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ORIGINAL ARTICLE

Prognostic factors in conversion surgery following nab-paclitaxel with gemcitabine and subsequent chemoradiotherapy for unresectable locally advanced pancreatic cancer: Results of a dual-center study

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Abstract

Background: In pancreatic ductal adenocarcinoma (PDAC), only radical surgery improves long-term survival. We focused on surgical outcome after induction gemcitabine along with nab-paclitaxel (GnP) and subsequent chemoradiotherapy (CRT) with S-1 administration for unresectable locally advanced (UR-LA) PDAC.

Methods: We retrospectively analyzed 144 patients with UR-LA PDAC between 2014 and 2020. The first-line regimen of induction chemotherapy was GnP for 125 of the 144 patients. Of the 125 patients who received GnP, 41 who underwent radical resection after additional preoperative CRT were enrolled. We evaluated the prognostic factors for this treatment strategy.

Results: The median length of preoperative GnP was 8.8 months, and 30 (73%) patients had normalized CA19-9 levels. R0 resection was achieved in 36 (88%) patients. Postoperative major complications of ≥Clavien–Dindo grade IIIa developed in 16 (39%) patients. With a median follow-up of 35.2 months, 14 (34%) patients developed distant metastasis postoperatively. Using the Kaplan–Meier method, prognostic analysis of the 41 cases revealed the 3-y overall survival rate (OS) was 77.4% and the 5-y OS was 58.6%. In univariate analysis, length of preoperative GnP (≥8 months), CA19-9 normalization, and good nutritional status at operation (prognostic nutritional index ≥41.7) were significantly associated with favorable prognosis. Multivariate analysis revealed CA19-9 normalization (hazard ratio [HR] 0.23; $P = .032$) and prognostic nutritional index ≥41.7 (HR 0.05; $P = .021$) were independent prognostic factors.

Conclusion: For surgical outcome after induction GnP and subsequent CRT for UR-LA PDAC, CA19-9 normalization and maintenance of good nutritional status during treatment until surgery were important for prolonged prognosis.

Takamichi Igarashi and Suguru Yamada Contributed equally to this research.

KEYWORDS
chemoradiotherapy, chemotherapy, pancreatic cancer, prognostic factor, unresectable locally advanced

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death, with an estimated 5-y survival rate of ~9%.[1] Unfortunately, only a small percentage of PDAC patients (~20%) present with a resectable tumor at diagnosis, while ~80% of patients were classified as having unresectable (UR) disease. Of these, 30%–50% are UR locally advanced (UR-LA) diseases that invade adjacent major blood vessels without distant metastases.[2] With the approval of novel chemotherapeutic regimens such as FOLFIRINOX (FFX) and gemcitabine along with nab-paclitaxel (GnP), the number of surgeries performed after downstaging for unresectable PDAC is increasing.[3–5] In addition, preoperative chemoradiation therapy (CRT) is increasingly utilized for locoregional control of inoperable tumors and to potentially decrease the likelihood of positive margins (R1/R2) in those patients undergoing resection.[6,7]

These data were used to advocate for combining induction chemotherapy and CRT, a well-known and promising option for enabling radical surgery after downstaging of locally advanced rectal cancer.[8] This novel therapeutic strategy has recently begun to be introduced to locally advanced PDAC.[9] However, little information is available on surgical outcomes or prognostic factors following this approach for UR-LA PDAC, and compelling evidence, such as prognostic implications or concrete indications for resection, is lacking. A unique feature of the present study is that it evaluated the results of a single regimen, induction GnP and subsequent CRT, whereas many previous reports have analyzed a mixed cohort of chemotherapy alone and CRT cases.[10–13] Most surgeries for UR-LA disease after long-term induction therapy are highly invasive and technically demanding with combined multiple vascular resection; therefore, it is necessary to identify factors that contribute to long-term prognosis in this therapeutic strategy.

In the present study we focused on surgical outcome in the use of a single regimen (induction GnP and subsequent CRT with S-1 administration) for UR-LA PDAC. This report is the first to examine prognostic factors to identify more effective surgical indications and perioperative management.

2 | METHODS

2.1 | Study design and patients

After approval from the Institutional Review Boards, a prospectively maintained pancreatic resection database at two regional centers, Toyama University Hospital (Toyama, Japan) and Nagoya University Hospital (Nagoya, Japan), was queried to identify 144 UR-LA patients who started initial treatment between January 2014 and June 2020. The eligibility criteria for inclusion in the current study were as follows: (a) histologically or cytologically confirmed PDAC; (b) initial tumor considered potentially UR-LA PDAC according to the National Comprehensive Cancer Network Guidelines (Version 1.2022)[14]; and (c) no detectable distant metastases or distant nodal disease. Patient eligibility was rigorously defined using thin-slice multidetector row computed tomography, and borderline resectable PDAC was strictly excluded. All images were reviewed by two experienced radiologists to reaffirm the preoperative staging. Among the 144 UR-LA patients, the first-line regimen of induction chemotherapy was GnP in 125 patients, modified FFX in eight patients, and other regimens in 11 patients. Of the 125 patients who received GnP, 41 who underwent radical resection after additional preoperative CRT were enrolled in this study.

