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ORIGINAL ARTICLE

Is multidisciplinary treatment effective for invasive intraductal papillary mucinous carcinoma?

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Abstract

Background: Surgical resection is standard treatment for invasive intraductal papillary mucinous carcinoma (IPMC); however, impact of multidisciplinary treatment on survival including postoperative adjuvant therapy (AT), neoadjuvant therapy (NAT), and treatment for recurrent lesions is unclear. We investigated the effectiveness of multidisciplinary treatment in prolonging survival of patients with invasive IPMC.

Methods: This retrospective multi-institutional study included 1183 patients with invasive IPMC undergoing surgery at 40 academic institutions. We analyzed the effects of AT, NAT, and treatment for recurrence on survival of patients with invasive IPMC.

Results: Completion of the planned postoperative AT for 6 months improved the overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) of patients with stage IIB and stage III resected invasive IPMC, elevated preoperative carbohydrate antigen 19–9 level, lymphovascular invasion, perineural invasion, serosal invasion, and lymph node metastasis on un-matched and matched analyses. Of the patients with borderline resectable (BR) invasive IPMC, the OS ($p=0.001$), DSS ($p=0.001$), and RFS ($p=0.001$) of patients undergoing NAT was longer than that of

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those without on the matched analysis. Of the 484 invasive IPMC patients (40.9%) who developed recurrence after surgery, the OS of 365 patients who received any treatment for recurrence was longer than that of those without treatment (40.6 vs. 22.4 months, $p < 0.001$).

Conclusion: Postoperative AT might benefit selected patients with invasive IPMC, especially those at high risk of poor survival. NAT might improve the survivability of BR invasive IPMC. Any treatment for recurrence after surgery for invasive IPMC might improve survival.

KEYWORDS
invasive IPMC, multidisciplinary treatment, neoadjuvant therapy, postoperative adjuvant therapy, recurrence

1 | INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) are pathologically categorized as low-grade dysplasia, high-grade dysplasia (HGD), and invasive intraductal papillary mucinous carcinoma (IPMC) based on the degree of cellular atypia and the growth pattern of the lining epithelium.[1] Invasive IPMC has high malignant potential, which can lead to metastasis and recurrence even after curative resection, similar to conventional pancreatic ductal adenocarcinoma (PDAC).[2,3] Many biological features of invasive IPMC are similar to those of conventional PDAC; however, some features are different such as pathological subtype, recurrence pattern, and survival.[4–6]

Although surgical resection is the standard treatment for invasive IPMC,[1,7] the impact of multidisciplinary treatment on survival including postoperative adjuvant therapy (AT), neoadjuvant therapy (NAT), and treatment for recurrent lesions is not clear. The CONKO-001 randomized trial clearly showed that AT after surgery is useful for prolonging survival and preventing the recurrence of conventional PDAC[8]; however, the effectiveness of AT has not been established for invasive IPMC. Several studies have shown no impact of AT on the survival of patients with resected invasive IPMC, whereas others have shown the usefulness of AT in improving survival, especially in patients with advanced resected invasive IPMC.[5,9–14] However, these studies had the following limitations: small sample size; unclear definition of tumor size, which T stage is based on, whether invasive component with or without noninvasive IPMN lesions; and no information on regimen or duration of AT. To evaluate the impact of postoperative AT on the survival of patients with invasive IPMC as accurately as possible, the Japan Pancreas Society (JPS) collected data from all of Japan, defined tumor size used to T stage as maximum invasive length without noninvasive IPMN region, and evaluated the correlation between AT regimen and survival. We defined the completion of postoperative AT as patients who received the planned AT for 6 months and evaluated the impact of AT completion on survival.

European guidelines on pancreatic cystic neoplasms do not recommend NAT even for locally advanced invasive IPMC because of insufficient data and suggest palliative chemotherapy for recurrent lesions after surgery for invasive IPMC although there is no supporting evidence available.[7] In this study, we assessed the impact of NAT on survival, especially for patients with borderline resectable (BR) invasive IPMC, as well as the impact of treatment for recurrent lesions.

To identify an effective treatment strategy to prolong the survival of patients with invasive IPMC, we analyzed the effects of AT, NAT, and treatment for recurrence after surgery on the survival of patients with invasive IPMC. This was a large cohort study of patients with invasive IPMC who underwent surgery in a project study by the JPS.

2 | METHODS

2.1 | Study population

A retrospective multi-institutional, observational study by the JPS evaluated patients undergoing surgical resection for invasive IPMC between January 1996 and December 2018. This study was based at 40 academic institutions. The inclusion criteria were as follows: histologically proven invasive component of carcinoma arising from IPMN, and no local residual tumor (R0) or microscopic residual tumor (R1) based on pathological findings. Patients with conventional PDAC concomitant with IPMN were excluded. A total of 1183 patients were included in this study. This study was approved by the institutional review board of each participating institution prior to initiation of the study and conducted in accordance with the Declaration of Helsinki.

2.2 | Clinical data collection

Age, sex, preoperative symptom, comorbidities, and preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen

19–9 (CA19-9) were evaluated. Furthermore, we also evaluated radiographic morphological type including branch duct type, mixed type, and main duct type based on preoperative cross-sectional imaging,[1] as well as the resectability, including resectable or BR invasive IPMC according to the resectability criteria established by the National Comprehensive Cancer Network.[15] Surgical procedure and peri-operative outcomes, histopathological features, AT, NAT, site of initial recurrence, and survival were also assessed.

The regimen of postoperative AT included oral S-1 monotherapy, intravenous gemcitabine monotherapy (GEM), and combination therapy with GEM and S-1 (GS), depending on the physician's instructions. The completion of postoperative AT was defined as receiving: (1) four cycles of S-1 for the first 28 consecutive days followed by a 14-day rest; (2) six cycles of 4 weeks of GEM on days 1, 8, and 15; and (3) eight cycles of 3 weeks of GEM on days 1 and 8 plus S-1 for first 14 consecutive days followed by a 7-day rest.

2.3 | Pathologic assessment

Invasive IPMC was defined as the presence of a continuous invasive component from HGD in pathological findings to distinguish it from conventional PDAC concomitant with IPMN.[16,17] In case of difficulty differentiating between invasive IPMC and conventional PDAC concomitant with IPMN, a central review was undertaken by a specialized pathologist (AY) who was blinded to the clinical outcomes.

The type of invasive component was classified as tubular or colloid based on differentiations in the invasive components. Invasive IPMC tumors were staged according to the Tumor, Node, and Metastasis Classification of Malignant Tumors, 8th edition, published by the American Joint Committee on Cancer and the Union for International Cancer Control (AJCC/UICC TNM staging system).[18,19] The tumor size was determined as the maximum length of invasive component without noninvasive IPMN, according to a previously reported method.[20,21] Resection margin status involvement (R1) was defined as the presence of the tumor at the resection margin under the microscope.

2.4 | Statistical analysis

Continuous variables are expressed as the median and range. Categorical variables are described as percentages (%). Recurrence was defined as convincing radiographic evidence of the disease initially during follow-up after surgery and was histologically confirmed when possible. The sites of recurrence were classified as the remnant pancreas and extra-pancreas. Recurrence in the remnant pancreas was defined as new development or progression of IPMN meeting the surgical indication in each institution, which meant suspected HGD or invasive IPMC, or metachronous development of conventional PDAC. Extra-pancreatic recurrence was defined as the appearance of tumors outside the pancreas including the local area (retroperitoneal or surgical bed), lungs, liver, peritoneal cavity, or bone.

Overall survival (OS) was defined by death events or censoring as of the last follow-up. Disease-specific survival (DSS) was defined as the time interval from surgery to death by disease or the last follow-up. Disease-free survival (DFS) was defined as the time interval from the date of surgical resection to diagnosis of recurrence on follow-up. The Kaplan–Meier method was used to estimate the incidence curves, which were compared by univariate analysis using the log-rank test.

