Comparative Study - Retrospective Cohort

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Impact of adjuvant therapy in patients with invasive intraductal papillary mucinous neoplasms of the pancreas: an international multicenter cohort study

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Background: Adjuvant therapy prolongs survival in patients with pancreatic ductal adenocarcinoma. However, no clear guidelines are available regarding the oncologic effects of adjuvant therapy (AT) in resected invasive intraductal papillary mucinous neoplasms (IPMN). The aim was to investigate the potential role of AT in patients with resected invasive IPMN.

Materials and methods: From 2001 to 2020, 332 patients with invasive pancreatic IPMN were retrospectively reviewed in 15 centres in eight countries. Propensity score-matched and stage-matched survival analyses were conducted.

Results: A total of 289 patients were enroled in the study after exclusion (neoadjuvant therapy, unresectable disease, uncertain AT status, and stage IV). A total of 170 patients were enroled in a 1:1 propensity score-matched analysis according to the covariates. In the overall cohort, disease-free survival was significantly better in the surgery alone group than in the AT group ($P = 0.003$), but overall survival (OS) was not ($P = 0.579$). There were no significant differences in OS in the stage-matched analysis between the surgery alone and AT groups (stage I, $P = 0.402$; stage II, $P = 0.179$). AT did not show a survival benefit in the subgroup analysis according to nodal metastasis (N0, $P = 0.481$; N+, $P = 0.705$). In multivariate analysis, node metastasis (hazard ratio, 4.083; 95% CI, 2.408 – 6.772, $P < 0.001$), and cancer antigen 19-9 greater than or equal to 100 (hazard ratio, 2.058; 95% CI, 1.247 – 3.395, $P = 0.005$) were identified as adverse prognostic factors in resected invasive IPMN.

Conclusion: The current AT strategy may not be recommended to be performed with resected invasive IPMN in stage I and II groups, unlike pancreatic ductal adenocarcinoma. Further investigations of the potential role of AT in invasive IPMN are recommended.

Keyword: adjuvant therapy, invasive IPMN, multicenter study, pancreas cancer, pancreatic IPMN

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Introduction

The prevalence of intraductal papillary mucinous neoplasm (IPMN) of the pancreas is continuously increasing due to advances in cross-sectional imaging[1,2]. IPMN of the pancreas is a mucin-producing neoplasm derived from the ductal system of the pancreatic gland and has a broad spectrum from low-grade dysplasia to invasive carcinoma. Among them, high-grade dysplasia and invasive IPMN are considered malignant diseases, and surgical resection with a clear margin is the best treatment option.

The International Association of Pancreatology Sendai guidelines in 2006[3], Fukuoka guidelines in 2012[4], and revised Fukuoka guidelines in 2017[5] have continuously evolved and attempted to define the appropriate indications for surgical resection. In particular, the prediction of IPMN with malignant potential and the development of risk prediction models in patients with branch duct–IPMN (BD-IPMN) are actively being conducted[6,7].

The incidence of invasive IPMN is ~23%, according to American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) data, and is associated with a poor prognosis compared to other types of IPMN[8]. For invasive IPMN, surgical treatment, and adjuvant therapy (AT) are offered and are treated similarly to pancreatic ductal adenocarcinoma (PDAC). Although the molecular alterations specific to invasive IPMN are poorly understood, evidence has shown that the genetic backgrounds of IPMN and PDAC are different[9,10]. When comparing survival between invasive IPMN and PDAC, the course of invasive IPMN is more indolent than PDAC, based on an optimized stage-to-stage comparison[11]. AT has been shown to be beneficial in prolonging survival for PDAC[12]. However, data on the utility of invasive IPMN are limited. Several smaller clinical studies have attempted to address this question, but it is challenging to secure a sufficient number of patients considering the lower prevalence of the disease[13–18]. Therefore, this study aimed to investigate the potential role of AT in improving overall survival (OS) in patients with resected invasive IPMN through an international multicenter study.

