for and efficacy of revision of portoenterostomy (PE) for biliary atresia (BA) needs to be reassessed in an era of liver transplantation. We therefore reviewed the long-term outcomes following revision of PE.

Methods: This was a retrospective study of the medical records of patients with BA who underwent PE and revision of PE. We investigated the role of revision on outcomes of jaundice-free native liver survival (approval number: 2015-0094).

Results: PE was performed in 76 patients, among whom 22 underwent revision.

Revision for recurrent jaundice was performed for four of 51 patients, who were transiently jaundice free after initial PE, but only one achieved native liver survival.

Revision for repeated cholangitis in two patients achieved native liver survival over ten years. Revision was performed in 16 of the 25 patients in whom initial PE failed; of these, four survived with their native liver (ages 3, 12, 12, and 14 years). The PE revision didn't significantly affect liver transplantation duration and survival outcome.

Conclusions: Revision of PE was suitable for repeated cholangitis. Revision for recurrent jaundice, regardless of whether the initial PE was successful, could have a limited but positive effect in preventing long-term progressive liver failure.

Main Text

Background

It is considered optimal for patients with biliary atresia (BA) to retain their native liver after Kasai portoenterostomy (PE). However, the outcomes of native liver survival without jaundice after initial Kasai PE have not improved over the past 20 years [1]. Moreover, liver transplantation has since been established as a radical operation that is suitable following the failure of PE, but the long-term prognosis is unclear, with evidence of an increased risk of cancer mortality [2, 3]. Before the introduction of liver transplantation, revision of Kasai PE was a routine procedure, but the number of revisions have recently been decreasing with the establishment of liver transplantation as a standard therapy [4]. Recently, it has been suggested that revision of PE could delay the need for liver transplantation and contribute to improved native liver survival. The indications for and efficacy of revision of PE are therefore subjects of considerable discussion [5]. We report our experiences of the long-term outcomes following revision of Kasai PE and discuss the clinical significance of those results.

Patients and Methods

Study design and patient selection

We obtained approval from our institutional review board for a retrospective review of the medical records of patients diagnosed with BA at our institution (approval number: 2015-0094). We included patients who underwent Kasai PE and revision of Kasai PE between January 1996 and January 2013. Patients were required to have a diagnosis of BA made by a combination of radiographic findings, surgical findings of uncorrectable

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2 type, and liver histology results. Patients with a total serum bilirubin (T-bil) level of 1.2
3
4 mg/dl or lower were regarded as having achieved a jaundice-free status. We decided the
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6 initial poor biliary drainage on observation of persistent white color stool and persistent
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8 jaundice about 3 or 4 weeks following the initial PE. Very few patients could achieve
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10 jaundice clearance 2 or 3 months following the initial PE after our decision. We
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12 recorded the following: sex and age at the time of initial surgery; preoperative T-bil
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14 level and lowest postoperative T-bil level; and interval from initial surgery, and T-bil
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16 level at the time of reoperation. We investigated the role of timing of revision of Kasai
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18 PE on outcomes and the rate of jaundice-free native liver survival.
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25 *Surgical procedures*

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28 The operative procedure has not drastically changed during the period. One of the most
29
30 important points is that the fibrous tissue in the hilar plate is dissected just before baring
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32 the liver parenchyma; it is not completely resected. The area between the right porta
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34 hepatis, in which the right anterior branch of the hepatic artery and portal vein enter the
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36 hepatic parenchyma and the left porta hepatis, in which the left branch of the portal vein
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38 enters the parenchyma, is dissected for anastomosis. The operative technique for
39
40 revision of Kasai PE was similar to that used for the initial Kasai PE. After operating to
41
42 remove dense peritoneal adhesions, the anastomosed Roux limb was dissected adjacent
43
44 to the hepatic hilum. Any developed extrahepatic granulation tissue was then resected,
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46 and the hilar plate was further dissected just before baring the liver parenchyma, as in
47
48 the initial Kasai PE. Re-portoenterostomy was performed after trimming the Roux limb.
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51 All postoperative management protocols were identical to those used for the initial
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2 In our study, all patients were operated by a single surgeon and the same team in a
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4 single institution, thereby minimizing any differences in surgical procedure or
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6 postoperative management. In patients included in the recurrent jaundice or cholangitis
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8 group who underwent successful initial PE and were jaundice free or in patients in
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10 whom jaundice did not reduce after the initial surgery, revision of Kasai PE was
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12 conducted based on parental decisions after giving detailed information. We informed
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14 all patients that the previous results in our institute and nationwide research included
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16 native liver survival of second Kasai PE.
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25 *Statistical analysis*

