Is surgery after neoadjuvant chemoradiotherapy feasible for elderly patients with resectable or borderline resectable pancreatic ductal adenocarcinoma?

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Abstract

Background

The benefit and safety of pancreas resection for pancreatic ductal adenocarcinoma for elderly patients, especially after preoperative adjuvant therapy, is still unknown. This study attempted to evaluate perioperative and long-term outcomes after pancreas resection in elderly patients with pancreatic ductal adenocarcinoma and to detect the potential impact of neoadjuvant chemoradiotherapy.

Methods

One hundred and thirty-four consecutive patients undergoing curative resection for resectable and borderline resectable pancreatic ductal adenocarcinoma between March 2008 and February 2018 at our institution were analyzed. Patients were divided into two groups: patients older than or equal to 75 years (the elderly group, n=46) and those younger than 75 years (the younger group, n= 88).

Results

There were no significant differences both in overall survival and relapse free survival between the two groups (P=0.270, P=0.699). Although the induction rate of adjuvant chemotherapy was not significantly different (P=0.458), the completion rate was significantly lower in elderly group than that in younger group (35% and 56%; P=0.022). Neoadjuvant chemoradiotherapy was performed for 82 patients (61%), and the induction and completion rates were not significantly different (P=0.668, P=0.794) between the two groups. The elderly patients with completion of adjuvant chemotherapy had significantly better overall survival than those without it (P=0.032). Neoadjuvant chemoradiotherapy did not significantly affect overall survival in elderly patients, however, there was a trend toward longer overall survival in patients who had neoadjuvant chemoradiotherapy (P=0.072).

Conclusions

Neoadjuvant chemoradiotherapy could be introduced and completed even for elderly patients without serious complications and might lead to improved prognosis for those who are difficult to complete postoperative adjuvant chemotherapy.

Background

With advances in perioperative management and surgical techniques in recent years, pancreas resection has become accepted as a safe and effective procedure even in elderly patients with acceptable morbidity and mortality rates. Several reports have emphasized that pancreaticoduodenectomy (PD) for elderly patients could be beneficial, as it is in younger patients [1–3]. However, large population-based studies showed a mortality of 4.5–15.5% after pancreas resection in patients aged 80 years or older [4–6]. A few recent series from large centers have indicated that pancreas resections should not be avoided for the reason of age itself even in elderly patients in terms of the short-term outcomes [7–11]. On the

other hand, Ogura et al [6] suggested that PD for pancreatic ductal adenocarcinoma (PDAC) in elderly patients should be carefully selected because it is associated with a higher incidence of severe postoperative complications and a small change of long-term survival. Thus, the efficacy and benefit of pancreas resections for PDAC in elderly patients remain controversial because it has been reported that the elderly patients with PDAC had a limited prognosis even though pancreas resection is the only curative treatment option [8, 9].

The CONKO-001 and JASPAC01 studies suggested that postoperative adjuvant chemotherapy (ACT) had an important effect in patients with PDAC [12, 13]. However, one-fourth of patients with PDAC postoperatively cannot receive ACT because of insufficient recovery or surgery-related complications [14], and this tendency is particularly evident among elderly patients.

Preoperative neoadjuvant therapy was not actually recommended for patients with resectable (R) PDAC in the NCCN guideline [15]. However, we already reported the efficacy and safety of preoperative neoadjuvant chemoradiotherapy (NACRT) in patients with R and borderline resectable (BR) PDAC [16]. Furthermore, our study also showed a high completion rate of NACRT. NACRT might compensate for a lack of such a postoperative adjuvant chemotherapy, especially for elderly patients with difficulty in induction and completion of ACT.

The aim of this study was to evaluate a safety and indication of pancreas resections in elderly patients in comparison with those in younger patients and to detect the influence of preoperative therapy, especially focusing on NACRT.

Methods

This study was retrospectively analyzed. The Institutional Review Board of Kagawa University approved the study. A total of 150 consecutive patients undergoing pancreas resections for PDAC between March 2008 and February 2018 were retrospectively examined. All 150 patients had PDAC that was histologically confirmed by at least two pathologists.

Patients

Of the 150 patients, 16 patients were excluded. Fourteen were classified as unresectable category based on the NCCN guideline [15], one underwent R2 resection, and one underwent preoperative therapy other than NACRT. The data from the remaining 134 patients were retrospectively analyzed.