HIGHLIGHTS

- The role of adjuvant therapy in resected invasive intraductal papillary mucinous neoplasm remains unclear.
- The adjuvant therapy did not show a survival advantage in the stage I and II group.
- It's time to reassess the postoperative adjuvant therapy strategy for invasive intraductal papillary mucinous neoplasm.

Materials and methods

Database and patient selection

This study included 332 patients who underwent surgical resection for invasive IPMN in 15 institutions in eight countries: South Korea (four centres), Japan (four centres), England (one centre), Taiwan (two centres), the United States (one centre), Singapore (one centre), Germany (one centre), and Mongolia (one centre) between January 2001 and December 2020. After excluding patients with unresectable stage IV disease, neoadjuvant therapy, and uncertain AT status, propensity score-matched (PSM) analysis was adopted in the remaining 289 patients to reduce the bias from several confounding factors (Fig. 1). This study included data on demographic, clinicopathological, and oncologic information such as age, sex, levels of cancer antigen 19-9 (CA 19-9), and stage based on the American Joint Committee on Cancer (AJCC) staging guidelines, 8th edition. All data were collected and analyzed at the Department of Surgery, Yonsei University College of Medicine, Korea. This study was approved by the Institutional Review Board of the Yonsei University College of Medicine (registration date: December 20, 2020; registration number:4-2020-1243). In addition, this study was registered at Clinical Research information Service (UIN: KCT0008256) in accordance with the World Medical Association's Declaration of Helsinki, 2013. This retrospective study has been reported in line with the STROCSS criteria[19]. Supplemental Digital Content 1, http://links.lww.com/JS9/A688.

Statistical analysis

All statistical analyses were performed using SPSS software (version 25.0; SPSS Inc.). Continuous variables are expressed as mean ± SD or range, and categorical variables are expressed as frequencies and percentages. Student's *t*-test was performed to compare continuous variables, and the χ^2 test and Fisher's exact test were performed to compare categorical data. The Kaplan–Meier method was used for disease-free survival (DFS) and OS analyses. Cox proportional hazards analysis was performed to estimate prognostic factors for OS throughout the population. The propensity score was generated by binary logistic regression, and patients with similar propensity scores were selected from the surgery alone (SA) and AT groups (1:1 matching) to reduce bias in patient distribution [covariate: R status, stage, lymphovascular invasion (LVI), and perineural invasion (PNI)]. Statistical significance was set at P less than 0.05.

Results

Clinicopathological characteristics

The demographic and tumour characteristics of 289 patients with invasive IPMN are presented in Table 1. Among them, 157

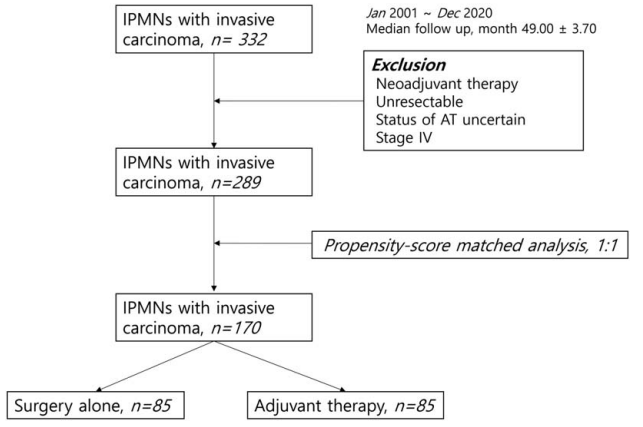

Figure 1. Study flow diagram. IPMNS, intraductal papillary mucinous neoplasm.

Table 1

Characteristics of patients who received adjuvant therapy vs. those who underwent surgery alone in the overall cohort after the PSM analysis.