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28 The statistical analysis was performed using Fisher's exact test for categorical variables
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30 and Wilcoxon's test for continuous variables. Values of $P < 0.05$ were considered
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32 statistically significant. Survival rates were calculated using the Kaplan–Meier estimator.
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35 The Kaplan–Meier survival curves were created for the days after initial Kasai PE with
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37 or without revision. We compared the survival curves for the two groups with the
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40 log-rank test.
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43 **Results**

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46 Patient flow in this study is summarized in Figure 1, and the demographic and clinical
47
48 characteristics of patients who underwent Kasai portoenterostomy are summarized in
49
50 Table 1. Kasai PE was performed in 76 patients with uncorrectable BA, which had a
51
52 definitive diagnosis and without another liver disease. Including those who underwent
53
54 revision of Kasai PE, 48 patients (63.2%) achieved jaundice-free native liver survival.
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57 Liver transplantation was performed in 26 patients (34.2%) and 3 patients (3.9%) died.
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2 Patients were divided into four groups on the basis of their postoperative jaundice
3
4 status: (1) patients who underwent successful PE and survived with native livers
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6 without jaundice (N = 41); (2) patients with recurrent jaundice (N = 7), cholangitis (N =
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8 2), or sudden death for unknown reason (N = 1) after successful initial PE and being
9
10 jaundice free; (3) patients who underwent revision of Kasai PE after initial failure (N =
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12 16); and (4) patients who required liver transplantation for survival after initial failure
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14 (N = 9).
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19 In 51 of the 76 patients (67.1%), T-bil was transiently normalized after initial Kasai PE.
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21 There were no significant differences in age at the time of initial surgery or in the T-bil
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23 level at the time of surgery among the 51 patients in whom T-bil normalized after initial
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25 surgery and the 25 patients in whom no reduction was observed after initial surgery
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27 (Table 1). Jaundice recurred in 7 patients, and revision of Kasai PE was performed in 4
28
29 of these patients (Fig. 1). The interval from the initial surgery to reoperation (the
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31 interval from the recurrence of jaundice to reoperation) was 52 (23), 71 (27), 146 (52),
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33 or 567 (117) days, and the T-bil transiently normalized in all but the patient with a
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35 567-day interval (117-day interval). T-bil then markedly increased again in two patients
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37 who subsequently needed liver transplantation at the age of 2 years. In the other patient
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39 with a 71-day interval, no jaundice recurrence was observed, and the patient achieved
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41 jaundice-free native liver survival at the age of 3 years.
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50 Second revisions of Kasai PE were needed to treat recurrent cholangitis with multiple
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52 bile lakes in 2 of the 51 patients who underwent revision. Both patients survived with
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54 their native livers without further bile lakes (both aged 14 years at the time of writing
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56 this manuscript). Among the six patients with a reduction in jaundice after initial PE
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2 who underwent revision, a transient jaundice-free status was achieved in 5 (83.3%) and
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4 native liver survival was achieved in 3 (50%) patients. Successful revision outcome
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6 after recurrent jaundice or cholangitis after being previously jaundice free was
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8 independent of the interval from the initial surgery to the revision (Table 2).
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12 In 25 of the 76 patients (32.9%), there was no reduction in jaundice levels after the
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14 initial Kasai PE. In 16 of these patients, revision was performed based on parental
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16 decisions after giving detailed information, and the interval from the initial surgery to
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18 revision was 20–56 days. T-bil normalized after reoperation in 5 of the 16 patients
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20 (31.3%), and 4 of these patients survived with their native livers (aged 3, 12, 12, and 14
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22 years at the time of writing this manuscript); however, in one of these patients, liver
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24 transplantation was necessary at the age of 1.5 years because of recurrent jaundice.
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26 Transient complete jaundice reduction delayed the timing of liver transplantation. If
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28 revision was not performed, patients needed earlier transplantation and had no native
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30 liver survival.
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38 Of the 16 patients who did not have reduced jaundice after the initial surgery and who
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40 needed reoperation, there were no significant differences in sex, age at the time of the
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42 initial operation, or T-bil level at the time of reoperation. Although this held for the four
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44 patients in whom T-bil was subsequently normalized and the 12 patients in whom no
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46 reduction was observed, the interval from initial surgery to reoperation was significantly
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48 shorter in the former ($P = 0.033$) (Table 2). The Kaplan–Meier survival curves for
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50 native livers from initial PE to revision were compared with those for patients without
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52 revision, but no significant differences existed (Fig. 2).
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58 Revision of Kasai PE was performed in a total of 22 patients. Median duration of
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2 surgery and blood loss were 235 min (range, 170–400 min) and 70 ml (range, 15–1071
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4 ml), respectively, and there were no significant differences between revision and initial
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6 Kasai PE, 285 min (range, 178–390 min; $P = 0.118$) and 60 ml (range, 5–363 ml; $P =$
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9 0.781). Three among 22 patients required blood transfusion. There were no
10
11 complications during the surgery, but two patients required additional operation after
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13 revision Kasai PE due to intestinal obstruction and duodenal perforation.
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17 A third surgery was performed in one patient with recurrent jaundice after the jaundice
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19 reduced following initial and revised surgery. A third surgery was also performed for
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21 four patients in whom jaundice did not reduce after initial and revision surgery.
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24 However, bilirubin did not normalize in any of these patients. Liver transplantation was
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26 performed in all patients but one. The one patient refused liver transplantation and later
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28 died. Two patients underwent a third Kasai PE to treat recurrent cholangitis with
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30 multiple bile lakes, and both survived with their native livers.
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34 Among the patients undergoing liver transplantation, we compared the operative time
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36 from skin incision to completion of total hepatectomy between those patients who did
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38 and did not undergo revision of PE. The median total hepatectomy time for revision of
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40 PE [288 (144–370) min] did not significantly differ from that in the no-revision group
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42 [235 (141–398) min] ($P = 0.38$). At 5 years after liver transplantation, there were no
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44 significant differences in survival rate between patients who received PE revision
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46 (100%) and those who only received a single PE (91.7%).
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55 Discussion