The patients were diagnosed with R-PDAC (n = 114) or BR-PDAC (n = 20). All surgical procedures were divided into the following three types: classic, pylorus-preserving, or subtotal stomach-preserving pancreaticoduodenectomy (PD) in 90 patients (67%); distal pancreatectomy in 37 (28%); and total pancreatectomy in 7 (5%). Patients who underwent laparoscopic surgery were not included in this series. Systematic lymph node dissection was performed in all operations. R0 resection was achieved in 128

patients (96%) and R1 was achieved in 6 (4%). Preoperative NACRT and postoperative ACT were given to 82 (61%) and 104 (78%) patients, respectively.

Patients were divided into two groups: patients older than or equal to 75 years (the elderly group, n = 46) and those younger than 75 years (the younger group, n = 88).

Preoperative NACRT

We introduced two kinds of NACRT during the period of this study. Short-term neoadjuvant hypofractionated chemoradiotherapy with S1 was performed between January 2009 and May 2016 as a prospective phase II trial, and already reported its efficacy and safety [16]. In this clinical trial, hypofractionated, external-beam radiotherapy (30 Gy in 10 fractions) with concurrent S1 (60 mg/m^2) was delivered 5 days per week for 2 weeks prior to pancreatectomy. Since June 2016, the next phase II trial is underway with external-beam radiotherapy (50 Gy in 25 fractions) and concurrent S1(60 mg/m^2) for 5 weeks. Short-term and extended NACRT were given to 54 and 28 patients, respectively.

Postoperative ACT and follow-up

Postoperative ACT was applied postoperatively unless contraindicated by the patients' conditions. Basically, the patients received gemcitabine, referring to the results of the CONKO-001 trial [12] between 2008 and 2012; or S-1, referring to the results of the JASPAC01 trial since 2013 [13], according to the recommended protocols.

The follow-up examinations were performed every 2–3 months for 1 year and every 6 months thereafter. Enhanced computed tomography was performed every 6 months. We moved the examination date forward or added magnetic resonance imaging or ^{18}F-fluorodeoxy glucose positron emission tomography (FDG-PET), if necessary.

Outcome measures

The preoperative variables included age; sex; body mass index (BMI); tumor location; resectability [15]; serum C-reactive protein (CRP), serum albumin, hemoglobin, and serum CA19-9 levels; neutrophil / lymphocyte ratio (NLR); lymphocyte count; modified Glasgow Prognostic Score [17]; the standardized uptake value (SUV) seen on FDG-PET; and induction or completion rate of NACRT. The intraoperative data, including the surgical procedure, operation time, estimated blood loss, blood transfusion, and portal vein resection and pathological variables were also collected to compare the elderly and younger groups. Postoperative data on morbidity according to the Clavien-Dindo (CD) classification [18], postoperative pancreatic fistula (POPF) [19], delayed gastric emptying (DGE) [20], and induction and completion rate of postoperative ACT were included.

Statistical analysis

The clinicopathological features of patients in the elderly and younger groups were compared. The categorical variables were compared between the groups using the chi-square test and Fisher's exact test.

Survival was calculated using the Kaplan–Meier method and was compared between the groups using the log-rank test. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS Statistics 25.0 for Windows software program (SPSS, Inc., Chicago, IL, USA).

Results

The median follow-up period was 21 (range: 0-121) months. In the entire group of patients, the median OS was 34 months, and the 3- and 5-year survival rates were 48.5% and 36.9%, respectively.

Among the 134 patients undergoing pancreas resections for PDAC, 46 patients (34%) were aged 75 years or older. The comparison of clinicopathologic characteristics and postoperative outcomes between the elderly and younger patients was shown in Table 1. Although the elderly patients had more risk and trend with aspect to hemoglobin level and NLR (P = 0.010, P = 0.062), there were no significant differences in the induction and completion rates of NACRT, intraoperative variables including the surgical procedures, incidence of portal vein resection, length of operation and blood loss, and pathological data of LN metastasis and resection status between the two groups.

