Complete title

A preoperative prognostic scoring system to predict prognosis for resectable pancreatic cancer: who will benefit from upfront surgery?

A short title Pre-ope prediction of R-PDAC

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Abstract

Background: Upfront surgery is recommended in patients with potentially resectable pancreatic ductal adenocarcinoma (R-PDAC) by National Comprehensive Center Network (NCCN) guidelines. However, even among R-PDACs, there is a subset that demonstrates extremely poor prognosis. The purpose of this study was to identify preoperative prognostic factors for upfront surgical resection of R-PDACs.

Methods: The records of 278 consecutive patients with PDAC who underwent curative resection between 2001 and 2015 in a single institution were retrospectively reviewed. Preoperative factors to predict prognosis in patients with R-PDAC according to the NCCN guidelines were analyzed.

Results: Of the 278 patients who underwent resection, 153 R-PDACs received upfront surgery with a median survival time (MST) of 26.4 months. Tumor location (pancreatic head) (odds ratio [OR] 1.97, 95% confidence interval [CI] 1.14–3.40; P = 0.015), preoperative cancer antigen 19-9 (CA19-9) >100 U/mL (OR 1.92, 1.31–2.80; P = 0.0009), and tumor size > 20 mm (OR 1.50, 1.02–2.19; P = 0.038), were identified as preoperative independent predictive risk factors for poor prognosis in patients with R-PDACs. In the patients with R-PDAC, 5-year survival was 60.7%, 21.5%, and 0% in patients with 0, 1 or 2, and 3 risk factors, respectively. There were significant differences in overall survival between the three groups (P < .0001).

Conclusions: A preoperative prognostic scoring system using preoperative tumor location, tumor size, and CA19-9 enables preoperative prediction of prognosis and facilitates selection of appropriate treatment for resectable pancreatic cancer.

key words

Resectable pancreatic cancer, preoperative prognostic scoring, upfront surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies[1, 2]. In 2017, it is estimated that there will be 53,670 new cases of pancreatic cancer in the USA, and PDAC is the fourth leading cause of cancer-related death[2]. Furthermore, in the USA, the number of patients with PDAC is expected to increase from 43,000 in 2010 to 88,000 by 2030, an increase projected to result in 63,000 deaths in 2030 compared to 36,888 in 2010[1].

National Comprehensive Center Network (NCCN) guidelines recommend upfront surgery for potentially resectable pancreatic cancer (R-PDAC), followed by postoperative adjuvant therapy, owing to the expectation of R0 resection and better prognosis[3]. However, in reality, upfront surgery for R-PDAC resulted in R0 resection in 81–88% of cases, postoperative recurrence was observed in 66–85% of cases, and the 5-year overall survival rate was 20.7–44.1%[4, 5]. These findings indicate that a subset of tumors with poor prognosis is included within R-PDACs. Several clinicopathological factors have been associated with prognosis following pancreatectomy for PDAC. These factors include the classical clinical factors such as tumor size, lymph node metastasis, surgical margin status, and tumor markers, as well as the recently recognized role played by the host systemic inflammatory response[6-8]. The combination of C-reactive protein (CRP) and albumin, known as the Glasgow Prognostic Score (GPS), has been evaluated preoperatively in patients undergoing potentially curative pancreatectomy for

PDAC[9-12].

The goal of the present study was to establish a prognostic prediction system in R-PDAC using preoperatively detectable factors.

Patients and Methods

Patients

Between August 2001 and July 2015, 278 consecutive patients with PDAC underwent curative resection in the Department of Gastroenterological Surgery II, Hokkaido University Hospital. According to NCCN guidelines[3], 164 tumors were categorized as resectable (R-PDACs), 74 were borderline resectable (BR-PDACs), and 40 were unresectable (UR-PDACs). Of the 164 patients with R-PDACs, 11 patients who received preoperative adjuvant therapy were excluded, and a total of 153 patients with R-PDACs who received upfront surgery were retrospectively analyzed. Preoperative workup was performed with multidetector computed tomography (MDCT) using a standard protocol optimized for pancreatic tumors. Patients were followed for a median of 72 months (range, 15.3–171) or until death. Postoperative follow-up investigations consisted of physical examination, laboratory studies, and CT imaging at 3- to 4-month intervals for the first 2 years, at 6-month intervals for years 3 through 5, and then at yearly intervals. In principle, preoperative laboratory tests were

measured within 14 days before surgery. For patients with biliary obstruction, CA19-9 was measured after biliary drainage with a total bilirubin under 3.0 mg/dl.