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58 The standard treatment algorithm for patients with BA consists of Kasai PE followed by
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2 liver transplantation if PE fails, and revision of Kasai PE has tended to be negatively
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4 viewed because of the possibility of future liver transplantation [6, 7, 8]. However, in
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6 2012, Bondoc et al. reported that they performed revision of PE in 24 of 181
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8 portoenterostomy-treated patients with BA and 13 (54%) of these patients did not
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10 require further surgical treatment [5]. When selection for revision is based on sudden
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12 bile flow cessation after there has been good bile drainage following a successful initial
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14 PE, reoperation by Kasai PE plays a role in offering long-term survival of the native
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16 liver or prolonging the time until liver transplantation, leading to improved
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18 transplantation outcomes [4, 9, 10].
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25 In our patients, revision of PE led to transient complete jaundice reduction in 5 of the 6
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27 patients (83.3%) with good jaundice reduction after the initial surgery. Jaundice-free
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29 survival with native livers has since been maintained for a prolonged period in 3 of the
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31 6 patients (50%), who were 3, 14, and 14 years old at the time of writing. The other
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33 three patients who underwent revision finally needed transplantation, but their native
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35 livers were retained until they were 2 years old, suggesting that revision can delay the
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37 timing of liver transplantation for patients in whom jaundice recurs after successful
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39 initial surgery.
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45 In our study, age at diagnosis and surgery had no statistically significant differences
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47 between reduction and not reduction jaundice after initial Kasai PE ($P=0.057$) but had a
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49 high probability of being related.
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53 In some reports, revision of PE has not been recommended for patients with poor
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55 reduction after the initial surgery, with the recommendation that it should be performed
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57 to re-establish bile flow achieved by the initial surgery because continuous bile drainage
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2 is important for native liver survival [11,12, 13]. However, the use of revision of Kasai
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4 PE for the treatment of poor jaundice reduction after initial surgery has not been
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6 evaluated. In our study, we performed revision for patients whose initial PE failed;
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8 among the 16 patients undergoing revision of PE for poor jaundice reduction following
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10 the initial PE, 5 (31.2%) became transiently jaundice free, and 4 of these patients
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12 achieved jaundice-free survival with their native liver (these patients were aged 3, 12,
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14 12, and 14 years at the time of writing). All four have retained normal liver function and
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16 are able to participate in normal daily activities free from jaundice, but would have
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18 needed liver transplantation if revision of Kasai PE had been withheld. Additionally,
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20 jaundice-free survival with retention of the native liver was extended in 1 of the 4
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22 patients (25%) who underwent revision of Kasai PE for recurrent jaundice after
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24 successful initial Kasai PE. The rate of jaundice-free long-term survival with retention
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26 of the native liver was 25% in both those patients with persistent jaundice and
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28 successful jaundice reduction after the initial PE. Thus, revision of PE offered a limited
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30 but positive effect not only for postponing the timing of liver transplantation but also for
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32 prolonging native liver survival. In many cases, poor drainage after the PE is attributed
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34 to liver pathology, but in some cases, it might show that surgical technique has some
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36 impact on the outcome of biliary drainage.
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46 Given our findings, revision of Kasai PE could be a possible option for the treatment of
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48 persistent jaundice in a subset of patients if the optimal timing could be determined. It is
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50 known, for example, that revision should not be delayed until after bile drainage
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52 becomes unfavorable [14]. Other reports have shown that revision could be effective for
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54 patients in whom jaundice suddenly recurred after favorable initial reduction,
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56 irrespective of the time since the initial surgery [13, 15]. In our study, the rate of
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2 successful jaundice reduction was significantly higher for revisions performed at shorter
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4 intervals after the initial PE, particularly in patients with poor jaundice reduction after
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6 the initial surgery. This is consistent with the belief that further liver damage is avoided
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8 by a shorter period of poor drainage. Therefore, it may be important to recommend
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10 performing revision as soon as irreversible jaundice has been recognized.
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14 Poor jaundice reduction could not be improved in five patients who underwent a third
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16 Kasai PE. In two patients, this was for cholangitis and intrahepatic bile lakes, and both
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18 are alive with their native liver (both were 14 years old at the time of writing). This
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20 suggests that a second revision may be appropriate for clinical conditions other than
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22 recurrent jaundice, and this is not indicated in patients who are never free of jaundice.
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26 In our comparison of initial PE versus revision of PE for patients undergoing liver
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28 transplantation, only slight differences were present. The use of revision of PE was not
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30 shown to increase mortality at the time of transplantation, but would be expected to
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32 introduce some increased technical difficulties at the time of transplantation [16]. These
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34 possible difficulties, however, are not sufficient to outweigh the potential benefit of
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36 preventing progressive liver failure.
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40 In conclusion, revision of Kasai PE was suitable for repeated cholangitis and
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42 intrahepatic bile lakes. Revision of PE for recurrent jaundice, regardless of the success
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44 of the initial PE, had a limited but positive effect on postponing the timing of liver
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46 transplantation and prolonging native liver survival. Revision should be employed
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48 immediately after confirming persistent jaundice. We require further survey for a subset
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50 of the BA patients, in whom the revision of PE is performed effectively at the optimal
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52 time.
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2 **Figure legends**
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5 **Fig. 1**
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8 Overview of patients with uncorrectable biliary atresia. This flowchart summarizes the
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10 jaundice statuses and the outcomes after initial portoenterostomy and revision. We
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12 divided 76 patients on the basis of treatment and outcome.
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16 Abbreviations: PE, portoenterostomy; LTx, liver transplantation
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22 **Fig. 2**
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25 Kaplan–Meier curves of time to native liver survival from initial portoenterostomy,
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27 comparing the groups with and without revision. The vertical dashes represent death or
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29 liver transplantation. The revision group is represented by the dashed curve, and the
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31 no-revision group is represented by the solid curve.
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Table 1. Demographic and clinical characteristics of patients who underwent Kasai portoenterostomy