Mortality occurred in a patient in the younger group. Morbidity [18] (≥ Grade IIIb) occurred in 7 (15%) in the elderly group. The elderly group experienced a significantly higher incidence of postoperative major complications (P = 0.046). The incidence of POPF was similar between the two groups, while DGE occurred more frequently in the elderly patients than in the younger patients (P = 0.001). Furthermore, postoperative hospital stay in

the elderly group was longer than that in the younger group (P = 0.008). The induction rate of ACT was similar between the two groups (74% vs 80%, P = 0.458), however, the completion (more than 6 months) rate was significantly lower in the elderly group than the younger group (P = 0.022). Only 16 (35%) patients could complete ACT in the elderly group.

NACRT was performed for 82 patients (61%). Twenty-seven (59%) patients in the elderly group received NACRT (2 weeks: n = 18 and 5 weeks: n = 9), and 55 (63%) in the younger group did (2 weeks: n = 36 and 5 weeks: n = 19). There were no significant differences about the induction of NACRT between the two groups (P = 0.668). As for the completion rate, 24 out of 27 (89%) completed NACRT protocol in the elderly group and 48 out of 55 (87%) in the younger group. There were no significant differences about the completion rate of NACRT between the two groups. More importantly, both groups had high completion rate of NACRT regardless of the treatment period.

The median overall survival (OS) time and 3-year OS rate in the elderly patients were 27 months and 45%, compared to 58 months and 52% in the younger patients, respectively (Fig. 1a). As well, the median relapse free survival time and 3-year relapse free survival rate (RFS) in the elderly patients were 18 months and 36%, compared to 16 months and 36% in the younger patients, respectively (Fig. 1b). The differences were not statistically significant both in OS and RFS between the two groups (P = 0.270, P = 0.699).

Table 2 shows the subgroup analysis for the clinicopathological factors in elderly patients with (n = 27) and without (n = 19) NACRT. The background factors such as age, sex, BMI, resectability [15], serum albumin and hemoglobin, NLR, intraoperative blood loss, transfusion, pathological LN metastases and resection status were not significantly different between the patients with and without NACRT. PD and TP were more frequently performed in patients with NACRT (P = 0.014). Portal vein was more frequently resected in the NACRT group (P = 0.044), and operation time was significantly longer in patients with NACRT (P = 0.049). As for perioperative outcomes, there were no significantly differences in morbidity, postoperative hospital stay and ACT induction and completion rates between the patients with and without NACRT.

The elderly patients with completion of postoperative ACT had significantly better OS than those without completion or induction of ACT (P = 0.032) (Fig. 2). The median OS and 3-year OS rate in the elderly patients with completion of ACT were 45 months and 66%, compared to 18 months and 33% in its counterpart. On the other hand, NACRT itself did not significantly affect OS in elderly patients, however, there was a trend toward improvement of OS (P = 0.072) (Fig. 3).

Figure 4 showed OS curves in the elderly group dividing into 4 groups with and without inductions of NACRT and ACT. Only patients who introduced both NACRT and ACT had significantly better OS than those who did either of NACRT or ACT or did not do either (P = 0.042, P = 0.017 and P = 0.002). It was suggested that performing NACRT before surgery and further performing ACT after surgery would improve OS for the elderly patients.

Discussion

Some studies have reported that even elderly patients achieved comparable short-term outcomes and similar rates of perioperative complications following pancreatic resections as younger patients thanks to recent improvements in surgical techniques and perioperative care [10, 11]. And yet at the same time, others demonstrated that a higher incidence of postoperative complication was seen in patients older than 75 or 80 years of age [5, 7–9, 21]. The current study revealed that the frequencies of major morbidity and DGE were significantly higher, and consequently, postoperative hospital stay was longer in the elderly patients. This might suggest that small problems for younger patients easily lead to big problems for elderly patients. Ballarin et al [10] described that age itself was not directly related to morbidity rate but that comorbidities might have a connection with it. They said that the presence of comorbidities such as hyperlipoproteinemia, diabetes, and coronary artery disease might be potential risk factors of morbidity. However, in this series, pancreatic resection was almost safely performed even in the elderly because mortality rate was zero. The careful management and patients’ selection in consideration of their backgrounds might be essential.

The efficacy of postoperative ACT was widely known and scientifically proven [12, 13]. However, surgical burden might preclude the induction or completion of ACT, especially for elderly patients. Khan et al [9] asserted that PD for PDAC in elderly patients could not be recommended because additional

chemoradiation or systemic chemotherapy was often not feasible in the population group. The current study also indicated that the ACT completion rate was significantly lower in the elderly patients than that in the younger patients although the induction rate was similar between the groups.