This study was conducted in accordance with the ethical standards of the Committee on Human Experimentation of our institution and was approved by the Institutional Review Board of Hokkaido University Hospital (No. 017-0363).

Surgery and adjuvant chemotherapy

Surgical resection with lymph node dissection was performed in all patients. Lymph node dissection around the celiac artery, common hepatic artery (CHA), superior mesenteric artery (SMA), superior mesenteric vein (SMV), and hepatoduodenal ligament was performed in patients who underwent pancreaticoduodenectomy. In patients who underwent distal pancreatectomy, lymph node dissection around the celiac artery, CHA, SMA, and SMV was performed. When the primary tumor was adherent to the portal vein (PV)/SMV, venous resection and reconstruction were performed at the surgeon's discretion. When a primary tumor located in the pancreatic body was adherent to the root of the splenic artery (generally within 10 mm), concomitant resection of the celiac artery and CHA were performed[13, 14]. Adjuvant therapy was initiated within 2 months after the operation unless contraindicated by the patient's condition or rejection. Most commonly, gemcitabine or S-1 (oral fluoropyrimidine agent

containing tegafur, gimeracil, and oteracil potassium) was administered[5].

Statistical analysis

Cumulative overall survival was estimated with the Kaplan-Meier method, and a comparison of the survival curves was performed using the log-rank test. Factors significant on univariate analysis were entered into the multivariate Cox proportional hazards model, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated. To define the cut-off value of continuous variables, age and body mass index (BMI) were used median. To define the cut-off value of tumor diameter, we evaluated tumor diameter 20mm, 25mm, 30 mm, and 35mm, as a result, 20mm was most clearly influenced the prognosis of R-PDACs. The cut-off value of CA19-9 was also decided by evaluated 100, 150, 200 and 300, as a result, 100 was most clearly influenced the prognosis of R-PDACs. All survival analyses were calculated from the time of surgery to death from any cause. The significance level was set at $P < 0.05$. Statistical analysis was performed using JMP 10.0 (SAS Institute, Inc., Cary, NC, USA) software for Windows.

Results

Clinical and pathological characteristics of patients

The clinical and pathological characteristics of the 153 patients with R-PDAC are shown in Table 1. There were 92 men (60%) and 61 women (40%), with a median age of 69.0 years (range 43–85). Concomitant portal and/or SMV resection was necessary in 55 (36%) patients, and the artery was concomitantly resected in 22 (14%) patients (celiac artery resection) to maintain the residual margin of the splenic artery during the distal pancreatectomy. The pathological stage was determined according to the 7th Tumor-Node-Metastasis (TNM) classification of the Union for International Cancer Control (UICC) [15]. Among the patients, 142 (92.8%) were categorized as having pT3 tumors, and 96 patients (62.7%) had regional lymph node metastases; therefore 143 patients (93.5%) had Stage II disease. Lymph node metastasis in the paraaortic area that proved to be an M1 lesion was diagnosed as stage IV disease in one patient. R0 resection was achieved in 138 (90.2%) patients. Of the 153 patients, 91 (60%) patients received adjuvant chemotherapy, and the remaining 62 (40%) did not.

Independent preoperative prognostic factors of R-PDAC

To identify the preoperative prognostic factors for postoperative overall survival (OS) in R-PDAC, the clinical factors that can be evaluated preoperatively are shown in Table 2. Univariate analysis revealed that the significant prognostic factors for OS of R-PDAC were sex (male), biliary drainage, tumor location (pancreatic head; ph), tumor size, PV/SMV invasion,

and CA19-9. After multivariate analysis, 3 parameters, including tumor location (ph) (P = 0.028), tumor size (P = 0.012), and CA19-9 (P = 0.002), were identified as the independent prognostic factors for OS. The mGPS showed the possibility of prognostic factors in both univariate (P = 0.057) and multivariate analysis (P = 0.071), but it did not reach statistical significance.

Overall survival curves were assessed using 3 independent prognostic factors (Figure 1). The median survival time for patients in the ph group was 20.5 months, while it was 46.7 months for those in the pancreatic body/tail (pbt) group (P = 0.0001). The median survival time for patients in the group with tumor size > 20 mm was 20.6 months, and it was 46.5 months for those in the group with tumor size ≤ 20 mm (P = 0.0003). For patients in the CA19-9 >100 U/mL group, the median survival time was 17.8 months, while it was 34.1 months for those in the CA19-9 ≤ 100 U/mL group (P = 0.0001).