	Total population			PSM		
	Surgery alone ($n=132$)	Adjuvant chemotherapy ($n=157$)	*P* value	Surgery alone ($n=85$)	Adjuvant chemotherapy ($n=85$)	*P*
Age	70.3 ± 9.9	67.2 ± 9.8	0.008	72.8 ± 9.0	66.6 ± 10.2	< 0.001
Sex, *n* (%)			0.043			0.539
Male	73 (55.3)	67 (42.7)		43 (50.6)	38 (44.7)	
Female	59 (44.7)	90 (57.3)		42 (49.4)	47 (55.3)	
BMI	23.2 ± 4.1	24.3 ± 4.6	0.038	23.2 ± 4.1	24.7 ± 5.0	0.035
Tumour location, *n* (%)			0.238			0.154
Head	92 (70.2)	92 (59.0)		58 (68.2)	42 (50.0)	
Head + body	0	3 (1.9)		0	3 (3.6)	
Body	14 (10.7)	28 (17.9)		11 (12.9)	18 (21.4)	
Tail	13 (9.9)	17 (10.9)		7 (8.2)	8 (9.5)	
Body + tail	9 (6.9)	11 (7.1)		7 (8.2)	10 (11.9)	
Entire pancreas	3 (2.3)	5 (3.2)		2 (2.4)	3 (3.6)	
Operative method, *n* (%)			0.260			0.097
PD/PPPD	87 (65.9)	89 (56.7)		53 (62.4)	39 (45.9)	
Distal pancreatectomy	30 (22.7)	43 (27.4)		20 (23.5)	28 (32.9)	
Total pancreatectomy	15 (11.4)	25 (15.9)		12 (14.1)	18 (21.2)	
Type of surgery, *n* (%)			0.018			0.091
Open	80 (60.6)	107 (68.2)		57 (67.1)	56 (65.9)	
Laparoscopic	35 (26.5)	44 (28.0)		17 (20.0)	25 (29.4)	
Robotic	17 (12.9)	6 (3.8)		11 (12.9)	4 (4.7)	
Morphologic type, *n* (%)			0.001			0.181
Branch	34 (26.4)	28 (18.8)		16 (19.5)	13 (16.0)	
Main	51 (39.5)	93 (62.4)		38 (46.3)	49 (60.5)	
Mixed	44 (34.1)	28 (18.8)		28 (34.1)	19 (23.5)	
Tumour size	5.4 ± 7.9	6.0 ± 13.1	0.633	5.4 ± 8.0	6.3 ± 15.3	0.639
N stage, *n* (%)			< 0.001			0.589
N0	108 (81.8)	75 (47.8)		61 (71.8)	55 (64.7)	
N1	21 (15.9)	75 (47.8)		21 (24.7)	27 (31.8)	
N2	3 (2.3)	7 (4.5)		3 (3.5)	3 (3.5)	
Stage, *n* (%)			< 0.001			0.758
IA	61 (46.2)	23 (14.6)		22 (25.9)	22 (25.9)	
IB	21 (15.9)	24 (15.3)		13 (15.3)	12 (14.1)	
IIA	23 (17.4)	27 (17.2)		23 (27.1)	21 (24.7)	
IIB	21 (15.9)	74 (47.1)		21 (24.7)	27 (31.8)	
III	6 (4.5)	9 (5.7)		6 (7.1)	3 (3.5)	
CA 19-9	1492.4 ± 11655.7	473.8 ± 1804.7	0.356	2327.0 ± 14600.3	276.0 ± 1244.7	0.236
LVI, *n* (%)	27 (21.8)	57 (37.3)	0.008	26 (32.1)	15 (18.5)	0.071
PNI, *n* (%)	37 (30.1)	98 (64.1)	< 0.001	37 (45.7)	34 (42.0)	0.751
LNR	0.0 ± 0.1	0.2 ± 0.3	< 0.001	0.1 ± 0.1	0.2 ± 0.4	0.036
R status, *n* (%)			0.01			0.095
R0	116 (87.9)	125 (79.6)		74 (87.1)	71 (83.5)	
R1	13 (9.8)	32 (20.4)		8 (9.4)	14 (16.5)	
R2	3 (2.3)	0		3 (3.5)	0	
Recurrence, *n* (%)	21 (16.4)	87 (56.5)	< 0.001	17 (20.5)	44 (53.0)	< 0.001

CA 19-9, cancer antigen 19-9; LNR, lymph node ratio; LVI, lymphovascular invasion; PD, pancreaticoduodenectomy; PNI, perineural invasion; PPPD, pylorus-preserving pancreaticoduodenectomy; PSM, propensity score-matched.