Recently, the efficacy of preoperative neoadjuvant chemotherapy or CRT for PDAC has been reported, especially for patients with BR- or locally advanced PDAC [22, 23]. Preoperative neoadjuvant therapy is not fully recommended for patients with R-PDAC in the NCCN guideline [15], presumably because of insufficient evidence. However, preoperative therapy possibly has a beneficial effect on patient survival in those with R-PDAC depending on patients. Several previous series [24, 25] and our clinical trial [16] demonstrated that NACRT had survival benefit for patients with R-PDAC as well as BR-PDAC. Additionally, in the current study, NACRT showed a trend toward improvement of OS in the analysis of the elderly group. In contrast to ACT, the completion rate of NACRT was very high even in the elderly group and comparable to the younger counterpart. Furthermore, in the subgroup analyses of the elderly patients, NACRT did not adversely affect perioperative outcomes, and more importantly, NACRT had little influence on induction and completion rate of postoperative ACT.

In this series, NACRT might have contributed to the comparable OS and RFS between the elderly and younger patients with R- and BR-PDAC. NACRT could benefit the elderly patients who had difficulty in the completion of ACT. In our subgroup analysis of OS, however, it was clearly demonstrated that NACRT alone was insufficient and NACRT plus ACT induction could prolong the survival in the elderly patients even if ACT was not completed. From these results, NACRT could be recommended to the elderly patients with PDAC.

We introduced two kinds of NACRT, and it might cause one of the serious limitations in the current study. However, a report from the M.D. Anderson Cancer Center contended that hypofractionated CRT (30 Gy) was associated with margin-negative resection rates, treatment effects, local control, and OS, similar to those associated with standard fractionated CRT (50.4 Gy) [26]. Moreover, there were no differences about the indication and completion rate of the two ways of NACRT between the elderly and younger group, therefore, we regarded them as a NACRT group in the current study.

The current study has several limitations. This was a retrospective study that was conducted at a single institution. Therefore, the sample size was small and a historical backdrop existed, and the current small-sized retrospective study cannot provide enough evidence to draw a definitive conclusion. We defined elderly patients as patients over 75 years old in the current study. However, we did not argue about very elderly patients aged 80 years or older in this study because the sample size of elderly group would become further small. As already mentioned, the two ways of NACRT existed. Ideally, the methods of NACRT should be integrated and analyzed.

Conclusion

Pancreas resections for elderly patients with PDAC could be safely performed though major complications and DGE rate was higher and the period of postoperative hospital stay became longer,

compared to younger patients. NACRT could be introduced and completed even for elderly patients without serious problem and might lead to improved prognosis for those who are difficult to complete postoperative adjuvant therapy.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the institutional review board of Kagawa University, and written informed consent was obtained from all individual participants before surgery for collection and analysis of the data. This article does not contain any studies with animals performed by any of the authors.

Consent for publish

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author (HS) on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

HS operated surgery and performed postoperative management of the patient and wrote the manuscript. MO, YA, HM gathered operated on the patients, gave advice on surgery and revised the manuscript for intellectual content. ST, TS, HK1(Hideki Kamada), HK2(Hideki Kobara) and TM gave substantial contribution to the acquisition, analysis and interpretation of data. KO and YS operated on the patients, and supervised and contributed to the final version of the report. All authors read and approved the final manuscript.

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Abbreviations

ACT: adjuvant chemotherapy

Alb: albumin

BMI: body mass index

BR: borderline resectable

CA19-9: carbohydrate antigen 19-9

CD: Clavien-Dindo classification

CI: Confidence Interval

CRP: C-reactive protein

DGE: delayed gastric emptying

DP: distal pancreatectomy

Hb: hemoglobin

HR: Hazard Ratio

LN: lymph node

NACRT: neoadjuvant chemoradiotherapy

NLR: neutrophil/lymphocyte ratio

OS: Overall Survival

PD: pancreaticoduodenectomy

PDAC: Pancreatic ductal adenocarcinoma

POPF: postoperative pancreatic fistula

R: resectable

SUV: Standardized Uptake Value

TP: total pancreatectomy

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Tables

[a]Median (min-max)

Table 1. Comparison of clinicopathologic characteristics and perioperative outcomes between the elderly and younger patients