Preoperative prognostic scoring system

The tumor location, tumor size, and preoperative CA19-9 levels, which could be easily evaluating prior to pancreatectomy, were selected as the independent prognostic factors to establish the preoperative prognostic scoring system. The criteria of the Preoperative Prognostic Score (PPS) are shown in Table 3. Adverse prognostic factors were tumor location in pancreatic

head, clinical tumor size > 20 mm, and preoperative CA19-9 levels > 100 U/mL, and these were allocated 1 point each. Tumor location in pancreatic body/tail, clinical tumor size ≤ 20 mm, and preoperative CA19-9 levels < 100 U/mL were allocated 0 points each. The total score was defined as the PPS, with scores ranging from PPS0 to PPS3.

The PPS scores were distributed as follows: PPS0, 19 patients; PPS1, 42 patients; PPS2, 61 patients; and PPS3, 31 patients. Because the survival rates of patients with scores of PPS1 and PPS2 were not statistically different (P = 0.35, Supplemental figure 1), PPS1 and PPS2 were combined during calculation of survival rates. The prognoses for PPS0, PPS1/2, and PPS3 were estimated with overall survival rates using the Kaplan–Meier method (Figure 2). The estimated overall 1-, 3-, and 5-year survival rates for the 19 patients with PPS0 were 94.7%, 94.7%, and 65.1%, respectively, while for the 103 patients with PPS1/2, they were 84.5%, 35.2%, and 22.7%, respectively. The median survival times for PPS0 and PPS1/2 were not reached and 26.0 months, respectively. In contrast, the prognosis was worse in the 31 patients with PPS3, with overall 1-, 3-, and 5-year survival rates of 61.3%, 9.7%, and 3.2%, respectively. The median survival time was 13.3 months. Patients with PPS3 had a significantly worse survival than patients with PPS0 or PPS1/2 (log-rank, P < .0001 and P < .0001, respectively) (Table 4). Recurrence occurred in 90.3% (28/31) of the patients in the PPS 3 group. The primary recurrence sites of them were liver (19/28: 67.9%), peritoneum (8/28: 28.6%), local

(3/28: 10.7%), lung (3/28: 10.7%), and lymph node (5/28: 17.9%) with overlaps. The median period to having recurrences after surgery were 5.6 month (1.4-34.7) in the liver, 5.4 month (3.5-34.7) in the peritoneum, 6.2 month (5.3-8.1) in the lung, and 7.6 month (3.3-14.7) in lymph node. These data suggest that the patients in the PPS3 group suffered systemic disease at the time of surgery.

Discussion

The rate of PPS scores of PPS3 in our study population was 20.3% among patients with R-PDAC, and the median survival time was 13.3 months, representing a worse prognosis than that of patients with locally advanced unresectable (UR-LA) PDAC[16, 17]. This result indicates a limitation of the treatment strategy according to the NCCN guidelines, because it includes a subset of patients with poor prognosis who derive no benefit from surgery even if diagnosed with R-PDAC. “Resctable” according to traditional imaging studies means surgically resectable but does not guarantee a survival benefit from surgery. The modern regimens such as Gemcitabine plus nab-PTX or FOLFIRINOX used in patients with high risk factors PPS1/2 might prolong the survival time. However, enforcing such powerful regimens could be used only for patients with fair systemic condition. The prognosis of patients in the PPS 3 group is almost comparable to that of patients with borderline resectable (BR) or some with unresectable

(UR) pancreatic cancer. As the status of tumor progression is resectable in imaging study even in the PPS 3 group, the main cause of poor prognosis might be potential metastasis. Therefore, for the patients in the PPS 3 group, we recommend systemic chemotherapy first according to the strategy for BR or locally advanced UR patients. Some reports indicated that prognosis of patients having BR PC who received preoperative treatment could be improved[18, 19]. On the other hand, there is a subset of patients with good prognosis, such as the PPS0 group (5-year survival, 65.1%). Recently, several clinical trials of neoadjuvant therapy have been conducted in R-PDAC to achieve better survival compared with an upfront surgical approach[20, 21]. In construction of a randomized controlled trial for R-PDAC in a neoadjuvant setting, a bias in the direction of the subsets with either poor or good prognosis could lead to misdirection in the results.