After staging laparoscopy (SL), at least three courses of GnP therapy were administered to the relevant patients, and imaging evaluations were performed every 3 months. Tumor marker measurements were performed monthly. Patients with shrinking or unchanged tumors and decreased marker levels were treated with preoperative CRT, and surgery was performed 3–6 weeks later. CRT consisted of a photon/proton external beam with 50.4 Gy delivered in 28 fractions combined with systemic chemotherapy involving oral S-1, which was administered twice daily (80 mg/m^2/d) from d 1 to 14 and from d 22 to 35.[15] Our treatment strategies for UR-LA PDAC are shown in Figure 1.

In preoperative CRT, a multileaf collimator is used to form the irradiation field. In principle, the beam center axis or isocenter should be located at or near the center of the target volume.

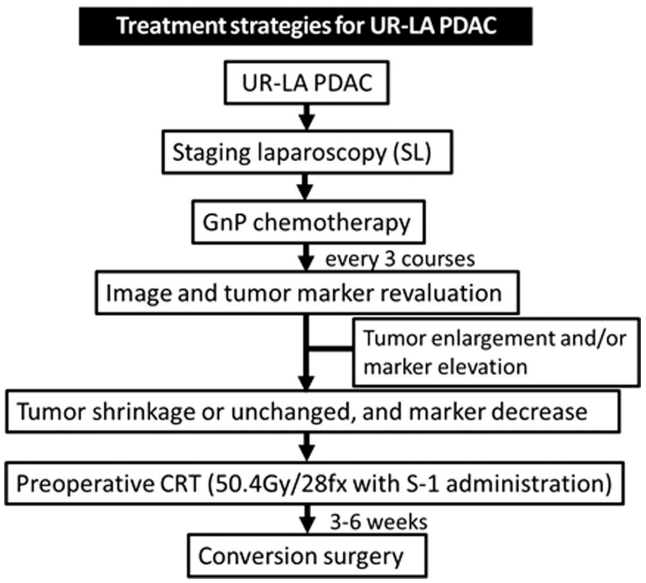

FIGURE 1 Schema of our treatment strategies for UR-LA PDAC

Three-dimensional conformal radiation therapy with three or more irradiators is used. The target volume was determined as follows: (a) Gross tumor volume (GTV): the primary tumor and enlarged lymph nodes that can be confirmed by imaging. Lymph nodes are considered targets if they are >1 cm in short diameter or positron emission tomography positive. (b) Clinical target volume (CTV): omit prophylactic lymph node areas and set up GTV with a 5-mm margin and consideration of microinvasion. (c) Planning target volume (PTV): CTV with a 5–15 mm margin to account for setup margin and organ movement.

The indication criteria for conversion surgery in our institutions are: (a) Tumor size shrinkage or unchanged; (b) No appearance of new metastatic sites; (c) Performance status maintained at 0-1; (d) Decrease in tumor marker values; and (e) Technically resectable, ie, "the SMA and tumor can be detached," "hepatic artery (CHA and PHA) invasion is suggested and requiring simultaneous resection, but reconstruction is possible," or "portal vein concomitant resection is required, but reconstruction is possible." Conversion surgery is considered when all of these criteria (a–e) are met. For the Lewis blood-group antigen-negative patients, other tumor marker values (DUPAN-2 and SPan-1) are consulted. If all markers are negative, and the indication for surgical resection is determined by (a–c) and (e).

2.2 | Surgical treatment

Based on tumor location, pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy with systematic lymphadenectomy was performed with curative intent after confirming the absence of peritoneal dissemination and distant metastases. En bloc resection of vascular structures was performed with or without formal revascularization dictated by anatomical necessity. Reconstruction of portal vein (PV), superior mesenteric vein (SMV), or PV/SMV confluence included patch venoplasty, end-to-end primary anastomoses, or interposition grafts via the left renal vein or internal jugular vein or superficial femoral vein grafts.[16] En bloc arterial resections included hepatic artery, celiac artery (CA), superior mesenteric artery (SMA), or multiple arterial resections. Arterial revascularizations included end-to-end primary anastomoses or interposition grafts via autologous grafts, such as the middle colic artery or second jejunal artery. At both institutions, all operations were performed by an experienced surgical team.

Postoperative adjuvant chemotherapy was applied unless contraindicated by the patient's condition. In short, the patients received gemcitabine or S-1 for 6 months according to the protocol that was available at the time of treatment.[17,18] Gemcitabine at a dose of 1000 mg/m^2 was administered weekly for 3 wk followed by 1 wk of rest; oral S-1 (80 mg/m^2/d) was administered from d 1 to 28 followed by a 2-wk rest period. Chemotherapy was initiated at <2 months after the operation in all patients who were considered eligible for the treatment. Computed tomography was routinely performed every 6 months as a postoperative follow-up imaging examination, and a blood test including the tumor marker was performed every 2 months to evaluate recurrent disease.

