# Outcomes of reduction hepatectomy and postoperative multidisciplinary therapy for 30 unresectable advanced hepatocellular carcinomas

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## Abstract

# Background

The role of volume reduction hepatectomy in the treatment of unresectable advanced hepatocellular carcinoma remains unclear. This study aimed to examine the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for unresectable advanced hepatocellular carcinoma.

# Methods

Thirty cases of unresectable advanced hepatocellular carcinoma, in which reduction hepatectomy was performed between 2000 and 2018 at the Department of Gastroenterological Surgery I, were divided into POCR(+) and POCR(-) groups, depending on whether postoperative complete remission (POCR) of the evaluable lesions was achieved through postoperative treatment. The cases in the POCR(-) group were subdivided into POCR(-)TKI(+) and POCR(-)TKI(-) groups, depending on whether tyrosine kinase inhibitors (TKIs) were administered postoperatively.

# Results

The 5-year overall survival rate and mean survival time (MST) after reduction hepatectomy were 15.7% and 28.40 months, respectively, for all cases; 37.5% and 56.55 months, respectively, in the POCR(+) group; and 6.3% and 14.84 months, respectively, in the POCR(-) group ($p = 0.0041$). Tumor size, vascular invasion, and the number of tumors in the remnant liver after the reduction hepatectomy were also found to be related to survival outcomes. The number of tumors in the remnant liver was the only factor that differed significantly between the POCR(+) group and POCR(-) group, and POCR was achieved significantly more frequently when $\leq 3$ tumors remained in the remnant liver ($p = 0.0025$). The MST was 33.52 months in the POCR(-)TKI(+) group, which was superior to the MST of 10.74 months seen in the POCR(-)TKI(-) group ($p = 0.0473$).

# Conclusions

Reduction hepatectomy and multidisciplinary postoperative treatment for unresectable advanced hepatocellular carcinoma resulted in a 5-year overall survival rate of 15.70% and an MST of 28.40 months. The treatment strategy was effective when POCR was achieved via multidisciplinary postoperative therapy. To achieve POCR, reduction hepatectomy should aim to ensure that $\leq 3$ tumors remain in the remnant liver. Even in cases in which POCR is not achieved, combined treatment with reduction hepatectomy and multidisciplinary therapy can improve survival outcomes when TKIs are administered.

# Background

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignant tumor, accounting for 85–90% of primary hepatic malignant tumors [1]. Advanced HCC (advHCC) is defined as progressive malignant HCC, which is hard to treat in a single hepatectomy procedure [2, 3]. This is one reason for the poor prognosis of advHCC because hepatectomy is an important curative option. In fact, it is more effective at achieving local control of advHCC than any other treatment [4]. Local ablation therapy (LAT), including radiofrequency ablation (RFA) and microwave coagulation therapy, can also be expected to result in long survival periods; however, LAT is designed to treat less advanced HCC than hepatectomy [5]. Other treatment options include transarterial infusion (TAI) therapies, such as transarterial chemoembolization (TACE) and intraarterial chemotherapy, and the systemic administration of tyrosine kinase inhibitors (TKIs); however, the outcomes of these treatments are unsatisfactory. For instance, the survival period after TKI treatment ranges from 10 to 11 months for advHCC [6, 7].

Although there are various treatment options for HCC, there are few reports about reduction hepatectomy for unresectable advHCC followed by multidisciplinary postoperative therapy, and the utility of this treatment strategy should be evaluated. In the present study, we evaluated the efficacy of combination treatment involving reduction hepatectomy followed by multidisciplinary therapy, including TKI treatment, against unresectable advHCC.