There have been several studies to identify factors to predict postoperative early recurrence of PDAC[9, 22, 23]. Matsumoto and colleagues reported a simple scoring system using three preoperative predictive risk factors including mGPS = 2, CA19-9 ≥ 300 U/mL, and tumor size ≥ 30 mm that predicts early recurrence from analysis of R-PDAC and BR-PDAC[9]. Of the three factors, tumor size and CA19-9 were also identified in the present study, but m-GPS was not. A value of mGPS = 2 showed possibility as a prognostic factor in both univariate (P = 0.057) and multivariate analysis (P = 0.071), but it did not achieve statistical significance in our

study. Because the proportion of patients with m-GPS = 2 in our study was 2.6% (4 out of 153), the statistical power may be low. Our study was limited to R-PDAC only; therefore, the m-GPS score was relatively preserved (91.5%, score 0). We felt that these differences regarding independent factors might be caused by the analysis set (including BR-PDAC or limited to R-PDAC) and outcome setting (early recurrence or prognosis).

In the present study, cancer in the pancreatic body/tail was associated with better prognosis than cancer in the pancreatic head, and tumor location was an independent prognostic factor. It is frequently mentioned that pancreatic body/tail cancer is diagnosed at an advanced stage, which leads to worse prognosis. However, there is a lack of data regarding stage at diagnosis and survival of pancreatic body/tail cancer compared to those of pancreatic head cancer. Moreover, there are increasing reports that pancreatic body/tail cancer may have good prognosis. Lau et al. reported that the incidence of pancreatic head cancer had remained stable, whereas the incidence of pancreatic body/tail cancers has been rising in the last 3 decades, and the authors also showed that the 3-year survival rate for local-stage pancreatic body/tail cancer is 20.0% compared with 9% for local-stage pancreatic head cancer[24]. In our study, the artery was concomitantly resected in 22 (14%) patients (celiac artery resection) to maintain the residual margin of the splenic artery during the distal pancreatectomy. When a primary tumor located in the pancreatic body was adherent to the root of the splenic artery (generally within 10

mm), we routinely performed distal pancreatectomy with en bloc celiac axis resection (DP-CAR). DP-CAR was developed for locally advanced pancreatic body cancer, and was resulted in the high R0 rate[13, 14]. Therefore one of the reasons for good prognosis in the pancreatic body-tail tumor in this study might be achieved by local control in DP-CAR. On the other hand, when the tumor is located at the pancreatic head, it becomes adaptation of pancreaticoduodenectomy (PD). Since PD has higher hospitalization days and complication rates than distal pancreatectomy (DP), it seems that the tumor location has become a prognostic factor because adjuvant chemotherapy is difficult to introduce in PD cases. However, in our study, there was no difference between PD and DP in performed adjuvant therapy (PD: 58/103(56%), DP: 33/50 (66%), P=0.25, data not shown in the results). Hence, the tumor location could not be influenced by the rate of adjuvant therapy, but might have other oncological behavior for the patient prognosis. Recently, Ling et al. showed that overall and disease-free survival were significantly higher in patients with pancreatic body/tail cancer compared to those with pancreatic head cancer at Stage II. The researchers found lower expression of miR-501-3p and higher expression of miR-375 in pancreatic body/tail cancer tissues compared with pancreatic head cancer tissues. The pancreatic body/tail cancer demonstrated a less malignant phenotype associated with deregulation of miR-501-3p compared with pancreatic head cancer[25]. Further oncological research will elucidate the differences in

malignant phenotype related to the tumor location.

This study was based on data from 153 resected pancreatic cancer patients over the course of 15 years. Indeed, it is one of the limitations of this study that the data was collected for the long period from the single institution. However, the surgical procedure had not changed in the period. The other limitation is heterogeneity of adjuvant therapy. Of course, the multi-institutional study including much more patients during shorter collection period should be done so as to make the results more definite.

Conclusion

Based on the results of the present study, three factors, tumor location in the pancreatic head, tumor size (> 20 mm), and CA19-9 (> 100 U/mL) can be used to distinguish a subset with poor prognosis in R-PDAC. Future clinical trials of neoadjuvant therapy targeting the subset of R-PDAC with poor prognosis should be performed.