2.3 | Data collection

We collected patient data from the medical records. Pretreatment factors included age, sex, body mass index, tumor size, and blood test results, including serum carbohydrate antigen 19-9 (CA19-9) levels. Preoperative factors included length of preoperative treatment and change in the CA19-9 level. Perioperative factors included surgical procedures, operative time, blood loss volume, blood transfusion, vascular resection, positive lymph node metastases, R0 margin status, Evans grade, incidence of postoperative complications according to the Clavien–Dindo classification,[19] length of hospital stay, readmission, and 90-d mortality.

The tumor-node-metastasis staging system for pancreatic tumors of the seventh edition of the Union for International Cancer Control (UICC) was applied.[20] The pathological data collected included tumor grade, number of positive lymph nodes, resection margins, perineural invasion, PV invasion, and artery invasion. The surgical margin in this study denoted either the stump of the pancreas or the bile duct or the dissected plane around the pancreas as described by Staley et al.[21] If viable cancer cells were detected microscopically at the tip of any of these sites, the surgical margin was noted as positive. If the tumor was located at a distance of > 1 mm from the surgical margin, the margin was noted as negative.

2.4 | Tumor markers (CA19-9, CEA, DUPAN-2, SPan-1) evaluation

Some reports suggested the use of serum CA19-9 as a potential marker in early detection, as it is expressed in 70%–90% of PDACs.[22,23] In addition, some reports indicated that CEA before preoperative CRT is a prognostic indicator of localized PDAC.[24] We examined CA19-9, CEA, DUPAN-2, and SPan-1 at the time of diagnosis and operation, and the presence of these normalization. Especially for CA19-9, the rate of decrease was also examined. Eight patients with normal serum CA19-9 levels at diagnosis were excluded from the analyses related to changes in CA19-9 because such individuals were considered to be possible nonsecretors of CA19-9 due to a lack of the Lewis blood-group antigen (Lewis a-b-).

2.5 | Nutritional status

In the current study we investigated several nutritional parameters at diagnosis and at operation to verify their impact on the operative outcome and prognosis: Glasgow prognostic score (GPS),[25] modified GPS (mGPS),[25] controlling nutritional status (CONUT),[26] prognostic nutritional index (PNI),[25,27] neutrophil/lymphocyte ratio (NLR),[25,28] and platelet/lymphocyte ratio (PLR).[25,28]

2.6 | Statistical analysis

A biostatistician (K.M.) was responsible for the statistical analysis. The Kaplan–Meier method was used to calculate survival rates, and the difference in survival curves was analyzed by the log-rank test. Overall survival was defined as the time from the start of the initial treatment to the patient's death, and disease-free survival was defined as the date of surgery to the day of confirmed recurrence. To detect prognostic factors for survival, we performed Cox proportional hazard analysis, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The optimal cutoff value was determined using the web application Cut-off Finder.[29] Differences in nominal data between the two groups were examined using the chi-square test or Fisher's exact test when the expected value was <5. Differences in quantitative variables were evaluated using Student's *t* test or the Mann–Whitney *U* test if the distribution was abnormal. A *P* value < .05 was considered statistically significant. All statistical analyses were performed using JMP statistical software (v. 16.0; SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Characteristics of UR-LA patients who underwent resection

The detailed cohort demographics of the 41 enrolled patients are summarized in Table 1. The median age was 66 years, and the male:female ratio was 23:18. Preoperative image examination revealed that any venous involvement was present in 68%, any arterial involvement in 95%, and both venous and arterial involvement in 63%. At diagnosis, the median baseline CA19-9 level was 188 U/mL; CEA was 3.0 ng/mL, DUPAN-2 was 71 U/mL, and SPan-1 was 36 U/mL. The median length of therapy was 8.8 months, and 33 (80%) patients received ≥6 months of therapy. Following preoperative therapy, at operation 30 (73%) patients showed normal CA19-9 levels. The median CA19-9 was 19.0 U/mL, and 16 (39%) patients had a ≥90% decrease in CA19-9 levels compared with that before therapy. The median CEA at operation was 3.0 U/mL, DUPAN-2 was 25 U/mL, and SPan-1 was 13 U/mL. Preoperative treatment normalized CA19-9 in 22 patients (54%), 18 of whom normalized during GnP and four during CRT; for CEA, it normalized in five patients (12%), DUPAN-2 in nine patients (22%), and SPan-1 in seven patients (17%). The median decrease in tumor size was 34%. Nutritional parameters were generally impaired after induction therapy, and their median values were as follows: CONUT: 2, GPS: 0, mGPS: 0, NLR: 2.0, PLR: 144, and PNI: 44.