		Elderly[b] (n=46) *n* (range or %)	Younger[c] (n=88) *n* (range or %)	*P* value
Age (years)		79 (75-90)[a]	67 (40-74)[a]	
Sex	Male	23 (50)	50 (57)	0.452
	Female	23 (50)	38 (43)	
BMI (kg/m^2)		21 (15-30)[a]	22 (14-28)[a]	0.752
Resectability[d]	R	40 (87)	74 (84)	0.658
	BR	6 (13)	14 (16)	
Alb		3.8 (2.5-4.6)[a]	3.9 (2.8-5.0)[a]	0.222
Hb		11.6 (8.5-16.3)[a]	12.2 (8.3-15.7)[a]	0.010
NLR		3.6 (0.8-59.1)[a]	2.9 (0.9-16.7)[a]	0.062
Induction of NACRT	Yes	27 (59)	55 (63)	0.668
	2 weeks	18	36	
	5 weeks	9	19	
Completion of NACRT protocol	Yes	24 (52)	48 (55)	0.794
	2 weeks	16	31	
	5 weeks	8	17	
Surgical procedure	PD	29 (63)	61 (69)	0.739
	DP	14 (30)	23 (26)	
	TP	3 (7)	4 (5)	
Portal vein resection		20 (43)	35 (39)	0.679
Operation time (min)		454 (220-710)[a]	472 (230-816)[a]	0.716
Blood loss (ml)		1278 (152-10564)[a]	946 (53-9268)[a]	0.179
Transfusion		18 (40)	24 (27)	0.160
LN metastases	Positive	20 (43)	41 (47)	0.731
Resection status	R0	42 (91)	86 (98)	0.181
Mortality		0 (0)	1 (1)	1.000
Morbidity[e]		7 (15)	4 (5)	0.046
POPF[f] (Grade B, C)		9 (20)	13 (15)	0.477
DGE[g] (Grade B, C)		20 (42)	16 (18)	0.001
Postoperative Hospital stay (day)		33 (14-153)[a]	24 (10-170)[a]	0.008
Induction of ACT		34 (74)	70 (80)	0.458

Completion of ACT (6 months)	16 (35)	49 (56)	0.022

[b]patients older than or equal to 75 years

[c]patients younger than 75 years

[d]according to the National Comprehensive Cancer Network guideline [15]

[e]Clavien-Dindo classification [18] ≥ grade IIIb

[f]according to the International Study Group of Pancreatic Surgery (ISGPS) classification [19]

[g]according to ISGPS classification [20]

[a]Median (min-max)

[b]according to the National Comprehensive Cancer Network guideline [15]

[c]Clavien-Dindo classification [18] ≥ grade IIIb

[d]according to the International Study Group of Pancreatic Surgery (ISGPS) [19]

[e]according to ISGPS classification [20]