# Methods

Patients

The clinical data for 30 patients who underwent reduction hepatectomy for advHCC between 2000 and 2018 at our department were retrospectively analyzed. Percutaneous transhepatic portal embolization was performed in 3 cases before hepatectomy, due to the calculated remnant liver volume being considered insufficient. In all 30 cases, residual tumor(s) were present in the remnant liver after hepatectomy, and 3 patients had extrahepatic metastases (in the lungs in 2 cases and in the bone in 1 case). The examined items were sex, age, prior or ongoing hepatitis B virus and/or hepatitis C virus infections; blood test data, including regarding alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II), total bilirubin (T-Bil), and albumin (Alb) levels, and the prothrombin time (PT); the indocyanine green retention rate at 15 minutes (ICGR15); liver damage; the number of tumors; tumor size; and pathological factors, including tumor differentiation, the presence/absence of vascular invasion, the presence/absence of extrahepatic metastasis, whether the hepatectomy was classified as an anatomical resection, the operation time, the amount of intraoperative blood loss, the number of tumors in the remnant liver, and in-hospital and 90-day mortality. The pre- and postoperative treatments employed after the reduction hepatectomy, the survival time, and whether the postoperative treatments resulted in postoperative complete remission (POCR) of the evaluable lesions were also examined. POCR was considered to have been achieved when no evaluable lesions were detected during the imaging study performed to evaluate the effects of treatment.

This research was approved by the institutional review board of Hokkaido University Hospital (approval number: 019–0115), and all analyses of the clinical data were carried out according to the ethical guidelines of Hokkaido University.

### Surgical indications

The preoperative investigations and hepatectomy were carried out according to the method described in our previous report [8]. All 30 patients were preoperatively evaluated using 3-phase dynamic contrast-enhanced computed tomography (CT). The preoperative whole-liver volume and tumor volume, the volume of the estimated remnant liver, and the effective resection ratio of the liver were calculated preoperatively using a 3D workstation. Liver function was evaluated through blood tests, the ICGR15, and Tc-GSA scintigraphy. HCC was assessed as unresectable when the predicted remnant liver volume after radical hepatectomy was considered to be insufficient, according to the Hokkaido University algorithm for hepatic resection.

### Evaluation of POCR

During the first 1 to 2 months after treatment, imaging studies were performed with contrast-enhanced CT or gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) to evaluate the effects of LAT or TAI treatment. All cases were divided into two groups, according to whether POCR was achieved at least once in the postoperative period. The cases in which POCR was achieved were included in the POCR(+) group, and those in which POCR was not achieved were included in the POCR(-) group.

### Statistical analyses

Some clinical data were converted to categorical variables. Pearson's chi-square test was used for the statistical analyses, except for variables with expected counts of $\leq 5$, for which Fisher's exact test was used instead. Overall survival (OS) was calculated using the Kaplan-Meier method and compared between the groups using the Wilcoxon test in the univariate analyses. Multivariate analysis of the variables that exhibited significance in the univariate analyses was carried out using the multivariate Cox proportional hazards model. Two-sided p-values of $< 0.05$ were considered significant. All analyses were performed with the software JMP (JMP Pro, version 14; SAS Institute Inc., Cary, NC).

## Results

### Clinicopathological characteristics

Table 1 summarizes the clinical data for the 30 cases. The in-hospital and 90-day mortality data were excluded from Table 1 because no deaths occurred in hospital or within 90 days. The subjects' mean age was 62.8 ± 11.8 years old (44–89 years old). The mean serum levels of AFP, PIVKA-II, T-Bil, and Alb were 10228.33 ± 7287.26 ng/mL (35–217390), 52534.8 ± 22566.31 (mAU/mL), 0.88 ± 0.08 mg/dL (0.4–1.9), and 3.71 ± 0.08 g/dL (2.9–4.6), respectively; the mean PT was 90.19 ± 2.75% (69.8–115.8), and the mean

ICGR15 was 17.34 ± 1.96% (2.6–43.8). The mean size of the largest tumor was 10.13 ± 1.02 cm (2.0–24.0). Anatomical hepatectomy was conducted in 27 cases, and non-anatomical hepatectomy (partial resection of the liver) was carried out in the remaining 3 cases. The median surgical time was 340 min (188–911), and the median amount of intraoperative blood loss was 690 mL (0–35820). The median follow-up time was 17.41 months (1.02–111.04).