Of the 1183 patients included in this study, 1143 who underwent surgical resection for invasive IPMC without NAT were analyzed for impact of postoperative AT on survival and risk factors of poor survival after surgery. To identify the risk factors associated with poor OS, DSS, and RFS, multivariate analysis was performed using the Cox proportional hazards regression model, which included variables found to be significant in univariate analysis ($p < 0.05$). Furthermore, the propensity score was generated by binary logistic regression, and patients with similar propensity scores were selected from patients with and without completion of AT to reduce bias in patient distribution [covariate: age, residual tumor status, lymphovascular invasion, perineural invasion, and lymph node metastasis]. We analyzed the impact of NAT on the survival of patients with invasive IPMC by comparing the survival between patients undergoing surgery with and without NAT, and we also performed propensity score matched analysis (PSM) with covariate of age, resectability, and operation to reduce bias between the patients with and without NAT. The recurrence pattern and impact of treatment for recurrent diseases on the survival were analyzed in 1183 patients with invasive IPMC who underwent surgery. All statistical analyses were performed with SPSS software (version 26; IBM Corp, Somers, NY, USA). Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Demographics and clinicopathologic characteristics of patients undergoing surgery without NAT

The demographics of 1143 patients who underwent surgical resection for histologically confirmed invasive IPMC without NAT between 1996 and 2018 are summarized in Table 1. The median age was 71 years (range: 35–91) and 671 (58.7%) patients were male. Of the 1143 patients, 486 (42.5%) received AT after surgery and 333 (29.1%) completed the planned AT for 6 months. The median follow-up duration after surgery was 46.8 months (range: 4.9–236.2 months).

The median OS of this cohort was 115.5 months and the estimated OS at 5 and 10 years was 63.7% and 49.2%, respectively. The median DSS was not reached and the estimated 5- and 10-year DSS rates were 71.5% and 61.8%, respectively. The median RFS was

TABLE 1 Clinicopathological characteristics of 1143 patients with resected invasive IPMC without NAT.

Parameter	Total	Frequency of postoperative AT (*n*=486)	p	Frequency of completion of postoperative AT (*n*=333)	p
Age, ≥70/<70, *n* (%)	647(56.6)/496(43.4)	254(39.3)/232(46.8)	0.011	165(25.5)/168(33.9)	0.002
Sex, Male/female, *n* (%)	671(58.7)/472(41.3)	277(41.3)/209(44.3)	0.313	192(28.6)/141(29.9)	0.645
Symptom, yes/no, *n* (%)	417(36.5)/726(63.5)	187(44.8)/299(41.2)	0.228	129(30.9)/204(28.1)	0.310
Jaundice, yes/no, *n* (%)	132(11.5)/1,011(88.5)	66(50.0)/420(41.5)	0.065	42(31.8)/291(28.8)	0.470
Diabetes mellitus, yes/no, *n* (%)	449(39.3)/694(60.7)	197(43.9)/289(41.6)	0.456	132(29.4)/201(29.0)	0.874
Serum CEA level, elevated/normal, *n* (%)	265(23.5)/865(76.5)	164(61.9)/481(55.6)	0.071	67(25.3)/265(30.6)	0.094
Missing	*n*=13				
Serum CA19-9, elevated/normal, *n* (%)	459(40.5)/673(59.5)	228(49.7)/257(38.2)	<0.001	141(30.7)/191(28.4)	0.396
Missing	*n*=11				
Morphological type, branch/mixed/main, *n* (%)	227(19.9)/651(57.0)/265(23.2)	106(46.7)/284(43.6)/96(36.2)	0.044	65(28.6)/200(30.7)/68(25.7)	0.306
Resectability, Resectable/BR, *n* (%)	1,097(96.0)/46(4.0)	460(41.9)/26(56.6)	0.050	322(29.4)/11(23.9)	0.426
Type of surgery, PD/DP/TP/CP, *n* (%)	655(57.3)/300(26.2)/172(15.0)/16(1.4)	279(42.6)/137(45.7)/70(40.7)/0(0)	0.004	186(28.4)/96(32.0)/51(29.7)/0(0)	0.047
Transfusion, yes/no, *n* (%)	184(16.1)/959(83.9)	70(38.0)/416(43.4)	0.180	36(19.6)/297(31.0)	0.090
Pathological findings, *n* (%)					
Invasive component, tubular/colloid	697(66.1)/357(33.9)	349(50.1)/236(66.1)	<0.001	232(33.3)/93(26.1)	0.016
Missing	*n*=89				
Lymphovascular invasion, yes/no	511(44.7)/632(55.3)	314(61.4)/172(27.2)	<0.001	202(39.5)/131(20.7)	<0.001
Perineural invasion, yes/no	436(38.1)/707(61.9)	267(61.2)/219(31.0)	<0.001	170(39.0)/163(23.1)	<0.001
Bile duct invasion, yes/no	156(13.6)/987(86.4)	81(51.9)/405(41.0)	0.011	51(32.7)/282(28.6)	0.293
Duodenal invasion, yes/no	210(18.4)/933(81.6)	113(53.8)/373(40.0)	<0.001	66(31.4)/267(28.6)	0.418
Serosal invasion, yes/no	269(23.5)/874(76.5)	172(63.9)/314(35.9)	<0.001	102(37.9)/231(26.4)	<0.001
Retropancreatic tissue invasion, yes/no	401(35.1)/742(64.9)	239(59.6)/247(33.3)	<0.001	149(37.2)/184(24.8)	<0.001
Portal vein invasion, yes/no	77(6.7)/1,066(93.3)	47(61.0)/439(41.2)	0.001	27(35.1)/306(28.7)	0.236
Arterial invasion, yes/no	21(1.8)/1,122(98.2)	13(61.9)/473(42.2)	0.070	5(23.8)/328(29.2)	0.588
Extra-pancreatic nerve plexus invasion, yes/no	79(6.9)/1,064(93.1)	50(63.3)/436(41.0)	<0.001	29(36.7)/304(28.6)	0.125
Other organ invasion, yes/no	30(2.6)/1,113(97.4)	16(53.3)/470(42.2)	0.225	8(26.7)/325(29.2)	0.763
Residual tumor status, R0/R1	1,049(91.8)/94(8.2)	428(40.8)/58(61.7)	<0.001	301(28.7)/32(34.0)	0.274

154.9 months, and the estimated 5- and 10-year RFS rates were 57.8% and 52.1%, respectively. The OS, DSS, and RFS were significantly shortened as the AJCC/UICC stage advanced ($p < 0.001$; Table 2 and Figure 1).