		Jaundice free after initial Kasai PE	Jaundice after initial Kasai PE	<i>P</i> -value
Characteristic	N = 76	51 (67%)	25 (33%)	
Male	34	24	10	0.561
Age at initial Kasai (days), median (min-max)	66 (32–209)	61 (35–144)	67 (32–209)	0.057
T-bil level at the time of surgery (mg/dl)	7.9 (3.9–20.9)	7.6 (3.9–14.1)	7.9 (5.1–20.4)	0.532
Native liver survival without jaundice (%)	48 (63.2)	44 (86.3)	4 (16)	<0.01
Liver transplantation (%)	26 (34.2)	6 (11.8)	20 (80)	<0.01
Died	3	1	2	0.25

Table 2. Demographic and clinical characteristics of patients who underwent revision Kasai portoenterostomy

	Recurrent jaundice or recurrent cholangitis after being jaundice free		<i>P</i> -value	Persistent jaundice		<i>P</i> -value
	Native liver	LTx or Died		Native liver	LTx or Died	
#	3	3		4	12	
Sex (male)	1	0	1.0	0	6	0.23
T-bil level at the time of revision (mg/dl)	11.1 (10.1–12.7)	9.6 (6.8–9.7)	0.08	8.5 (3.5–10.4)	7.5 (5.1–13.7)	0.54
Age at the time of initial Kasai PE	101 (67–105)	44 (38–61)	0.08	64 (62–100)	67 (55–124)	0.39
Bottom of T-bil after initial PE	0.7 (0.6–1.0)	0.7 (0.4–1.0)	1.0	3.5 (2.1–5.3)	3.9 (2.0–6.2)	0.81
Interval from the initial to revision Kasai	134 (71–309)	146 (52–567)	1.0	28 (27–31)	35 (20–56)	0.033*