Peri-surgical treatment

Table 2 summarizes the peri-surgical treatments, including both preoperative and postoperative treatments, employed in the 30 cases. Preoperative treatment was performed in 6 cases. Postoperative treatment was employed in 26 cases, and POCR was and was not achieved during the postoperative period in 8 cases (26.7%; POCR(+) group) and 22 cases (73.3%; POCR(-) group), respectively. POCR was achieved in the following cases: 1 of 1 cases that were treated with a second hepatectomy, partial lung resection, TAI therapy, and chemotherapy after the reduction hepatectomy; 1 of 1 cases that were treated with a second hepatectomy, TAI therapy, chemotherapy, and external beam radiotherapy (ERT) for palliative purposes after the reduction hepatectomy; 1 of 1 cases that were treated with partial lung resection, LAT, TAI therapy, chemotherapy, and ERT after the reduction hepatectomy; 2 of 2 cases that were treated with LAT and TAI therapy with/or without ERT after the reduction hepatectomy; 1 of 6 cases that were treated with TAI therapy and chemotherapy with/or without ERT after the reduction hepatectomy; and 2 of 9 cases that were treated with TAI therapy with/or without ERT after the reduction hepatectomy. All 6 patients that received postoperative TKI treatment were included in the POCR(-) group.

Prognostic factors for OS

Among all 30 cases, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 72.4%, 31.3%, and 15.7%, respectively, and the mean survival time (MST) after reduction hepatectomy was 28.40 months. In the POCR(+) group, the 1-year, 3-year, and 5-year OS rates were 100%, 75.0%, and 37.5%, respectively, and the MST was 56.55 months, whereas in the POCR(-) group the 1-year, 3-year, and 5-year OS rates were 61.9%, 12.6%, and 6.3%, respectively, and the MST was 14.84 months ($p = 0.0041$, Fig. 1). Univariate analyses revealed significant intergroup differences in tumor size ($p = 0.0485$), the frequency of vascular invasion ($p = 0.0053$), the number of tumors in the remnant liver ($p = 0.0283$), and the frequency of POCR ($p = 0.0041$) (Table 1). Multivariate analysis of these variables was performed. Vascular invasion was the only factor that displayed significance in the multivariate analysis (hazard ratio: 6.7254, 95% confidence interval: 0.2350–1.5855, $p = 0.0069$).

Comparison between the POCR(+) and POCR(-) groups

The clinical data for the POCR(+) and POCR(-) groups are shown in Table 3. Only the number of tumors in the remnant liver exhibited significant intergroup differences. The proportion of cases in which $\leq 3$ tumors were seen in the remnant liver was higher in the POCR(+) group than in the POCR(-) group ($p = 0.0025$).

The cases in the POCR(-) group were subdivided into two groups according to whether postoperative TKI treatment was administered. Cases involving TKI treatment were included in the POCR(-)TKI(+) group, and those that did not involve TKI treatment were included in the POCR(-)TKI(-) group. In the POCR(-)TKI(+) group, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 100%, 31.3%, and 0%, respectively, and the MST was 33.52 months, whereas in the POCR(-)TKI(-) group the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 46.7%, 6.7%, and 6.7%, and the MST was 10.74 months ($p = 0.0473$, Fig. 2).

# Discussion

In the present study, the survival rate of the POCR(+) group was better than that of the POCR(-) group ($p = 0.0041$), suggesting that achieving POCR after reduction hepatectomy could have an important impact on survival in patients with unresectable HCC. Moreover, even in the cases in which POCR was not achieved the administration of TKIs resulted in an improvement in survival outcomes; i.e., the survival rates of the POCR(-)TKI(+) group were better than those of the POCR(-)TKI(-) group ($p = 0.0473$). Thus, reduction hepatectomy could be effective against unresectable advHCC, especially when POCR is achieved via postoperative multidisciplinary therapy. Even in cases in which POCR is not achieved, the administration of TKIs should be considered in the postoperative period.