3.2 | Risk factors of poor OS, DSS, and RFS in patients undergoing surgery without NAT

The results of univariate and multivariate Cox regression analyses for OS, DSS, and RFS are shown in Table 3. Multivariate analysis showed that the independent risk factors of poor OS were age ≥ 70 years (hazard ratio [HR] 1.42; $p = 0.001$), diabetes mellitus (HR 1.30; $p = 0.013$), elevated serum CEA level (HR 1.45; $p < 0.001$), elevated serum CA19-9 level (HR 1.25; $p = 0.049$), BR (HR 1.86; $p = 0.003$), transfusion (HR 1.71; $p < 0.001$), tubular type of invasive component (HR 1.78; $p < 0.001$), perineural invasion (HR 1.57; $p < 0.001$), serosal invasion (HR 1.78; $p < 0.001$), R1 (HR 1.71; $p = 0.001$), and lymph node metastasis (HR 1.97; $p < 0.001$). The following independent risk factors of poor DSS were found by multivariate analysis: age ≥ 70 years (HR 1.32; $p = 0.031$), BR (HR 1.80; $p = 0.013$), transfusion (HR 1.56; $p = 0.002$), tubular type of invasive component (HR 1.96; $p < 0.001$), lymphovascular invasion (HR 1.46; $p = 0.041$), perineural invasion (HR 1.89; $p < 0.001$), serosal invasion (HR 1.80; $p < 0.001$), R1 (HR 1.81; $p < 0.001$), and lymph node metastasis (HR 2.38; $p < 0.001$). The independent risk factors of poor RFS on multivariate analysis were elevated serum CEA level (HR 1.27; $p = 0.037$), BR (HR 1.59; $p = 0.030$), transfusion (HR 1.39; $p = 0.010$), tubular type of invasive component (HR 1.56; $p < 0.001$), lymphovascular invasion (HR 1.53; $p = 0.004$), perineural invasion (HR 1.50; $p = 0.002$), serosal invasion (HR 1.82; $p < 0.001$), portal vein invasion (HR 1.43; $p = 0.034$), R1 (HR 1.86; $p < 0.001$), and lymph node metastasis (HR 2.29; $p < 0.001$) (Table 3).

3.3 | Frequency of introduction and completion of AT after surgery for invasive IPMC without NAT

Of the 1143 patients with invasive IPMC, 657 (57.5%) did not receive AT after surgery because of the early stage of invasive IPMC ($n = 288$), poor condition of the patients including old age ($n = 129$), patients' refusal ($n = 122$), and physician's policy that invasive IPMC is not an indication for AT ($n = 118$). AT after surgery was more often introduced to patients with invasive IPMC aged <70 years ($p = 0.011$), elevated serum CA19-9 level ($p < 0.001$), branch or mixed type ($p = 0.044$), colloid type of invasive component ($p < 0.001$), lymphovascular invasion ($p < 0.001$), perineural invasion ($p < 0.001$), bile duct invasion ($p = 0.001$), duodenal invasion ($p < 0.001$), serosal invasion ($p < 0.001$), retropancreatic tissue invasion ($p < 0.001$), portal vein invasion ($p = 0.001$), extra-pancreatic nerve plexus invasion ($p < 0.001$), R1 ($p < 0.001$), advanced T stage ($p < 0.001$), advanced *n* stage ($p < 0.001$), and advanced stage ($p < 0.001$) (Table 1).

TABLE 1 (Continued)

Parameter	Total	Frequency of postoperative AT (*n*=486)	p	Frequency of completion of postoperative AT (*n*=333)	p
AJCC/UICC stage (8th)					
T stage, T1a/T1b/T1c/T2/T3/T4, *n* (%)	376(33.9)/32(11.0)/188(17.0)/297(26.8)/123(11.1)/2(0.4)	60(16.0)/57(46.7)/114(60.6)/181(60.9)/70(56.9)/2(100)	<0.001	48(12.8)/43(35.2)/87(46.3)/111(37.4)/42(34.1)/1(50.0)	<0.001
Missing	*n*=35				
N stage, N0/N1/N2, *n* (%)	807(70.6)/212(18.5)/124(10.8)	257(31.8)/144(67.9)/85(68.5)	<0.001	86(23.0)/102(48.1)/45(36.3)	<0.001
Stage, IA/IB/IIA/IIB/III/IV, *n* (%)	573(51.2)/149(13.3)/60(5.4)/205(18.3)/105(9.4)/27(2.4)	149(26.0)/77(51.7)/29(48.3)/140(68.3)/70(66.7)/20(74.1)	<0.001	120(20.9)/49(32.9)/17(28.3)/99(48.3)/40(38.1)/8(29.6)	<0.001
Missing	*n*=24				

Abbreviations: AJCC/UICC, American Joint Committee on Cancer and the Union for International Cancer Control; AT, adjuvant therapy; BR, borderline resectable; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CP, central pancreatectomy; DP, distal pancreatectomy; IPMC, intraductal papillary mucinous carcinoma; NAT, neoadjuvant therapy; PD, pancreatoduodenectomy; TP, total pancreatectomy.

TABLE 2 Overall survival, disease-specific survival, and recurrence-free survival based on AJCC/UICC stage (8th) in 1143 patients with invasive IPMC who underwent surgery without NAT.

Stage	Number (%)	Median OS (m)	*p*	Median DSS (m)	*p*	Median RFS (m)	*p*
T stage							
T1a	376 (33.9)	NR	<0.001	NR	<0.001	153.4	<0.001
T1b	122 (11.0)	NR		NR		128.1	
T1c	188 (17.0)	87.5		NR		91.9	
T2	297 (26.8)	57.9		83.5		25.6	
T3	123 (11.1)	29.3		34.7		15.4	
T4	2 (46.3)	25.2		25.2		20.7	
N stage							
N0	807 (70.6)	156.0	<0.001	NR	<0.001	198.3	<0.001
N1	212 (18.5)	46.0		64.6		20.1	
N2	124 (10.8)	21.0		23.3		9.7	
Stage							
IA	573 (51.2)	NR	<0.001	NR	<0.001	198.3	<0.001
IB	149 (13.3)	123.8		NR		NR	
IIA	60 (5.4)	61.0		126.6		31.5	
IIB	205 (18.3)	46.1		25.1		20.7	
III	105 (9.4)	22.1		25.1		10.3	
IV	27 (2.4)	17.3		17.3		5.7	
All stage	*n*=1,143						
AT, yes/no	486 (42.5)/657 (57.5)	72.7/151.9	0.102	88.4/NR	<0.001	38.2/198.3	<0.001
Completion of AT, yes/no	333 (29.1)/810 (70.9)	87.5/140.6	0.555	108.1/NR	0.105	61.6/198.3	0.054
Stage IA	*n*=573						
AT, yes/no	149 (26.0)/424 (74.0)	108.1/NR	0.102	NR/NR	0.007	NR/198.3	0.064
Completion of AT, yes/no	120 (20.9)/453 (79.1)	108.1/NR	0.198	NR/NR	0.064	NR/198.3	0.397
Stage IB	*n*=149						
AT, yes/no	77 (51.7)/72 (48.3)	119.7/123.8	0.695	NR/NR	0.571	106.1/NR	0.220
Completion of AT, yes/no	49 (32.9)/100 (67.1)	119.7/123.8	0.284	NR/NR	0.681	106.1/NR	0.896
Stage IIA	*n*=60						
AT, yes/no	29 (48.3)/31 (51.7)	68.7/61.0	0.696	126.6/NR	0.695	25.2/NR	0.477
Completion of AT, yes/no	17 (28.3)/43 (71.7)	71.0/43.2	0.547	126.6/NR	0.627	31.5/27.7	0.778
Stage IIB	*n*=205						
AT, yes/no	140 (68.3)/65 (31.7)	46.1/38.0	0.253	65.9/55.8	0.917	19.3/22.4	0.902
Completion of AT, yes/no	99 (48.3)/106 (51.7)	71.5/28.1	0.002	83.5/51.1	0.016	25.7/15.3	0.006
Stage III	*n*=105						
AT, yes/no	70 (66.7)/35 (33.3)	28.0/13.8	<0.001	30.2/13.9	0.001	14.6/6.8	0.001
Completion of AT, yes/no	40 (38.1)/65 (61.9)	36.7/15.8	<0.001	39.0/16.6	<0.001	18.2/6.8	<0.001
Stage IV	*n*=27						
AT, yes/no	20 (74.1)/7 (25.9)	18.3/9.1	0.115	18.3/9.1	0.230	5.7/5.7	0.874
Completion of AT, yes/no	8 (29.6)/19 (70.4)	23.3/5.3	0.072	23.3/15.3	0.089	7.2/5.7	0.441
In propensity score matched analysis							
All stage	*n*=666						
AT, yes/no	249 (37.4)/417 (62.6)	81.3/134.3	0.169	100.3/NR	0.003	45.1/NR	0.016
Completion of AT, yes/no	333 (50.0)/333 (50.0)	87.5/85.7	0.109	108.1/NR	0.430	61.6/57.3	0.199