After preoperative therapy, 31 (76%) patients underwent pancreatoduodenectomy, nine (22%) underwent distal pancreatectomy, and one (2%) underwent total pancreatectomy. En bloc vascular resection was required in 27 (66%) patients, with any venous resection in 22 (54%), any arterial resection in 13 (32%), and combined venous/

TABLE 1 Baseline characteristics of 41 enrolled patients who underwent resection after induction chemotherapy and subsequent chemoradiotherapy

Variable	n = 41
Sex (male/female)	23/18
Age, y[a]	66 (42–79)
Body mass index[a]	21.5 (16–27)
Tumor location	
Head/uncinate	30 (73%)
Body/tail	11 (27%)
Vascular involvement	
Any venous	28 (68%)
Any arterial	39 (95%)
Both venous and arterial	26 (63%)
Tumor size at diagnosis, mm[a]	30 (13–65)
CA19-9 at diagnosis, U/mL[a]	188 (1–16 910)
Normal	8 (20%)
Elevated	33 (80%)
≥500	9 (22%)
CEA at diagnosis, ng/mL[a]	3.0 (0.9–44.9)
DUPAN-2 at diagnosis, U/mL[a]	71 (25–1600)
SPan-1 at diagnosis, U/mL[a]	36 (4–190)
Nutrition at diagnosis	
CONUT[a]	2 (0–6)
GPS[a]	0 (0–2)
mGPS[a]	0 (0–2)
NLR[a]	2.6 (0.5–6)
PLR[a]	178 (63–500)
PNI[a]	47 (35–65)
Length of preoperative therapy, mo[a]	8.8 (2.7–34.2)
≥6 mo	33 (80%)
Tumor size at operation, mm[a]	20 (8–43)
Tumor size decrease rate, %[a]	34 (23–80)
CA19-9 at operation, U/mL[a]	19 (1–362)
Normal	30 (73%)
Elevated	11 (27%)
CA19-9 normalized	22 (54%)
Under GnP	18
Under CRT	4
CA19-9 decrease, %[a]	85 (88–100)
≥90	16 (39%)
CEA at operation, ng/mL[a]	3.0 (1.0–28.9)
DUPAN-2 at operation, U/mL[a]	25 (25–270)
SPan-1 at operation, U/mL[a]	13 (3–170)
CEA normalized	5 (12%)
DUPAN-2 normalized	9 (22%)
SPan-1 normalized	7 (17%)
Nutrition at operation	

TABLE 1 (Continued)

Variable	n = 41
CONUT[a]	2 (0–6)
GPS[a]	0 (0–2)
mGPS[a]	0 (0–2)
NLR[a]	2.0 (0.9–8.1)
PLR[a]	144 (79–374)
PNI[a]	44 (35–52)
Surgical procedure	
Pancreatoduodenectomy	31 (76%)
Distal pancreatectomy	9 (22%)
Total pancreatectomy	1 (2%)
Operative time, min[a]	632 (274–1212)
≥10 h	22 (54%)
Blood loss volume, mL[a]	955 (146–8480)
≥1,000	18 (44%)
Operative PRBC transfusion	14 (34%)
Vascular resection	
Any venous resection	22 (54%)
Any arterial resection	13 (32%)
Celiac axis	8
Hepatic artery	4
Superior mesenteric artery	1
Both venous and arterial	7 (17%)
Positive lymph nodes	5 (12%)
R0 margin status	36 (88%)
Evans grade	
I	1 (2%)
IIa	12 (29%)
IIb	15 (37%)
III	7 (17%)
IV	6 (15%)
Complications	30 (73%)
Major (≥Grade IIIa)	16 (39%)
DGE (B/C)	2 (5%)
POPF (B/C)	6 (15%)
PPH (B/C)	2 (5%)
Length of stay, d[a]	27 (12–121)
Readmission	2 (5%)
90-d operative mortality	0 (0%)
Adjuvant chemotherapy	30 (73%)
Recurrent disease[b]	19 (46%)
Liver	4
Lung	3
Peritoneum	3
Para-aortic lymph node	2
Other distant	2
Local	6
Vital status at last follow-up	
Alive, no evidence of recurrence	21 (51%)
Alive, with recurrence	9 (22%)
Deceased	11 (27%)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CONUT, controlling nutritional status; CRT, chemoradiation therapy; DGE, delayed gastric emptying; GnP, gemcitabine along with nab-paclitaxel; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage; PRBC, packed red blood cells.

[a]Values are medians (ranges).

[b]Some patients had multiple metastases.

arterial resections in seven (17%). Combined resection of the celiac axis, hepatic artery, or SMA was performed in eight patients, four patients, and one patient, respectively. The median operative time and blood loss were 632 minutes and 955 mL, respectively. In terms of pathologic evaluation, regional lymph node metastases were identified in five (12%) patients. Negative margin (R0) resection was achieved in 36 (88%) patients with a median margin distance of 5 mm. Evans grade ≥III response was observed in 13 (32%) patients.