In ovarian carcinoma, the maximal resection of any primary or metastatic carcinoma followed by postoperative chemotherapy has become the standard treatment strategy [9]. However, there are only a limited number of reports about reduction hepatectomy for HCC [10–13]. In the latter studies, it was reported that the OS rate after reduction hepatectomy for HCC ranged from 52–67.7% at 1 year, from 20.0–40.6% at 3 years, and from 10–21.7% at 5 years [11–13]. As different patients were selected and different treatment options were employed in different eras, it is hard to simply compare OS rates, although the OS rates described in previous reports were similar to those obtained in the present study.

The potential prognostic factors identified in the univariate analyses in the current study were tumor size, vascular invasion, the number of tumors in the remnant liver, and whether POCR was achieved. Vascular invasion, which was diagnosed based on pathological examinations, was the only independent prognostic factor that exhibited significance in the multivariate analysis. However, pathological vascular invasion cannot be detected preoperatively. Thus, we decided to focus on POCR, which can be set as an aim of multidisciplinary therapy after reduction hepatectomy.

Achieving POCR using postoperative multidisciplinary treatment had an important impact on survival in the current cases. When the cases were limited to those in which POCR was achieved, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 100%, 75.0%, and 37.5%, respectively, and the MST was 56.55 months. This suggests that reduction hepatectomy followed by postoperative treatment that aims to achieve POCR could be an effective treatment strategy for advHCC.

The postoperative treatments employed after reduction surgery for HCC are different from those used to treat other malignancies. Firstly, the recovery of the remnant liver after hepatectomy enables further

treatment for tumors in the remnant liver, which is considered to affect prognosis in most cases of HCC [14]. In fact, tumors were detected in the remnant liver after reduction hepatectomy in all of the present cases, but extrahepatic metastases were only detected in 3 cases. Secondly, there are established additional non-surgical treatments for HCC localized in the liver, such as LAT and TAI therapy. RFA is indicated for cases of HCC involving ≤ 3 tumors and a maximum tumor size of ≤ 3 cm and is sometimes employed as an alternative to hepatectomy [5]. TACE is indicated for cases of unresectable HCC involving large or multifocal tumors without vascular invasion or extrahepatic metastases [5]. R0 resection is the first-choice treatment for some advanced malignancies, even in cases involving distant metastases. For distant metastases from HCC, there are not enough data supporting the validity of this approach, and the efficacy of surgical resection for lung metastases [15, 16], adrenal gland metastases [17], and brain metastases [18] is disputed.

In the present study, the number of tumors in the remnant liver after the reduction hepatectomy was the only factor that differed significantly between the POCR(+) and POCR(-) groups. This indicates that it is important that reduction hepatectomy is performed with the aim of reducing the number of tumors in the remnant liver to ≤ 3, which agrees with the conclusion of the study by Hai et al. [13].

In the current study, there were only 6 cases in which TKIs were orally administered. Two reasons are considered as possible explanations for the low frequency of TKI treatment. The first reason is the small number of cases included in the present study; i.e., only 30. Second, the treatment options for HCC changed during the study period. The most important change was the introduction of TKIs as a treatment option. Sorafenib, a TKI, was reported to improve the prognosis of HCC in 2008 [19], and it started to be used in the clinical setting in Japan in 2009. Moreover, lenvatinib, another TKI, was reported to be non-inferior to sorafenib in the REFLECT trial in 2018 [6].

In the present study, TKIs were only administered in the cases in which POCR was not achieved. This might have been due to the fact that TKIs were mainly administered when surgery, LAT, and TAI therapy were not indicated; i.e., TKIs were used when the abovementioned treatments were not expected to be effective, although concomitant TKI and TAI therapy has been suggested to be effective in some studies [20, 21]. The MST of the POCR(-)TKI(+) group was 33.52 months, which is superior to the outcomes described in other studies in which unresectable HCC was treated with TKIs [6, 19].