Figures

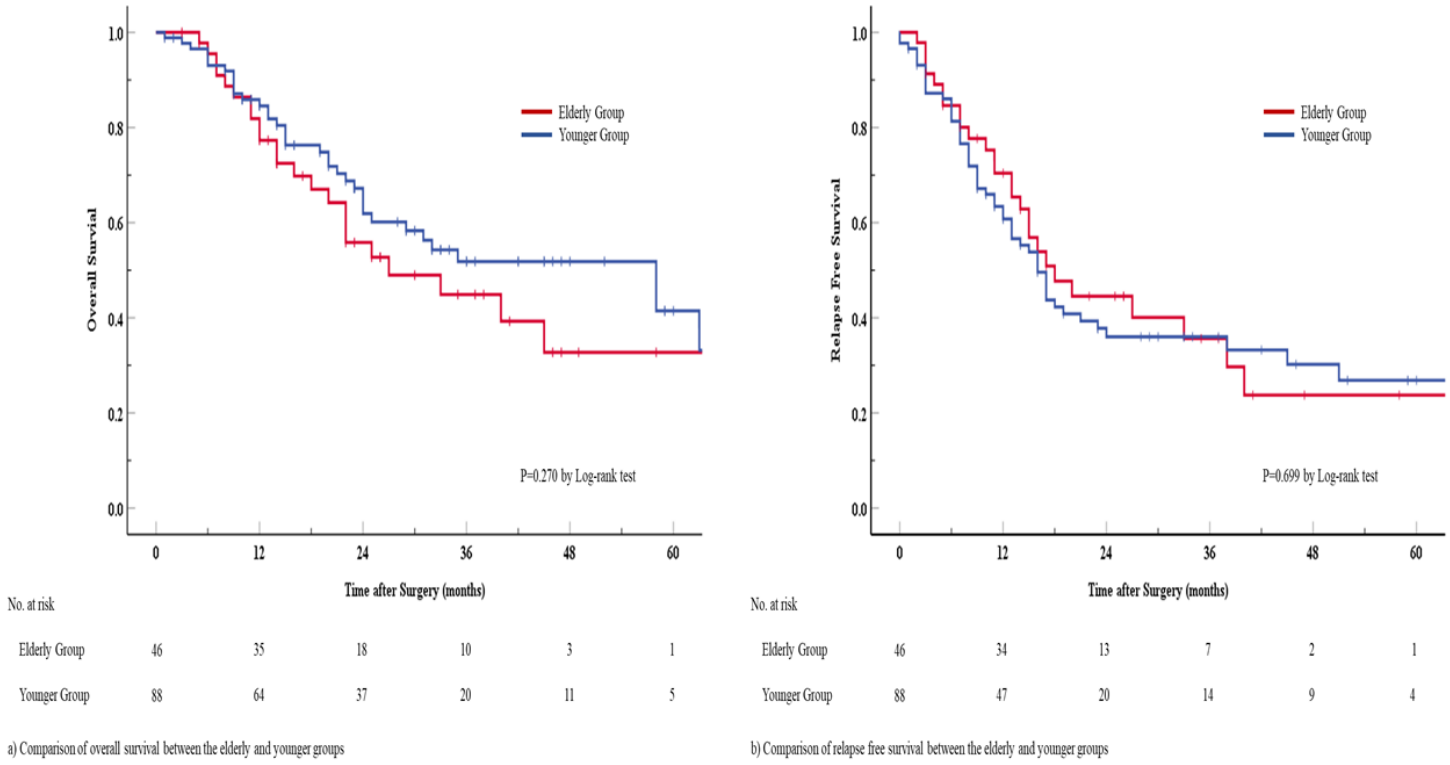


Figure 1

Table 2. Comparison of clinicopathological factors and perioperative outcomes in elderly patients with and without NACRT

		with NACRT (n=27) (range or %)	w/o NACRT (n=19) (range or %)	*P* value
Age (yr)		80 (75-83)[a]	78 (75-90)[a]	0.922
Sex	Male	11 (41)	12 (63)	0.134
	Female	16 (59)	7 (37)	
BMI (kg/m^2)		22 (15-29)[a]	21 (17-30)[a]	0.629
Resectability[b]	R	23 (85)	17 (89)	0.671
	BR	4 (15)	2 (11)	
Alb		3.8 (2.6-4.6)[a]	3.7 (2.5-4.6)[a]	0.960
Hb		11.5 (8.5-14.1)[a]	11.9 (9.2-16.3)[a]	0.292
NLR		4.3 (1.1-59.0)[a]	2.5 (0.8-20.4)[a]	0.133
Surgical procedure	PD	20 (74)	10 (53)	0.014
	DP	4 (15)	9 (47)	
	TP	3 (11)	0 (0)	
Operation time (min)		485 (327-692)[a]	423 (220-710)[a]	0.044
Blood loss (ml)		1438 (354-6970)[a]	944 (152-10564)[a]	0.347
Portal vein resection		15 (56)	5 (26)	0.049
Transfusion		13 (48)	5 (26)	0.135
LN metastases		12 (46)	7 (37)	0.532
Resection status (R0)		23 (88)	19 (100)	0.125
Morbidity[c]		5 (19)	2 (11)	0.457
POPF[d] (Grade B, C)		4 (15)	5 (26)	0.477
DGE[e] (Grade B, C)		13 (48)	7 (41)	0.651
Postoperative Hospital stay (day)		33 (14-153)[a]	28 (17-98)[a]	0.290
Induction of ACT		22 (81)	12 (63)	0.165
Completion of ACT (6 months)		10 (34)	6 (32)	0.702

1a, 1b Comparison of overall survival (OS, Figure 1a) and relapse free survival (RFS, Figure 1b) between the elderly and younger groups. There was no significant difference both in OS and RFS (P=0.270, P=0.699).