* $P < 0.05$

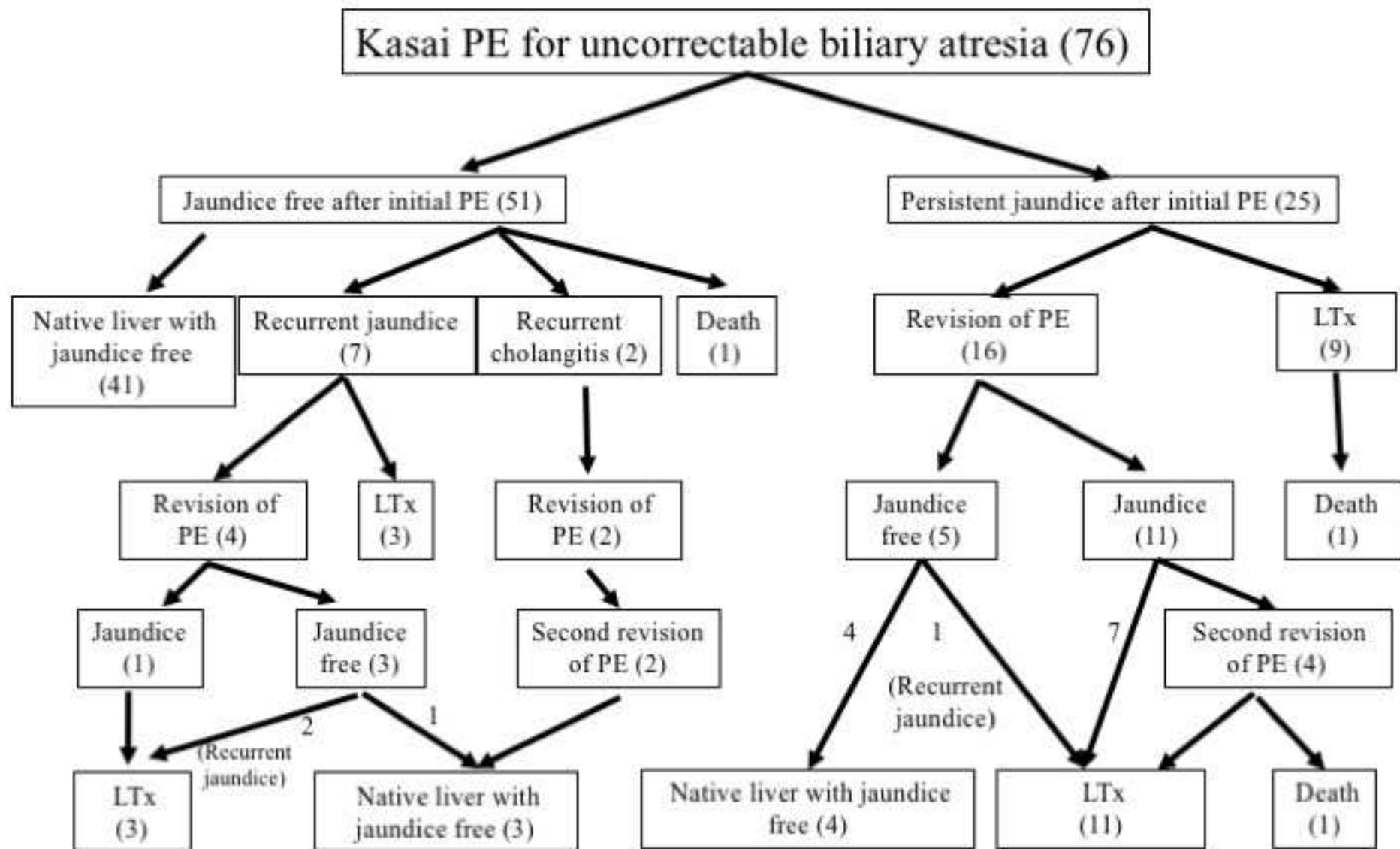