According to the present study, POCR might not need to be achieved via surgery alone, and even patients in whom POCR is achieved using LAT or TAI therapy can be good candidates for reduction surgery. Furthermore, the findings of the current study suggest that some patients would benefit from reduction hepatectomy even if POCR is not achieved. Patients that are likely to benefit from TKI treatment can also be good candidates for reduction hepatectomy.

This study had several limitations. The first is the inevitable selection bias caused by the study's retrospective and single-center design. One of the most important processes in reduction hepatectomy for advHCC is the selection of cases that would benefit from such treatment. Of course, the safety of surgery should be considered to be the most important factor from an ethical viewpoint. There were no surgery-

related deaths in the present study. At the same time, surgical safety also has an important impact on whether postoperative multidisciplinary treatment can be performed. Other limitations of this study include the small number of cases and the short follow-up periods in some of the cases.

# Conclusions

The 5-year OS rate and MST after reduction hepatectomy for unresectable advHCC were 15.7% and 28.40 months, respectively. Achieving POCR via multidisciplinary therapy after such reduction surgery is the key to success. To achieve POCR, reduction hepatectomy should be performed with the aim of reducing the number of tumors in the remnant liver to ≤ 3. Even in cases in which POCR is not achieved, TKI treatment might improve the prognosis of advHCC after reduction hepatectomy, and innovations in systemic therapy might provide further advantages.

# Abbreviations

advHCC: advanced hepatocellular carcinoma, AFP: alpha-fetoprotein, Alb: albumin, CT: computed tomography, EOB-MRI: gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging, ERT: external beam radiotherapy, HCC: hepatocellular carcinoma, ICGR15: indocyanine green retention rate at 15 minutes, LAT: local ablation therapy, MST: mean survival time, OS: overall survival, PIVKA-II: protein induced by vitamin K absence or antagonist-II, POCR: postoperative complete remission, PT: prothrombin time, RFA: radiofrequency ablation, TACE: transarterial chemoembolization, TAI: transarterial infusion, T-Bil: total bilirubin, TKI: tyrosine kinase inhibitor

# Declarations

### Ethical approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was not obtained from the enrolled patients because this study was a retrospective study and did not include any potentially identifiable patient data. This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 019-0115), and all analyses of the clinical data were performed according to the ethical guidelines of Hokkaido University.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used during this study are available from the corresponding author on reasonable request.

### Competing interests

All of the authors declare that they have no competing interests.

### Funding

None declared

### Authors' contributions

YA analyzed and interpreted the patient data, was involved in the data acquisition, made substantial contributions to the study conception and design, and was a major contributor during the writing of the manuscript. TK participated in drafting the article and critically revising it. TK, TO, SS, AN, YS, and HK revised the draft manuscript by adding intellectual insights and providing critical advice. AT provided critical comments to improve the manuscript and gave final approval for submission. All of the authors have read and approved the final manuscript.

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# Tables

Due to technical limitations, table 1, 2, 3 is only available as a download in the Supplemental Files section.