Postoperative complications developed in 30 (73%) patients, with 16 (39%) patients having major complications of ≥Clavien–Dindo grade IIIa. The median length of hospital stay was 27 d, with only two 90-d readmissions (5%) and no overall 90-d mortality events. Thirty (73%) patients completed adjuvant chemotherapy. With a median follow-up of 35.2 months, 19 (46%) patients developed recurrences (15% local and 34% distant). At the last follow-up, 73% of patients were alive, and 51% were without recurrence.

3.2 | Survival analysis

We identified 41 patients who underwent radical surgery after induction GnP and subsequent CRT with S-1 administration for UR-LA PDAC. The prognostic significance in terms of overall survival (OS) and disease-free survival (DFS) rates is shown in Figure 2. The 2-y DFS rate was 52.1%, and the 5-y survival rate was 44.4% (Figure 2A). The 2-y OS rate was 92.1%, the 3-y survival rate was 77.4%, and the 5-y survival rate was 58.6% (Figure 2B). There was no significant difference in prognosis according to the timing of CA19-9 normalization (DFS: $P = .203$, OS: $P = .655$). In the OS comparison between resected (n = 41) and nonresected (n = 84) UR-LA cases, the resected cases had a significantly better prognosis ($P < .001$; Figure 3). In addition, among resected cases OS comparison between cases in which CA19-9 normalized (n = 22) during preoperative treatment and cases in which CA19-9 remained high (n = 11) showed that CA19-9 normalized cases had a significantly better prognosis

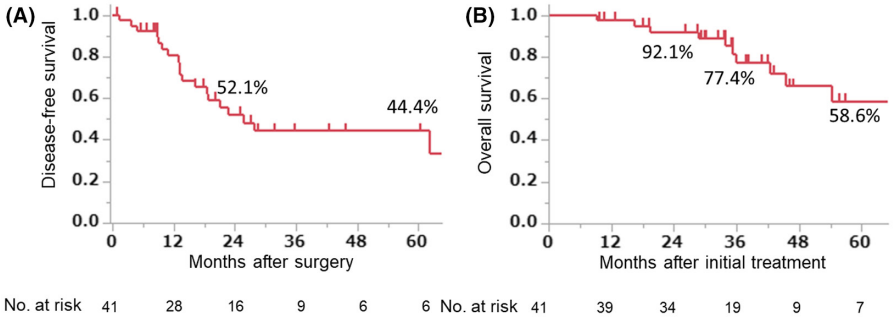

FIGURE 2 (A) Kaplan–Meier curves of disease-free survival for UR-LA PDAC patients who underwent radical surgery after induction GnP and following CRT with S-1 administration (n = 41). (B) Kaplan–Meier curves of overall survival for UR-LA PDAC patients who underwent radical surgery after induction GnP and following CRT with S-1 administration (n = 41)

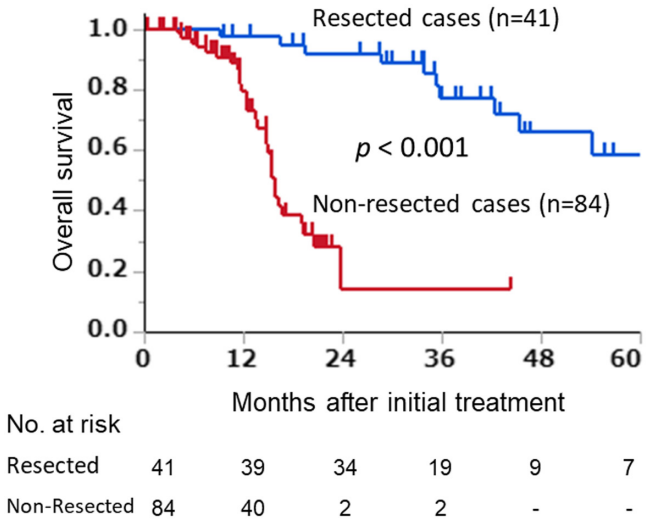

FIGURE 3 Kaplan–Meier curves of overall survival for UR-LA PDAC patients who underwent radical surgery after induction GnP and following CRT with S-1 administration (n = 41) and nonresected UR-LA cases (n = 84)

(*P* = .006; Figure 4A). Similarly, of the resected cases, those with PNI ≥41.7 (n = 27) had significantly better OS than those with PNI <41.7 (n = 14) (*P* = .007; Figure 4B).