TABLE 2 (Continued)

Stage	Number (%)	Median OS (m)	p	Median DSS (m)	p	Median RFS (m)	p
Stage IA	n=266						
AT, yes/no	129 (48.5)/145 (54.5)	122.7/NR	0.426	NR/NR	0.221	NR/NR	0.994
Completion of AT, yes/no	120 (45.1)/146 (54.9)	108.1/NR	0.187	NR/NR	0.100	NR/NR	0.839
Stage IB	n=97						
AT, yes/no	65 (67.0)/32 (33.0)	119.7/143.5	0.312	NR/NR	0.954	106.1/NR	0.889
Completion of AT, yes/no	49 (50.5)/48 (49.5)	119.7/143.5	0.368	NR/NR	0.654	106.1/NR	0.910
Stage IIA	n=33						
AT, yes/no	22 (66.7)/11 (33.3)	71.0/22.3	0.009	126.6/29.3	0.175	31.5/8.7	0.112
Completion of AT, yes/no	17 (51.5)/16 (48.5)	71.0/32.0	0.215	126.6/43.2	0.460	31.5/19.6	0.154
Stage IIB	n=164						
AT, yes/no	126 (76.8)/38 (23.2)	56.5/34.3	0.071	71.5/51.7	0.383	20.8/18.5	0.128
Completion of AT, yes/no	99 (60.4)/65 (39.6)	71.5/25.3	<0.001	83.5/34.3	0.005	25.7/12.3	0.003
Stage III	n=76						
AT, yes/no	58 (76.3)/18 (23.7)	28.8/14.6	0.001	31.1/14.6	0.007	15.4/5.0	0.007
Completion of AT, yes/no	40 (52.6)/36 (47.4)	36.7/16.6	<0.001	39.0/19.8	<0.001	18.2/5.6	<0.001
Stage IV	n=22						
AT, yes/no	17 (77.3)/5 (22.7)	18.3/9.1	0.145	18.3/9.1	0.324	5.7/3.0	0.724
Completion of AT, yes/no	8 (36.4)/14 (63.6)	23.3/14.7	0.021	23.3/14.7	0.029	7.2/5.5	0.353

Abbreviations: AJCC/UICC, American Joint Committee on Cancer and the Union for International Cancer Control; IPMC, intraductal papillary mucinous carcinoma; NAT, neoadjuvant therapy; AT, postoperative adjuvant therapy; NR, not reached.

A total of 303 patients (29.1%) completed the planned postoperative AT for 6 months, whereas 108 patients could not complete it due to adverse events, and 45 patients due to recurrence.

3.4 | Comparison of OS, DSS, and RFS between invasive IPMC patients with and without AT after surgery

In the 1143 patients with invasive IPMC without NAT, the DSS ($p<0.001$) and RFS ($p<0.001$) in patients receiving postoperative AT were worse than those in patients who did not receive this therapy, although the OS was not different (Table 2). The OS, DSS, and RFS were not different between patients undergoing surgery with and without completion of postoperative AT (Table 2). In the 666 patients with invasive IPMC on the PSM analysis, we found similar results to those on un-matched 1143 patients (Table 2).

Based on the AJCC/UICC stage, completion of postoperative AT could improve the OS, DSS, and RFS in patients with stage IIB and III invasive IPMC, although the introduction of postoperative AT could improve the OS, DSS, and RFS for patients with stage III invasive IPMC (Table 2). The PSM analysis also showed similar results (Table 2).

The completion of postoperative AT could improve the OS, DSS, and RFS for patients with invasive IPMC with elevated preoperative serum CA19-9 level (MST before PSM; OS: 69.0 vs. 45.7 months, $p=0.011$; DSS: 93.0 vs. 85.7 months, $p=0.027$; RFS: 46.9 vs. 25.2 months, $p=0.028$, MST after PSM; OS: 69.0 vs. 24.7 months, $p<0.001$; DSS: 93.0 vs. 41.9 months, $p<0.001$; RFS: 46.9 vs. 18.4 months, $p<0.001$; Figure 2A–C), lymphovascular invasion (MST before PSM; OS: 64.6 vs. 30.2 months, $p<0.001$; DSS: 71.5 vs. 41.3 months, $p=0.001$; RFS: 29.3 vs. 15.8 months, $p<0.001$, MST after PSM; OS: 64.6 vs. 27.2 months, $p<0.001$; DSS: 71.5 vs. 41.3 months, $p=0.001$; RFS: 29.3 vs. 14.5 months, $p<0.001$; Figure 2D–F), perineural invasion (MST before PSM; OS: 52.9 vs. 29.3 months, $p<0.001$; DSS: 64.8 vs. 34.3 months, $p=0.002$; RFS: 28.6 vs. 15.4 months, $p=0.001$, MST after PSM; OS: 52.9 vs. 25.5 months, $p<0.001$; DSS: 64.8 vs. 30.7 months, $p=0.001$; RFS: 28.6 vs. 11.3 months, $p<0.001$; Figure 2G–I), serosal invasion (MST before PSM; OS: 64.6 vs. 22.5 months, $p<0.001$; DSS: 64.6 vs. 22.5 months, $p<0.001$; RFS: 21.8 vs. 10.7 months, $p=0.001$, MST after PSM; OS: 64.6 vs. 18.3 months, $p<0.001$; DSS: 93.0 vs. 22.4 months, $p<0.001$; RFS: 21.8 vs. 7.2 months, $p<0.001$; Figure 2J–L), and lymph node metastasis (MST before PSM; OS: 46.1 vs. 20.5 months, $p<0.001$; DSS: 67.5 vs. 24.4 months, $p<0.001$; RFS: 21.7 vs. 9.4 months, $p<0.001$, MST after PSM; OS: 46.1 vs. 20.5 months, $p<0.001$; DSS: 67.5 vs. 23.0 months, $p<0.001$; RFS: 21.7 vs. 8.0 months, $p<0.001$; Figure 2M–O).

Regarding the postoperative AT regimen, of the 333 patients who completed postoperative AT, the OS, DSS, and RFS of those whose regimen was S-1 ($n=226$) were significantly better than those whose regimen was GEM ($n=97$) or GS ($n=10$) (MST of S-1, GEM, and GS; OS: 126.6, 64.8, and 43.3 months, respectively, $p=0.001$; DSS: 127.6, 83.5, and 43.4 months, respectively, $p=0.001$; RFS: not reached, 33.8, and 16.3 months, respectively, $p=0.001$; Figure 3).