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Figure Legends

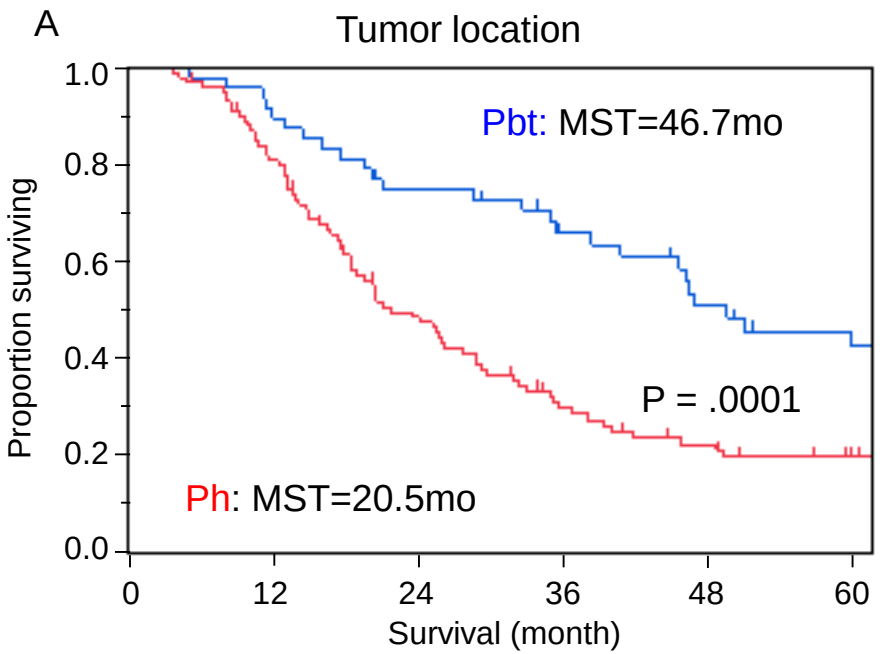
Figure 1

Overall survival in 153 patients with pancreatic cancer was statistically analyzed on the basis of (A) Tumor location, (B) Clinical tumor size, and (C) Preoperative CA19-9. MST = median survival time.

Figure 2

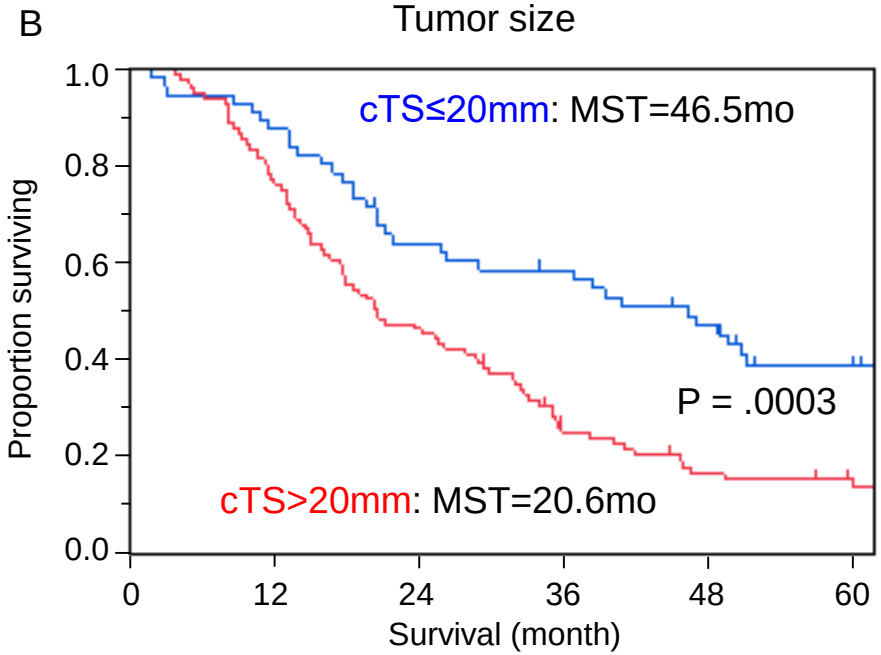
Estimated overall survival curves for patients with resectable pancreatic cancer according to preoperative prognostic scoring system. Because patients in PPS1 and PPS2 groups were not statistically different in prognosis, PPS1 and PPS2 were combined. There were significant differences in overall survival between PPS0, PPS1/2, and PPS3 groups ($P < .0001$, log rank test). PPS = preoperative prognostic score.