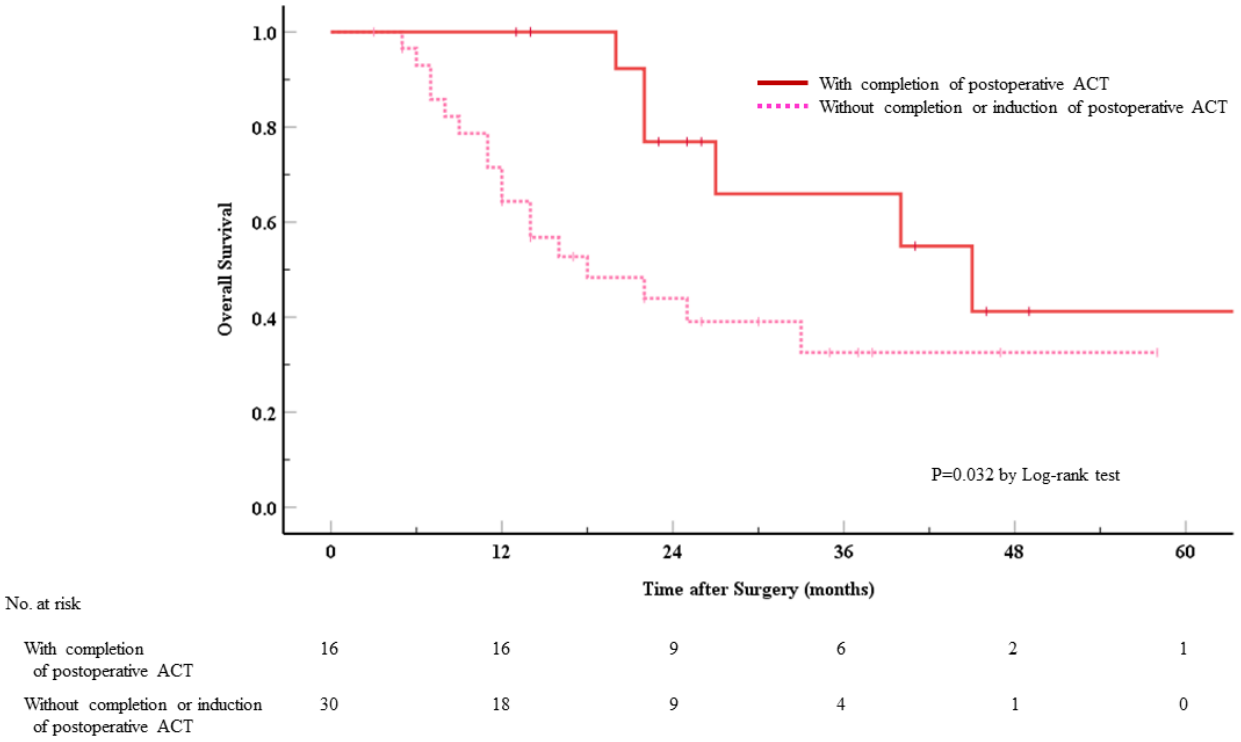
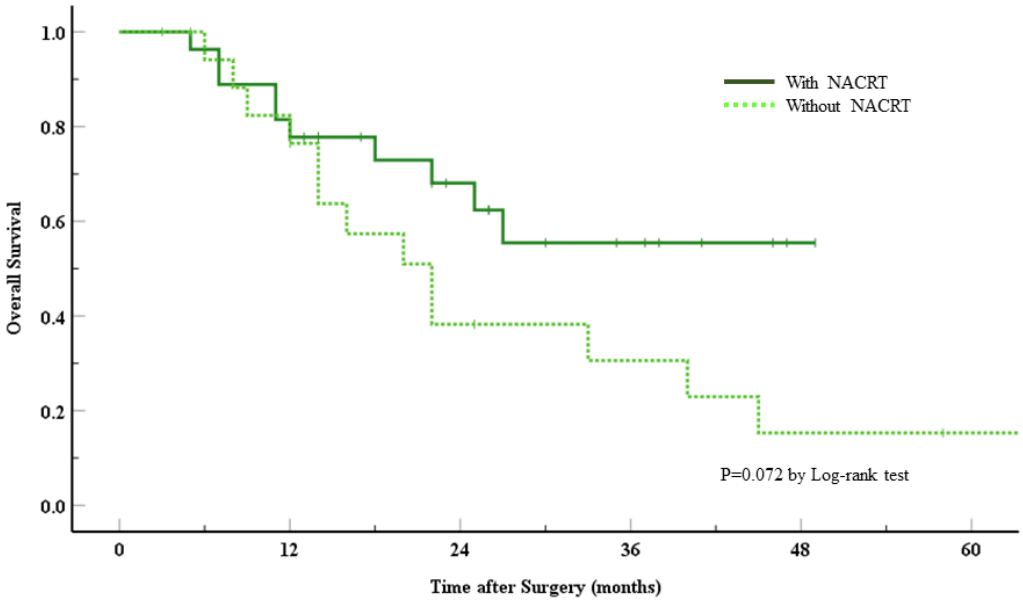