3.3 | Prognostic factors in patients undergoing resection

We analyzed the postoperative prognostic factors in patients who underwent this treatment strategy (Table 2). Univariate analysis with the Cox proportional hazard model revealed that more than 6 months of preoperative therapy and normalization of the CA19-9 level were significantly associated with DFS; however, no independent predictors were found in multivariate analysis. Univariate analysis for overall analysis revealed that more than 8 months of preoperative therapy, normalization of CA19-9 level, and PNI at operation were significantly associated with prolonged survival. Using the Cut-off Finder web application on overall survival,[29] 41.7 was calculated as the optimal cutoff value for PNI. We used the significance of correlation with survival variable method, which fitted Cox proportional hazard models to the dichotomized variable and the survival variable. The adequate cutoff value was defined as the point with the most significant split. On the other hand, no nutritional parameters at diagnosis were significantly related to either DFS or OS, and more than 10 months of preoperative therapy was not associated with these parameters. In addition, negative resection margins (R0) and the implementation of adjuvant chemotherapy did not improve survival. Multivariate analysis revealed that CA19-9 normalization (HR 0.23; *P* = .032) and PNI ≥41.7 at operation (HR 0.05; *P* = .021) were independent prognostic factors for overall survival; however, the length of preoperative therapy was not (Table 3). These results motivated us to examine the influence of induction chemotherapy on nutritional status, including PNI. During preoperative therapy, PNI worsened over time and after therapy at operation, PNI decreased significantly compared with that before induction GnP therapy at diagnosis (*P* = .02). On the other hand, there were no significant differences in PNI comparisons at diagnosis and before CRT (*P* = .62) or before CRT and at operation (*P* = .69) (Figure 5).

4 | DISCUSSION

In the last decade, novel chemotherapeutic regimens, including FOLFIRINOX and GnP, have emerged as new standard therapies for PDAC, which was formerly a lethal disease, and many studies have demonstrated promising survival rates.[3,4,28] Moreover, it was also recently reported that the radical surgery rate increased after downstaging with these new regimens for UR-LA PDAC patients.[5,6,8,9] CRT in combination with this treatment strategy, including novel chemotherapy, can be a promising option in UR-LA PDAC patients. However, there is no established consensus on the detailed method and indication for achieving long-term survival using the combination of chemotherapy and additional CRT.

In the present study we retrospectively reviewed 41 patients with UR-LA PDAC who underwent radical surgery after downstaging by induction GnP chemotherapy and subsequent CRT. Preoperative CRT seems to be effective in locoregional control of locally advanced cancer and is presumed to reduce the rate of positive margins after resection. Philip et al[30] reported that the R0 resection rate of UR-LA PDAC patients who underwent radical surgery after six courses of GnP was 41%. In this study, the R0 resection rate and the node-negative rate were relatively high, at ~90%. However, UR-LA PDAC is both a locally advanced disease and a

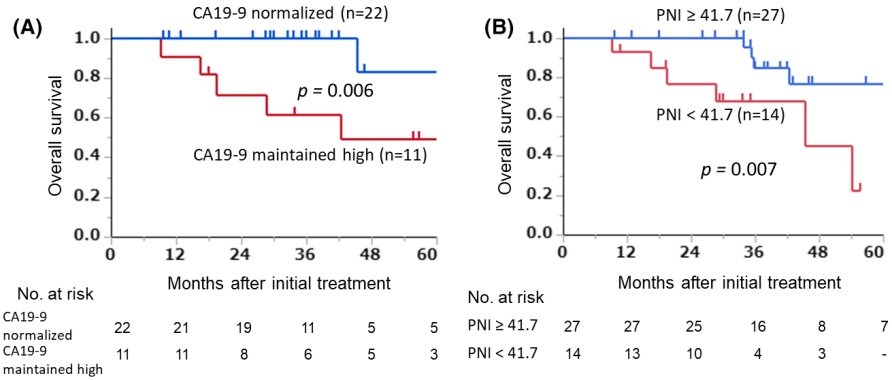

FIGURE 4 (A) Among resected cases, overall survival comparison between cases in which CA19-9 normalized (n = 22) during preoperative treatment and cases in which CA19-9 remained high (n = 11). (B) Comparison of overall survival of resected cases with preoperative PNI ≥41.7 (n = 27) and PNI < 41.7 (n = 14)

systemic disease, and CRT does not prevent distant metastasis in fatal systemic disease. Distant recurrence was also observed in 34% of patients in this study. Satoi et al[23] reviewed that among patients who underwent conversion surgery based on clinical response and decreased CA19-9 levels after multimodal treatment, resectability and MST ranged from 2% to 24% (median, 4.1%) and from 24.1 to 64 months (median, 36 months), respectively. Our prognostic results are acceptable in reference to this report. In addition, previous reports often analyzed mixed cohorts of patients, including those with borderline resectable and UR-LA PDAC.[9,31] Surgical strategies and outcomes usually differ between borderline resectable and UR-LA PDAC cases, and it seems inappropriate to discuss the efficacy of a treatment strategy using such a mixed group.

We demonstrated that long-term OS was significantly associated with CA19-9 normalization and with good nutritional status, such as a PNI of more than 40, at the time of operation but not at diagnosis. Several studies have reported that preoperative nutrition indices, such as CONUT, mGPS, and PNI, are linked to the prognosis of various malignancies.[26,32,33] In pancreatic cancer, some indices have also been reported to have an independent association with survival in patients with resectable or borderline resectable PDAC after pancreatectomy[32]; however, no other study has conducted a similar analysis on additional resection after GnP and subsequent CRT for UR-LA PDAC, a more invasive surgery.