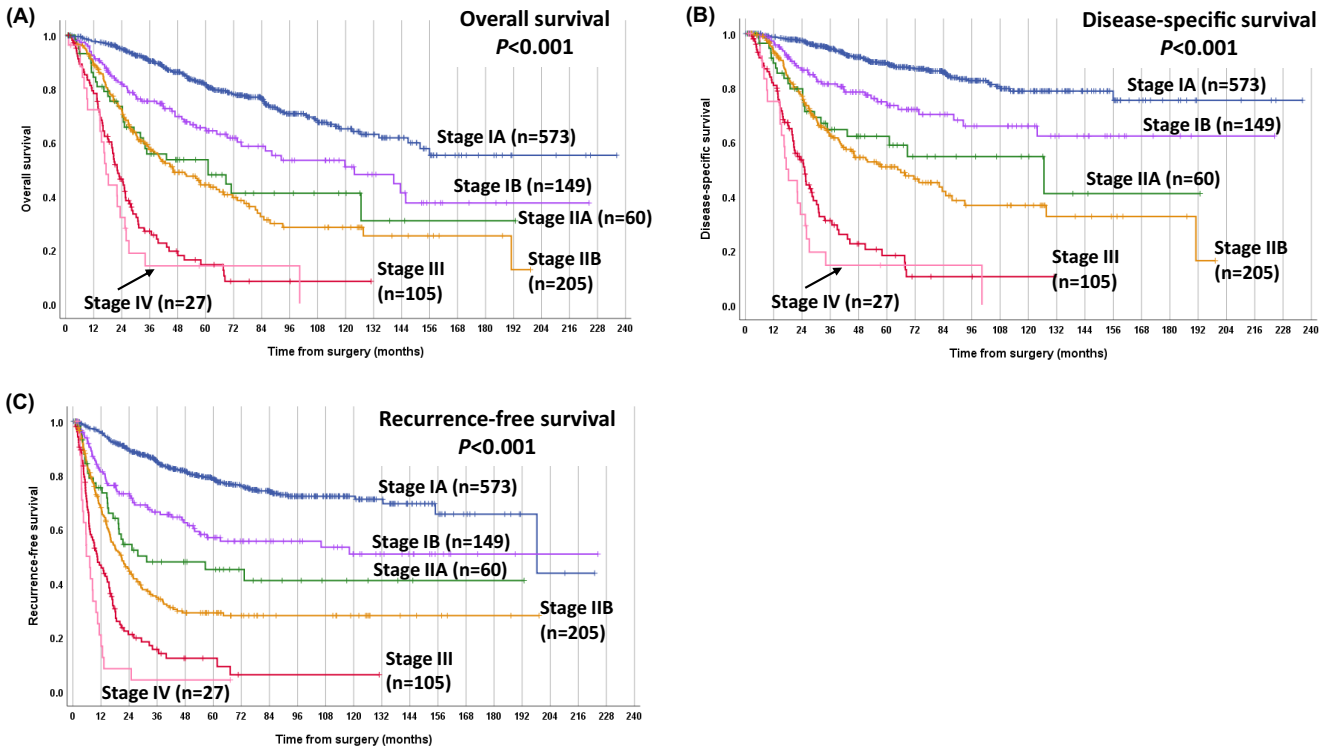

FIGURE 1 The overall survival (OS) ($p<0.001$), disease-specific survival (DSS) ($p<0.001$), and recurrence-free survival (RFS) ($p<0.001$) of invasive intraductal papillary mucinous carcinoma (IPMC) were significantly shortened as the AJCC/UICC stage advanced.

3.5 | Impact of NAT on the survival of patients with invasive IPMC

Forty patients with invasive IPMC received NAT before surgery. The rate of BR invasive IPMC was higher in patients with invasive IPMC receiving NAT than in those without NAT (60.0% vs. 4.0%; $p<0.001$). Patients with invasive IPMC receiving NAT before surgery more often received transfusion ($p=0.002$) and postoperative AT ($p=0.002$), and completion of postoperative AT ($p=0.005$). Pathologically, the incidences of perineural invasion ($p=0.005$), serosal invasion ($p=0.006$), and portal vein invasion ($p<0.001$) were higher in patients with invasive IPMC with NAT than in those without. When the survival of invasive IPMC patients who underwent surgical resection with and without NAT was compared, OS ($p=0.003$) and DSS ($p=0.006$) in invasive IPMC patients without NAT were better than those with NAT. The PSM analysis showed no significant differences of OS ($p=0.763$), DSS ($p=0.953$), and RFS ($p=0.327$) between the patients undergoing surgery for invasive IPMC with ($n=40$) and without NAT ($n=40$).

Of the 70 patients with BR invasive IPMC, 24 (34.3%) received NAT before surgery. There were no significant differences in the OS, DSS, and RFS between patients with invasive IPMC with and without NAT (MST; OS: 51.6 vs. 24.6 months, $p=0.108$; DSS: 51.6 vs. 25.2 months, $p=0.146$; and RFS: 24.2 vs. 13.9 months, $p=0.183$). However, in the 36 patients with BR invasive IPMC on the PSM analysis, we found that NAT could improve the OS (51.6 vs. 14.9 months, $p=0.001$; Figure 4A), DSS (51.6 vs. 14.9 months, $p=0.001$; Figure 4B), and RFS (24.2 vs. 5.3 months, $p=0.001$; Figure 4C).

3.6 | Pattern and treatment of postoperative recurrence in patients with invasive IPMC who underwent surgery

Postoperative recurrence was found in 484 patients (40.9%) at a median of 14.2 months, including remnant pancreatic recurrence in 94 patients (7.9%) and extra-pancreatic recurrence in 390 patients (33.0%). The 5- and 10-year cumulative incidences of remnant pancreatic recurrence were 10.0% and 15.8%, respectively, and those of extra-pancreatic recurrence were 32.8% and 49.1%, respectively. Of the 94 patients who developed remnant pancreatic recurrence, 27 developed metachronous PDAC and 67 developed recurrent IPMC in the remnant pancreas. A total of 390 patients with initial extra-pancreatic recurrence after surgery included only local recurrence in 104 patients (26.7%), only liver metastasis in 87 patients (22.3%), only lung metastasis in 71 patients (18.2%), only peritoneal dissemination in 59 patients (15.1%), only bone metastasis in two patients (0.5%), and multiple recurrences in 67 patients (17.2%).

Of the 484 patients who developed any recurrence after surgery for invasive IPMC, 365 received treatment for the recurrence including chemotherapy in 299 patients, surgical resection in 93 patients, and radiation therapy in 21 patients. The OS of patients who received any treatment for recurrence was significantly better than that of those who did not (MST; 40.6 vs. 22.4 months; $p<0.001$) (Figure 5A). In the 94 patients who developed remnant pancreatic recurrence, the OS of 63 patients who underwent surgical resection for the remnant pancreatic recurrence was significantly better than that of 31 patients who did not (MST; 153.6 vs. 69.9 months; $p<0.001$) (Figure 5B).

TABLE 3 Univariate and multivariate analyses of clinicopathological parameters for poor overall, disease-specific, and recurrence-free survival in 1143 patients with invasive IPMC without NAT.