# Figures

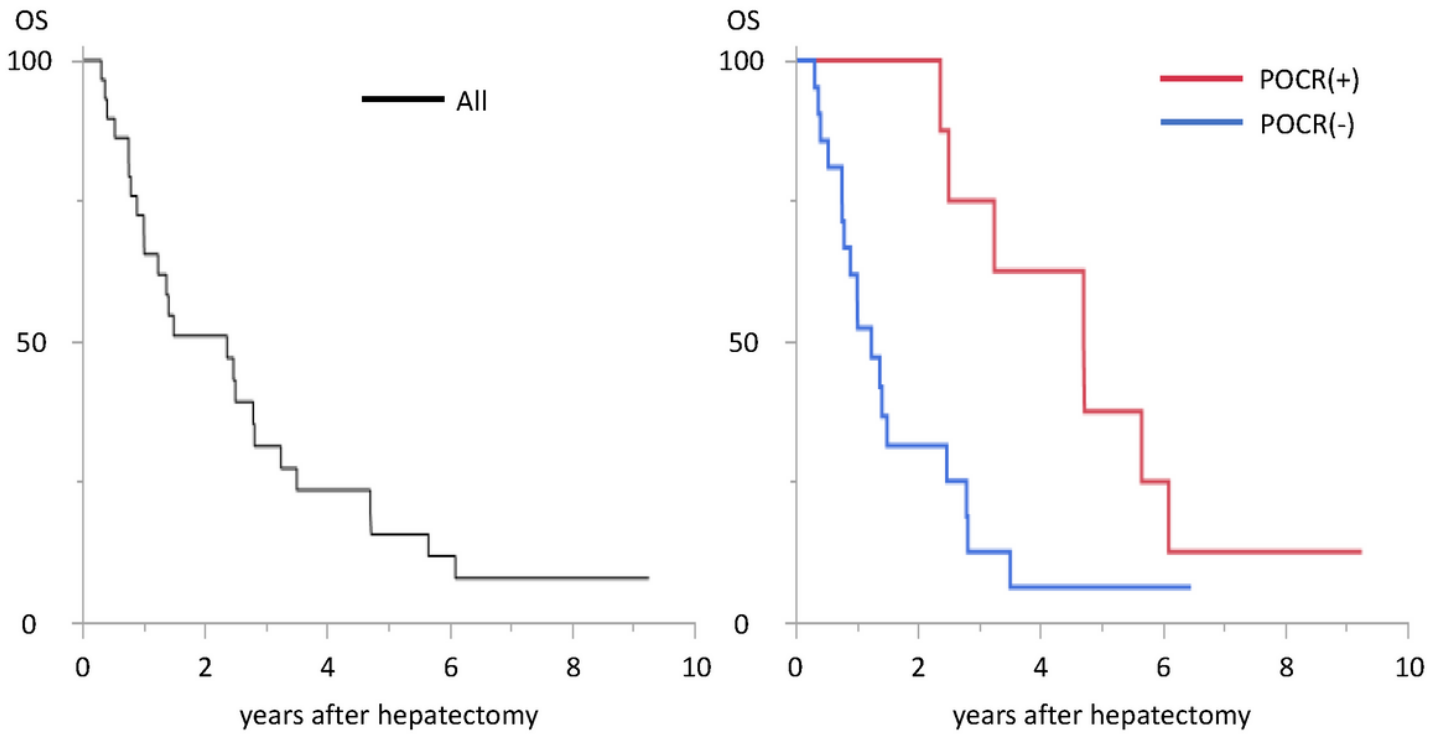


**Figure 1**

The survival curves obtained after reduction hepatectomy a: The survival curve for all 30 cases of unresectable advanced HCC after reduction hepatectomy b: The survival curves of the POCR(+) (red line) and POCR(-) (blue line) groups after reduction hepatectomy POCR: postoperative complete remission of evaluable lesions induced by multidisciplinary treatment after reduction hepatectomy