Figure 1



No. at risk

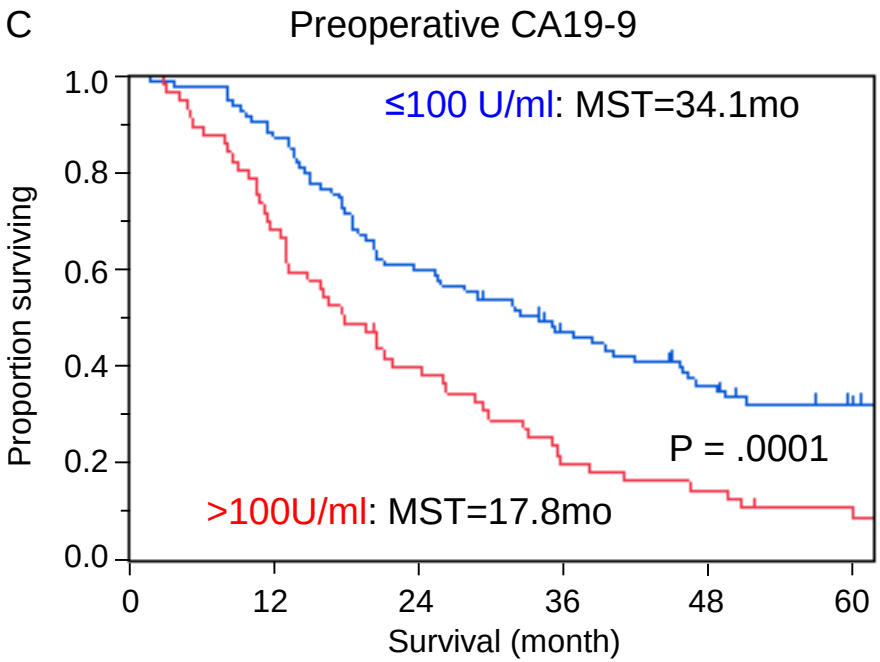
Pbt	50	44	35	27	20	16
Ph	103	80	45	25	17	11



No. at risk

≤20	56	49	35	31	24	17
>20	97	75	45	21	13	10

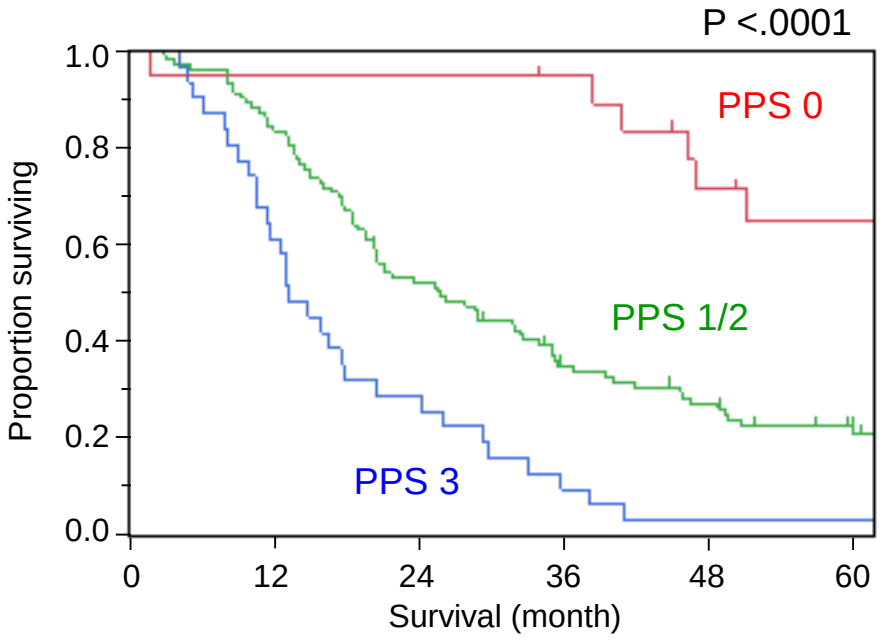
Figure 1 (continue)



No. at risk

≤100	96	86	59	41	29	23
>100	57	39	22	11	8	5

Figure 2



No. at risk

PPS 0	19	18	18	17	12	10
PPS 1/2	103	87	53	32	24	16
PPS 3	31	19	9	3	1	1