This study also showed that nutritional status, as indicated by factors such as PNI, was worse during multidisciplinary treatment. These results strongly suggest the need for continuous nutritional support during induction chemotherapy. A side effect of systemic chemotherapy is worsened nutritional status due to loss of appetite or dysgeusia. Active nutritional support during induction therapy may minimize malnutrition, possibly improving the survival of UR-LA PDAC patients. As there is no evidence regarding specific nutritional intervention methods, we are planning new clinical studies using an immune-modulating diet to improve PNI.

Our results indicated that novel chemotherapeutic regimens, such as GnP, can also be key drugs in the pursuit of radical surgery. Faisal et al[34] reported that longer induction chemotherapy might play a more important role in prognosis. In our study, the duration of preoperative therapy had a significant effect on survival in univariate analysis but not in multivariate analysis. Although the optimal duration of induction therapy remains debatable, subsequent surgery is recommended when the CA19-9 level decreases to the normal range. Some reports have also referred to a decrease in CA19-9 as an effective response surrogate,[9,35,36] and our results could confirm previous hypotheses that the CA19-9 level may be an important factor for determining preoperative duration and subsequent surgery. In the present study, CA19-9 normalization was observed in 54% of patients; these patients also responded well to induction GnP therapy. If the tumor is technically resectable and CA19-9 normalizes after induction chemotherapy, the patient would be a candidate for careful radical surgery following additional CRT, although major vascular resection may be necessary.

Our results revealed that achievement of R0 resection and adjuvant chemotherapy did not contribute to prognosis in univariate analysis, indicating that the treatment until surgery is more significant than these factors, which are generally considered prognostically important. Induction GnP chemotherapy followed by CRT with S1 administration may provide good local control, but controlling distant metastases after radical surgery is crucial to prolonging prognosis. It is important to continue systemic chemotherapy while maintaining nutritional status after radical surgery. Patients in this study received adjuvant chemotherapy with S-1 or gemcitabine according to the guidelines for the treatment of pancreatic cancer. In the future, we will consider administering GnP again as adjuvant chemotherapy for patients who underwent conversion surgery after successful GnP, such as the cohort in the present study.

Despite the promising findings of this study, our analysis had some limitations. First, the retrospective and nonrandomized design resulted in selection bias. Second, the small sample size might have influenced the results, as radical surgery for UR-LA PDAC is a very rare event. Further studies with more patients and longer observations are needed to evaluate the optimal and detailed strategy for UR-LA PDAC.

5 | CONCLUSION

In conclusion, radical surgery following induction GnP and subsequent CRT for UR-LA PDAC has favorable outcomes, and CA19-9

TABLE 2 Univariable analysis for survival in patients who underwent resection after induction chemotherapy and subsequent chemoradiotherapy