Fig. 1

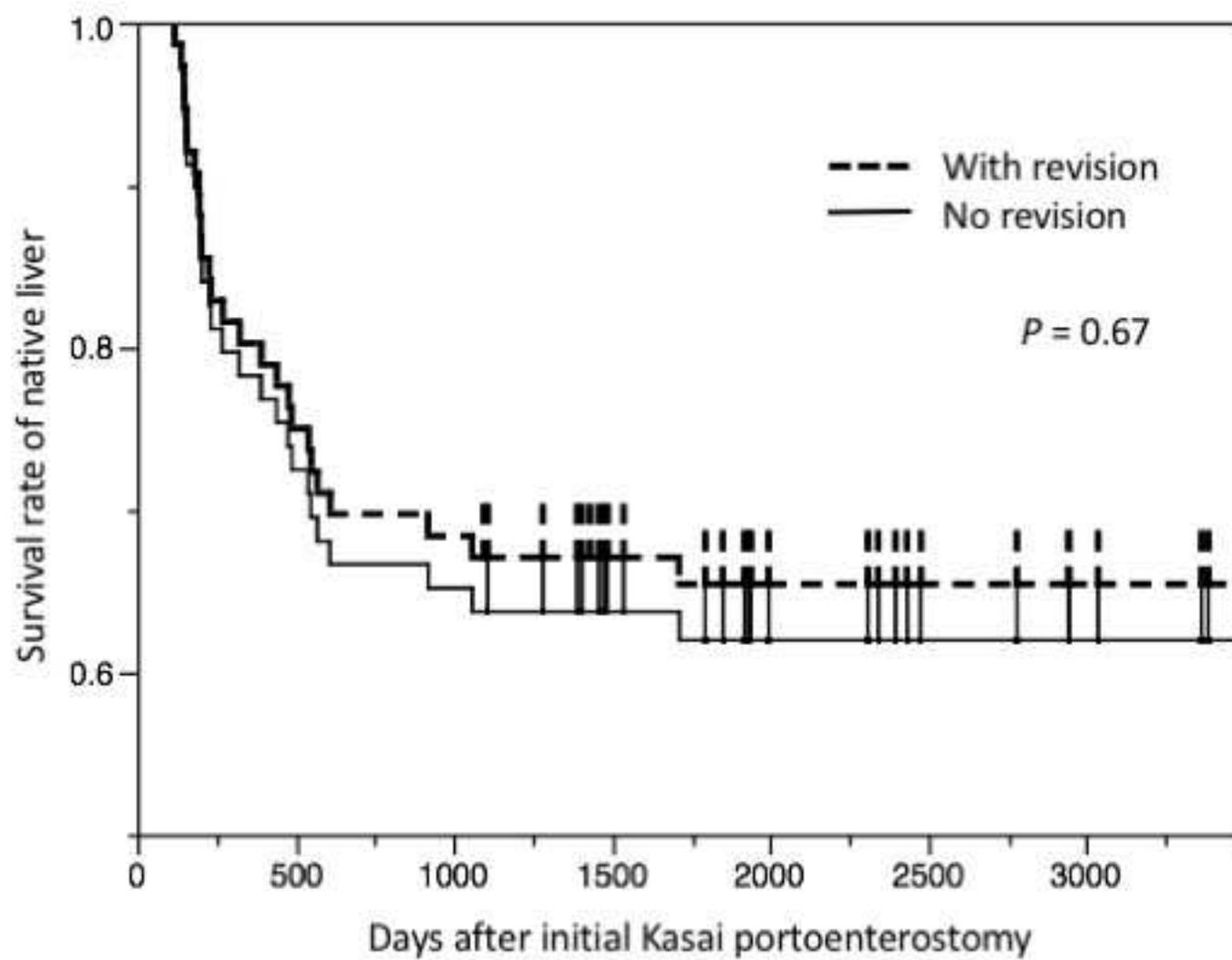


Fig. 2