Figure 2

Comparison of overall survival (OS) in the elderly group between patients with completion of postoperative adjuvant chemotherapy (ACT) and without completion or induction of ACT. The elderly patients with completion of ACT had significantly better OS than those without completion or induction of ACT (P=0.032).

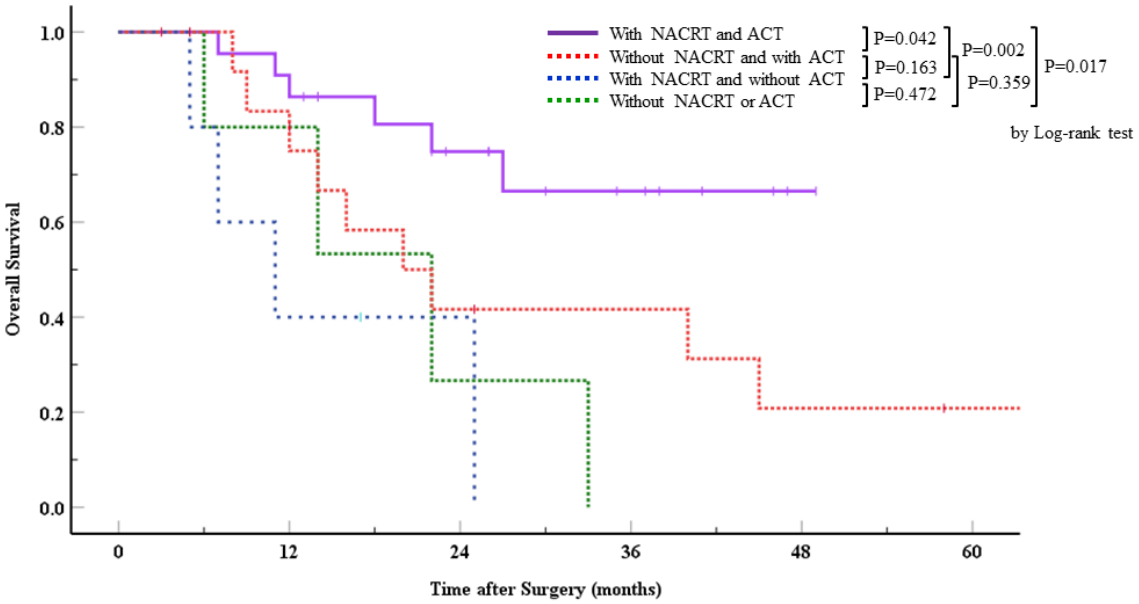


No. at risk

With NACRT	27	21	12	6	1	0
Without NACRT	19	13	6	4	2	1

Figure 3

Comparison of overall survival (OS) in the elderly group between patients with and without preoperative neoadjuvant chemoradiotherapy (NACRT). NACRT did not significantly affect OS in elderly patients, however, there was a trend for improvement of OS (P=0.072).



No. at risk						
With NACRT and ACT	22	19	11	6	1	0
Without NACRT and with ACT	12	9	5	4	2	1
With NACRT and without ACT	5	2	1	0	0	0
Without NACRT or ACT	7	3	1	0	0	0

Figure 4

Overall survival (OS) curves in the elderly group dividing into 4 groups with and without the inductions of preoperative neoadjuvant chemoradiotherapy (NACRT) and postoperative adjuvant chemotherapy (ACT). Only patients who introduced NACRT and ACT had significantly better OS than those who did either of NACRT or ACT or did not do either (P=0.042, P=0.002 and P=0.017).