		Disease-free survival		Overall survival	
Variable	**n**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex (male)	23	0.69 (0.28–1.68)	.412	0.96 (0.28–3.33)	.947
Age (≥65 y)	23	1.46 (0.58–3.70)	.421	1.44 (0.43–4.80)	.552
Tumor location (head/uncinate)	30	0.78 (0.27–2.22)	.640	2.60 (0.32–21.1)	.371
Tumor size at diagnosis (≥30 mm)	23	0.91 (0.38–2.20)	.836	0.40 (0.12–1.36)	.142
CA19-9 at diagnosis (≥230 U/mL)	18	3.03 (0.95–9.60)	.060	1.97 (0.38–10.2)	.418
CEA at diagnosis (≥5.0 g/mL)	37	1.83 (0.42–8.03)	.423	2.18 (0.28–17.3)	.460
DUPAN-2 at diagnosis (≥150 U/mL)	25	1.17 (0.30–4.53)	.822	1.83 (0.46–7.36)	.394
SPan-1 at diagnosis (≥30 U/mL)	16	3.52 (0.63–19.7)	.151	2.99 (0.27–33.1)	.371
Nutrition at diagnosis					
CONUT (≥5)	4	1.22 (0.16–9.44)	.848	3.45 (0.36–33.0)	.283
GPS (≥1)	8	0.76 (0.21–2.70)	.667	2.20 (0.56–8.67)	.258
mGPS (≥1)	10	0.93 (0.30–2.94)	.906	1.60 (0.41–6.28)	.498
NLR (≥2)	26	1.74 (0.61–4.93)	.301	1.30 (0.34–4.92)	.701
PLR (≥150)	21	1.24 (0.49–3.17)	.647	1.14 (0.34–3.75)	.833
PNI (≥41.7)	32	0.60 (0.13–2.65)	.497	0.68 (0.13–3.42)	.637
Length of preoperative therapy					
≥6 mo	33	0.40 (0.16–0.99)	.047*	0.31 (0.09–1.03)	.055
≥8 mo	25	0.51 (0.21–1.24)	.513	0.27 (0.08–0.94)	.039*
≥10 mo	15	0.58 (0.21–1.63)	.300	0.33 (0.07–1.52)	.155
Tumor size at operation (≥20 mm)	21	1.22 (0.50–2.97)	.656	1.08 (0.33–3.61)	.896
Tumor size decrease rate (≥30%)	22	0.58 (0.23–1.42)	.231	0.41 (0.12–1.42)	.161
CA19-9 normalized	22	0.32 (0.11–0.91)	.032*	.09 (0.01–0.78)	.028*
CA19-9 decrease (≥90%)	17	1.40 (0.50–3.93)	.523	0.83 (0.18–3.86)	.816
CEA normalized	5	0.22 (0.01–3.59)	.224	0.26 (0.02–4.22)	.342
DUPAN-2 normalized	9	0.44 (0.04–5.07)	.437	0.30 (0.03–3.32)	.324
SPan-1 normalized	7	0.58 (0.05–6.38)	.654	0.19 (0.02–2.31)	.194
Nutrition at operation					
CONUT (≥5)	5	0.84 (0.19–3.72)	.817	1.01 (0.12–8.23)	.993
GPS (≥1)	11	0.42 (0.12–1.47)	.175	0.68 (0.14–3.22)	.629
mGPS (≥1)	12	0.56 (0.18–1.71)	.308	0.61 (0.13–2.84)	.525
NLR (≥2)	21	2.11 (0.86–5.17)	.102	1.74 (0.52–5.81)	.370
PLR (≥150)	21	1.25 (0.51–3.08)	.624	0.85 (0.25–2.84)	.790
PNI (≥41.7)	33	0.67 (0.23–1.95)	.462	0.19 (0.05–0.71)	.013*
Operative time (≥10 h)	22	0.55 (0.22–1.38)	.200	0.37 (0.11–1.30)	.122
Blood loss (≥1000 mL)	18	0.69 (0.28–1.69)	.415	0.66 (0.19–2.29)	.516
Any vessel resection	28	0.86(0.32–2.27)	.757	0.58 (0.17–2.01)	.391
Resection margin status (≥R1)	5	1.62 (0.46–5.70)	.452	1.08 (0.13–8.66)	.945
POPF (B/C)	6	0.57 (0.13–2.48)	.453	0.60 (0.08–4.76)	.632
Length of stay (≥21 d)	32	0.53 (0.18–1.54)	.243	0.61 (0.12–3.00)	.539
Adjuvant chemotherapy	30	0.91 (0.35–2.42)	.857	1.43 (0.35–5.91)	.615

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CONUT, controlling nutritional status; GPS, Glasgow prognostic score; HR, hazard ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; POPF, postoperative pancreatic fistula.

*$P < .05$.

TABLE 3 Multivariable analysis for overall survival in patients who underwent resection after induction chemotherapy and subsequent chemoradiotherapy

	Overall survival	
Variable	**HR (95% CI)**	***P***
Length of preoperative therapy ≥8 mo	0.17 (0.01-2.01)	.158
CA19-9 normalized (Yes)	0.23 (0.02-0.88)	.032*
PNI at operation (≥41.7)	.05 (0.01-0.62)	.021*

Abbreviations: CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; PNI, prognostic nutritional index.
*$P < .05$.

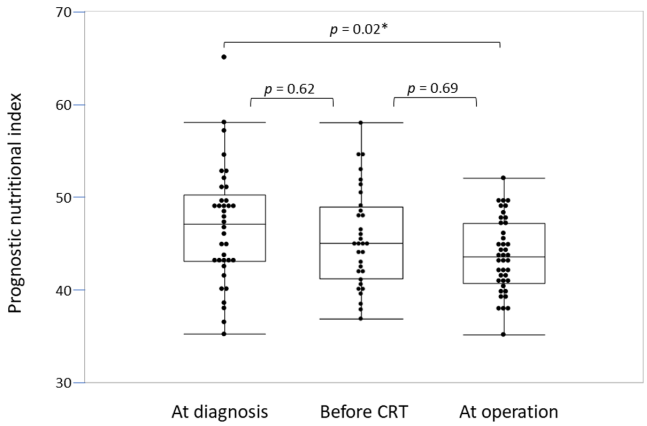

FIGURE 5 Boxplot comparison of three groups of PNI at diagnosis, before CRT, and at operation

normalization and maintenance of good nutritional status are important for prolonged prognosis.

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ETHICAL APPROVAL

The study was reviewed and approved (ref. No. R2019153) by the Institutional Review Board and complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[37] All procedures in this study were performed in accordance with the guidelines of the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent for treatment was obtained from each patient prior to the start of treatment, and consent for the use of data for research was obtained on an opt-out basis.

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