Variable	Overall survival Univariate analysis *p*	Multivariate analysis *p*	HR (95% CI)	Disease-specific survival Univariate analysis *p*	Multivariate analysis *p*	HR (95% CI)	Recurrence-free survival Univariate analysis *p*	Multivariate analysis *p*	HR (95% CI)
Age, ≥70 years	0.001	0.001	1.42 (1.15-1.76)	0.002	0.031	1.32 (1.03-1.71)	0.025	0.491	
Sex, male	0.778			0.402			0.113		
Preoperative symptom	0.031	0.503		0.001	0.103		0.002	0.511	
Preoperative jaundice	<0.001	0.982		<0.001	0.722		<0.001	0.117	
Diabetes mellites	<0.001	0.013	1.30 (1.06-1.59)	0.010	0.083		0.024	0.167	
Morphological type									
Branch	0.005	0.553		0.002	0.253		0.006	0.593	
Mixed									
Main									
Serum CEA, elevated	<0.001	<0.001	1.45 (1.16-1.82)	0.001	0.057		<0.001	0.037	1.27 (1.01-1.60)
Serum CA19-9, elevated	<0.001	0.049	1.25 (1.00-1.56)	<0.001	0.199		<0.001	0.126	
Resectability, BR	<0.001	0.003	1.86 (1.23-2.82)	<0.001	0.013	1.80 (1.13-2.87)	<0.001	0.030	1.59 (1.05-2.41)
Operation									
TP	0.297			0.369			0.212		
PD									
DP									
CP									
Transfusion	<0.001	<0.001	1.71 (1.35-2.16)	<0.001	0.002	1.56 (1.18-2.08)	<0.001	0.010	1.39 (1.08-1.78)
Pathological findings									
Invasive component, tubular	<0.001	<0.001	1.78 (1.38-2.29)	<0.001	<0.001	1.96 (1.43-2.70)	<0.001	<0.001	1.56 (1.23-1.98)
Lymphovascular invasion	<0.001	0.187		<0.001	0.041	1.46 (1.02-2.10)	<0.001	0.004	1.53 (1.15-2.04)
Perineural invasion	<0.001	<0.001	1.57 (1.22-2.02)	<0.001	<0.001	1.89 (1.40-2.51)	<0.001	0.002	1.50 (1.16-1.92)
Bile duct invasion	<0.001	0.088		<0.001	0.821		<0.001	0.968	
Duodenal invasion	<0.001	0.764		<0.001	0.796		<0.001	0.415	
Serosal invasion	<0.001	<0.001	1.78 (1.40-2.28)	<0.001	<0.001	1.80 (1.37-2.37)	<0.001	<0.001	1.82 (1.45-2.28)
Retropancreatic tissue invasion	<0.001	0.856		<0.001	0.238		<0.001	0.381	
Portal vein invasion	<0.001	0.173		<0.001	0.182		<0.001	0.034	1.43 (1.03-2.00)
Arterial invasion	0.022	0.265		0.017	0.127		0.005	0.100	
Extra-pancreatic nerve plexus invasion	<0.001	0.296		<0.001	0.145		<0.001	0.407	
Other organ invasion	<0.001	0.425		<0.001	0.659		0.002	0.973	
Residual tumor status, R1	<0.001	0.001	1.71 (1.26-2.32)	<0.001	<0.001	1.81 (1.29-2.53)	<0.001	<0.001	1.86 (1.38-2.49)
Lymph node metastasis	<0.001	<0.001	1.97 (1.56-2.46)	<0.001	<0.001	2.38 (1.80-3.16)	<0.001	<0.001	2.29 (1.82-2.90)
Era of surgery, 1996-2008	0.016	0.234		0.034	0.439		0.299		
Introduction of AT	0.102			<0.001	0.892		<0.001	0.837	
Completion of AT	0.555			0.105			0.054		

Abbreviations: AT, adjuvant therapy; BR, borderline rese; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; IPMC, intraductal papillary mucinous carcinoma; NAT, neoadjuvant therapy.

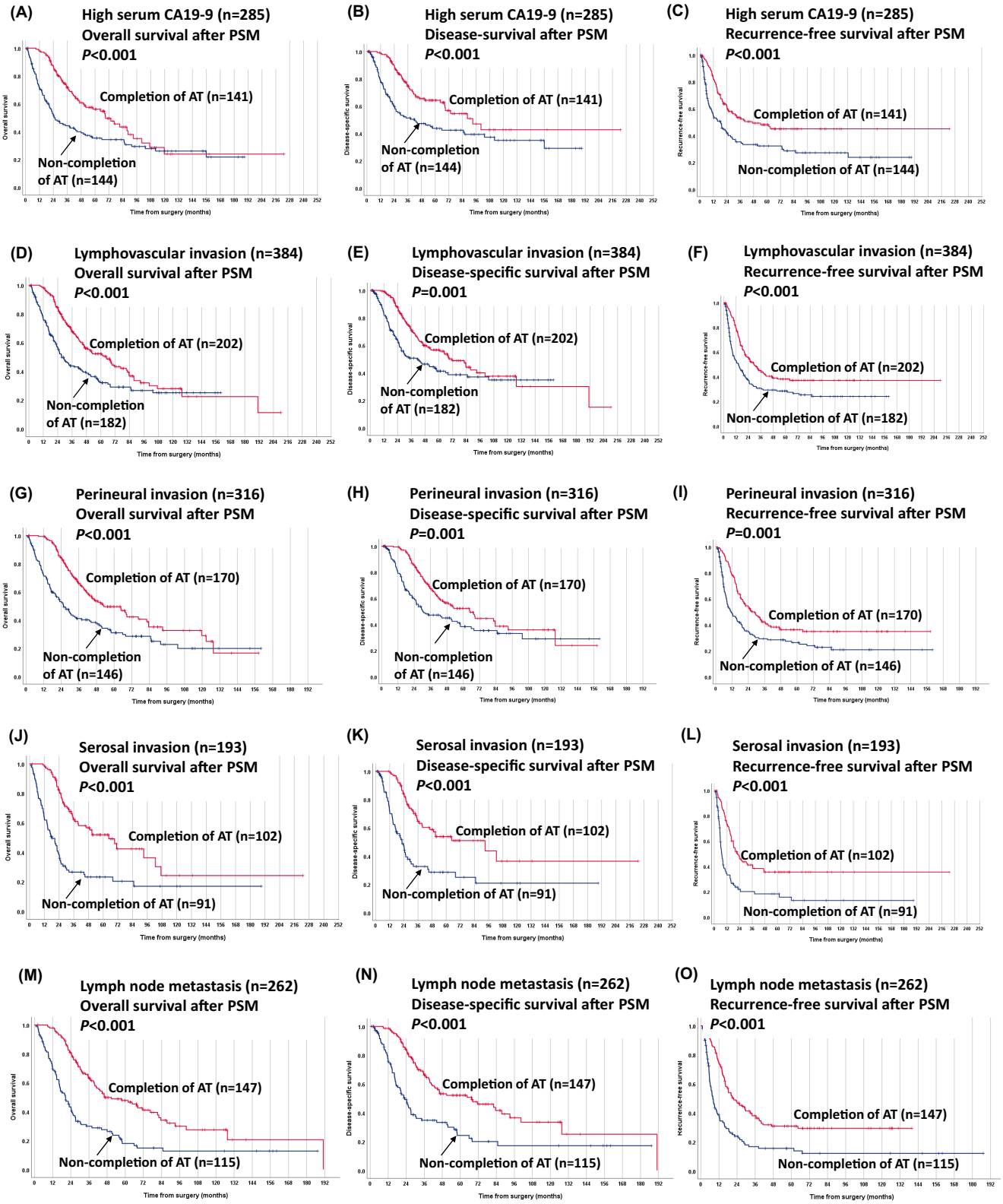

FIGURE 2 Completion of the planned postoperative adjuvant therapy (AT) for 6 months could prolong the OS, DSS, and RFS for patients with invasive IPMC with high preoperative carbohydrate antigen 19–9 level (A–C), lymphovascular invasion (D–F), perineural invasion (G–I), serosal invasion (J–L), and lymph node metastasis (M-O).