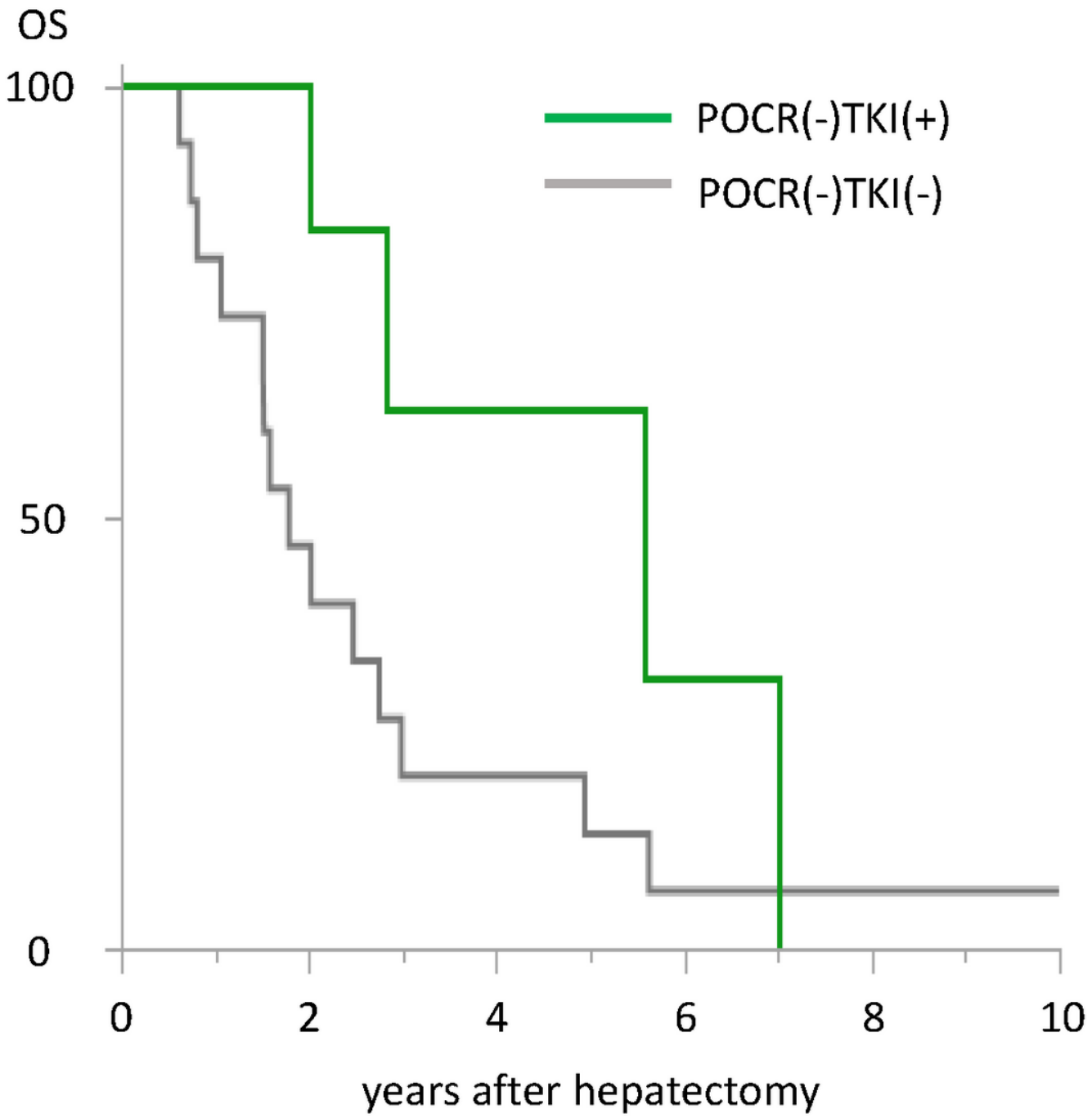


**Figure 2**

The survival curves of the POCR(-)TKI(+) and POCR(-)TKI(-) groups after reduction hepatectomy The cases in which POCR was not achieved despite TKI treatment being administered in the postoperative period were included in the POCR(-)TKI(+) group (green line). The cases in which POCR was not achieved and TKIs were not administered in the postoperative period were included in the POCR(-)TKI(-) group (gray line).

# Supplementary Files

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- Table1reductionhepatectomyWJSObest.xlsx
- Table2reductionhepatectomyWJSO.xlsx
- Table3reductionhepatectomyWJSO.xlsx