4 | DISCUSSION

This was one of the largest cohort studies of patients with invasive IPMC who underwent curative resection. First, we assessed the applicability of the 8th edition of the AJCC/UICC TNM staging system for invasive IPMC. In most previous reports investigating the applicability of the staging system for invasive IPMC, it was unclear how to measure the tumor size, which could cause a lack of

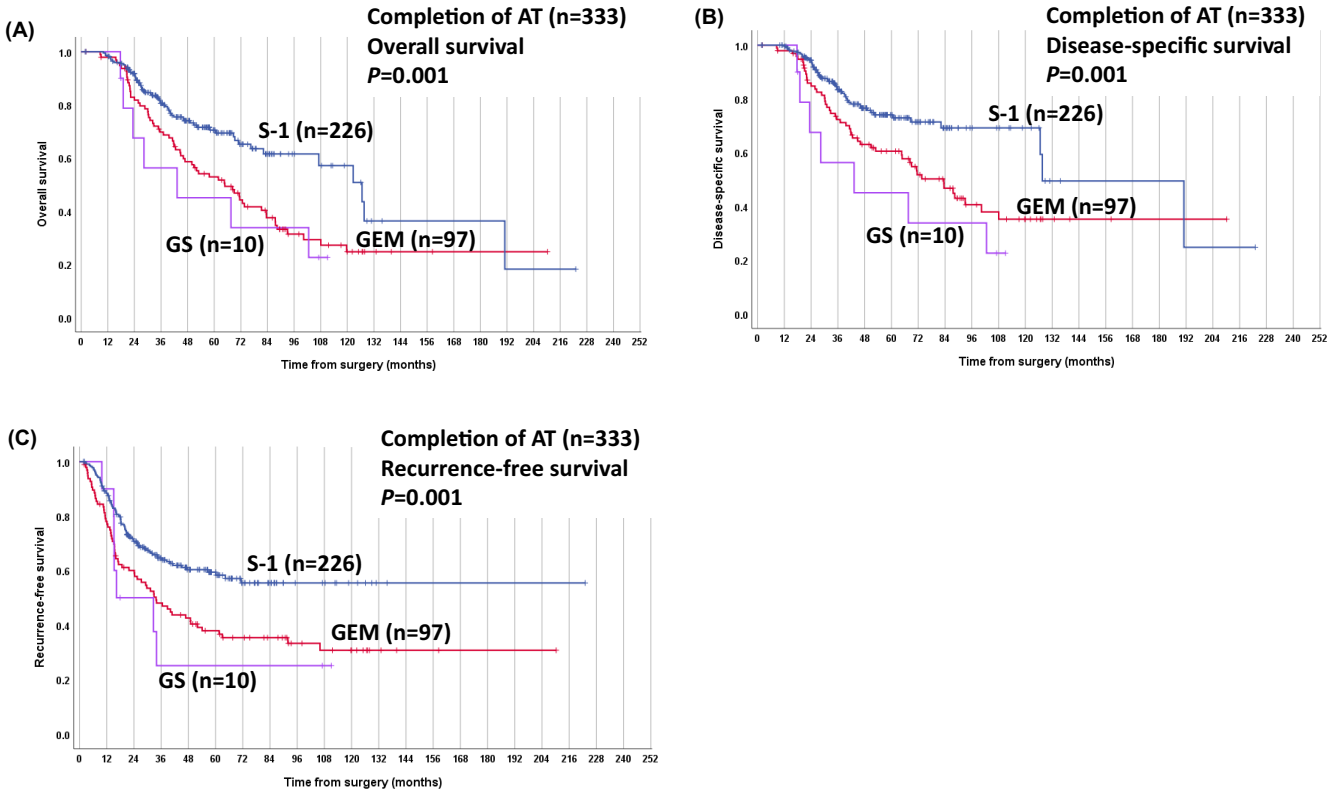

FIGURE 3 Of the 333 patients who completed the postoperative AT, the OS ($p=0.001$), DSS ($p=0.001$), and RFS ($p=0.001$) of those whose regimen was S-1 monotherapy ($n=226$) were significantly better than those whose regimen was gemcitabine (GEM) monotherapy ($n=97$) or combination therapy with GEM and S-1 (GS) ($n=10$).

coherence of T stage on 8th edition of AJCC/UICC staging system, possibly leading to unreliable conclusions. Margonis et al.[22] reported that this TNM staging system was only moderately accurate in predicting OS in 275 patients with invasive IPMC, whereas Kaiser et al.[9] reported that it could classify OS well in 424 patients. In this study, the 8th edition of the AJCC/UICC TNM staging system, from which T stage is determined by invasive length without the noninvasive IPMN region, provided a reliable prognostic classification for 1143 patients with resected invasive IPMC without NAT. Our results indicate that this staging system is useful for the prediction of survival for invasive IPMC, similar to conventional PDAC.

Previous studies assessing the effectiveness of postoperative AT for invasive IPMC based on National Cancer Data Base have demonstrated that patients with invasive IPMC with advanced stage invasive IPMC benefit from postoperative AT.[10,11] These databases did not clarify how to determine T stage depending on tumor size, only evaluated the impact of AT introduction on prognosis, and did not focus on the duration of AT. When we defined the completion of postoperative AT as receiving the planned AT for 6 months, completion of postoperative AT improved OS, DSS, and RFS for the invasive IPMC patients with stage IIB and III, elevated preoperative serum CA19-9 level, lymphovascular invasion, perineural invasion, serosal invasion, and lymph node metastasis. Our results indicate that completion of postoperative AT might benefit selected invasive IPMC patients, including those with high-risk of poor survival, whereas it will not benefit patients with early-stage invasive IPMC. However, in this study, the frequency of completion of postoperative AT by patients with early-stage invasive IPMC and/or poor condition was lower than in those without, which may have caused huge bias. Therefore, a future large-scale prospective study is required to establish the role of AT after surgery for invasive IPMC.

When we assessed the impact of postoperative AT regimen on survival, we found that S-1 was superior to GEM or GS for improvement of OS, DSS, and RFS. This result might be similar to that of the JASPAC01 trial, which is a randomized controlled trial (RCT) that compared survival between postoperative AT using S-1 vs. GEM for conventional PDAC.[23] A possible reason to explain the survival advantage of S-1 might be good toleration for S-1 compared to GEM or GS. However, in this study, of 333 patients who received completion of postoperative AT, the rate of reduction of the dose required due to side effects was not different between in the use of S-1 (19.9%), GEM (19.6%), and GS (50.0%) ($p=0.068$). Therefore, the superior toleration for S-1 to that for GEM or GS was not proved in this study, and the reason to explain the survival advantage of S-1 is unclear. A prospective study is essential to confirm which regimen, including multi-agent chemotherapy regimens, is most useful to prolong the survival of patients with invasive IPMC.

There have been few reports about the impact of NAT on the survival of patients with invasive IPMC. BR-PDAC defined as radiologic invasion to major vessels has aggressive malignant potential and is associated with a high risk of positive surgical margins even after extended dissection of nerve plexus and lymph nodes and vessel

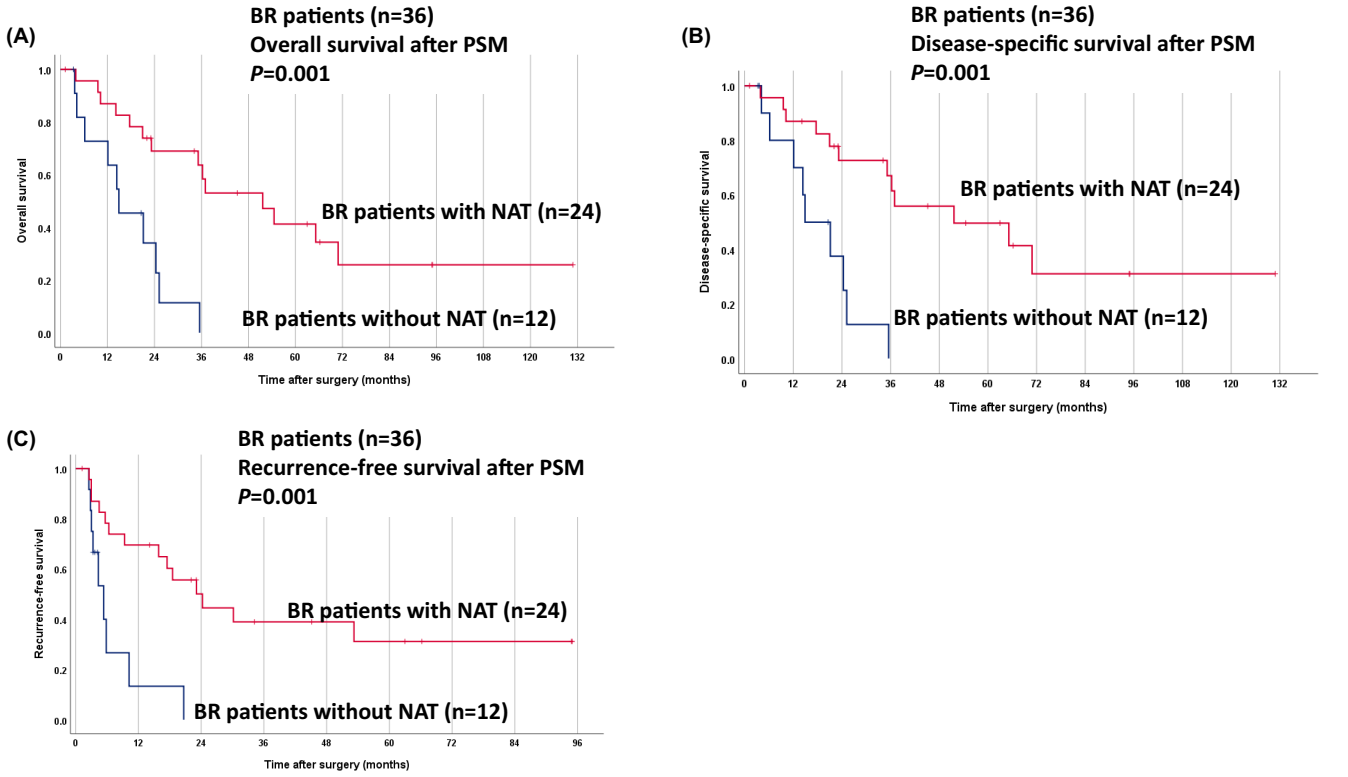

FIGURE 4 Of the 70 patients with borderline resectable (BR) invasive IPMC, (A) the OS ($p=0.027$) and (B) DSS ($p=0.040$) of the 14 patients who received neoadjuvant therapy (NAT) followed by surgery and completion of postoperative AT were significantly better than the other 56 patients with BR invasive IPMC, although the difference in (C) RFS between them did not reach statistical significance ($p=0.088$).

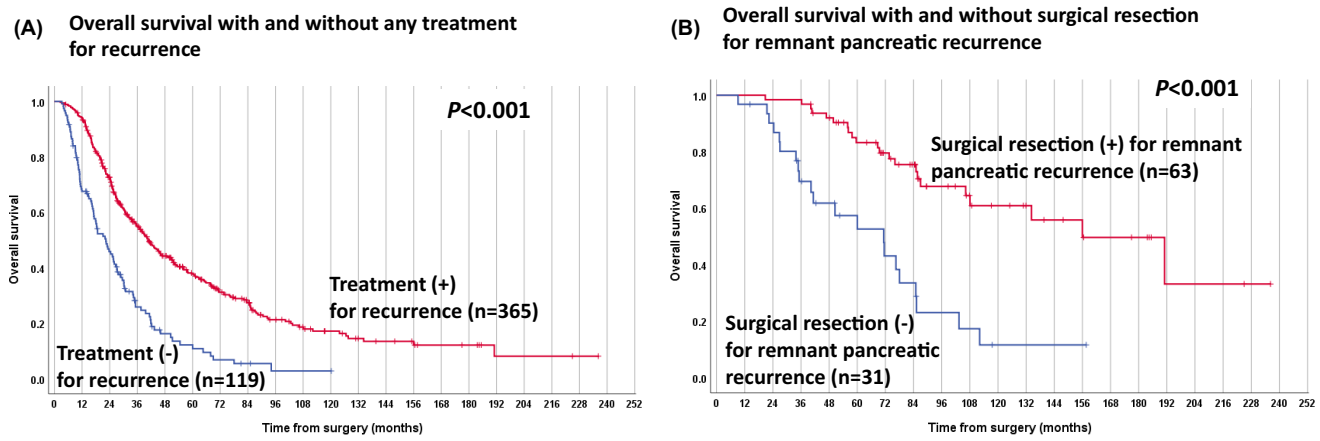

FIGURE 5 (A) Of the 484 patients who developed any recurrence after surgery for invasive IPMC, the OS of 365 patients receiving any treatment for the recurrence was significantly better than that of those who did not ($p<0.001$). (B) In the 94 patients who developed remnant pancreatic recurrence, the OS of 63 patients who underwent surgical resection for remnant pancreatic recurrence was significantly better than that of the 31 patients who did not ($p<0.001$).

resection, and the presence of occult distant metastasis.[24] NAT might lead to systemic treatment for undetected micrometastasis, R0 resection rate increment, and optimal selection of patients for surgery. Several studies showed that NAT followed by surgery could improve the survival of patients with BR-PDAC, compared to up-front surgery.[25–28] In the current study, we found that NAT followed by surgery might improve the survival of patients with BR-invasive IPMC by the PSM analysis. However, additional studies are essential to confirm our findings.

In this study, the postoperative recurrence in 40.9% of 1183 patients with invasive IPMC, including extra-pancreatic recurrence in 33.0% and remnant pancreatic recurrence in 7.9%, which were similar to those of previous reports.[10,29] Winter et al.[21] showed 24% of postoperative recurrences even in patients with T1 (invasive

length ≤ 20 mm) invasive IPMC. Furthermore, we also found that any treatment for recurrent diseases, especially surgical resection for remnant pancreatic recurrence, could improve survival. Our results suggest that the same close surveillance after surgery as that of conventional PDAC might be necessary for invasive IPMC, to detect the recurrence early and offer patients a chance for treatments.

This study had several limitations. As it was a multi-institutional retrospective study from 40 different academic institutes, our findings are subject to selection bias, particularly with respect to operative variations between surgeons and institutional characteristics, and to surveillance protocol after surgery. Moreover, the cohort who received AT after surgery for invasive IPMC more often had advanced stage disease. Such bias might limit the validity of the study's findings, although we performed the PSM analyses to reduce potential sources of bias.

In conclusion, when we defined tumor size as the length of invasive component separately from noninvasive IPMN region, the 8th edition of AJCC/UICC TNM staging system was applicable as a prognostic predictor for invasive IPMC patients. This study found that completion of postoperative AT for 6 months after surgery might prolong survival of patients with stage IIB and III invasive IPMC, elevated preoperative CA19-9 level, lymphovascular invasion, perineural invasion, serosal invasion, and lymph node metastasis. In addition, our results indicate that systemic treatment by AT in addition to local treatment by surgical resection are necessary for these aggressive tumors. NAT followed by surgery might improve the survival of patients with BR invasive IPMC. Finally, any treatment for recurrence after surgery for invasive IPMC, especially surgical resection for remnant pancreatic recurrence, might improve survival. However, our study is limited by its retrospective nature; thus, prospective studies are needed to confirm our findings.

AUTHOR CONTRIBUTIONS

Conceptualization, design, and methodology: SH Acquisition of data: SH, RH, GH, SN, ME, NG, HT, MU, TS, MO, YS, IM, TK, HI, DH, YS, HN, KH, SH, YN, SM, HT, KS, HS, TA, YK, TR, MN, IE, YS, AH, TH, HA, TU, TI, KH, SS, KO, HM, FM, YF, and ST. Analysis and interpretation of data: SH, AY, and HY. Writing, review, and/or revision of the manuscript: SH, RH, GH, SN, ME, NG, HT, MU, TS, MO, YS, IM, TK, HI, DH, YS, HN, KH, SH, YN, SM, HT, KS, HS, TA, YK, TR, MN, IE, YS, AH, TH, HA, TU, TI, KH, SS, KO, HM, FM, YF, ST, AY, YT, KO, SS, and HY. Study supervision: SH, AY, and HY.

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Approval of the research protocol: This study was approved by the institutional review board of each participating institution prior to initiation of the study.
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