(54.3%) were in the AT group. Patients who received AT were significantly younger, with a mean age at diagnosis of 67.2 years vs. 70.3 years in the SA group. There were no differences in tumour location between the two groups, but for the morphological type, the type of the main duct showed a much higher incidence in the AT group ($P < 0.001$). Other differences were found between the two groups in terms of type of surgery ($P = 0.018$), N stage ($P < 0.001$), AJCC 8th stage ($P < 0.001$), LVI ($P = 0.008$), PNI ($P < 0.001$), and R status ($P = 0.01$). After the PSM analysis, there were no differences between the two groups, except for age and body mass index. The mean duration of follow-up was 36.34 months (SD = 33.47).

Patients were included in the AT group if they had received adjuvant chemotherapy. Gemcitabine-based ($n = 70$), 5-fluorouracil based ($n = 5$), titanium silicate (TS)-1 ($n = 8$), capecitabine ($n = 1$), and pembrolizumab ($n = 1$) were administered postoperatively as AT to those in the invasive IPMN group. Of these, three patients underwent radiation therapy for recurrence as a palliative aim. (Table 2).

Comparison of survival in the overall cohort

After adjusting for major confounders, we found no significant benefit of AT for OS but not in DFS. Patients who received AT

Table 2

Distribution of regimen of adjuvant chemotherapy.

Regimen	Total, $n=85$, n (%)
Gemcitabine-based	70 (82.35)
Fluorouracil based	5 (5.88)
TS-1	8 (9.41)
Capecitabine	1 (1.17)
Pembrolizumab	1 (1.17)

TS-1, titanium silicate-1.

had a 5-year OS rate of 56.5% compared with 60.3% in patients who underwent SA ($P=0.579$, Fig. 2B). The 5-year DFS rate in patients who received AT was 43.8% compared with 72.6% in patients who underwent SA ($P=0.003$, Fig. 2A).

Subgroup analysis

In the staged matched analysis of OS, no significant survival differences were found between the AT and SA groups according to the stage (stage I group, $P=0.402$, Fig. 3A; stage II group, $P=0.179$, Fig. 3B). In the comparison of OS according to lymph node (LN) metastasis, there were no differences in OS according to AT in the N0 and N+ groups (N0 group, $P=0.481$, Fig. 4A; N+group, $P=0.705$, Fig. 4B). A comparison of the clinicopathological characteristics between the SA and AT groups according to the nodal status is described in the Supplementary Table, Supplemental Digital Content 2, http://links.lww.com/JS9/A689.

Univariable and multivariable survival analysis for resected inv-IPMN

The association of OS with patient, tumour, and treatment variables was evaluated using univariate and multivariate analyses. Multiple factors, such as CA 19-9 greater than or equal to 100, AJCC stage, R status, LVI, PNI, and adjuvant chemotherapy, were associated with OS after the resection of invasive IPMN (Table 3). On multivariable analysis, CA 19-9 greater than or equal to 100 and LN metastasis were independently associated with an unfavourable prognosis. Based on the hazard ratio, LN metastasis was identified as the strongest predictor of survival in patients with resected invasive IPMN.

Discussion

This study aimed to investigate the potential role of AT in improving OS in patients with invasive IPMN through an international multicenter study. To this end, we collated a large retrospective cohort of patients who underwent pancreatic resection for invasive IPMN. In the PSM analysis, especially in stage I and II groups, we found that AT did not have a significant survival benefit in OS and DFS. Additionally, there were no significant survival benefits of AT in patients with node metastasis, regardless of stage. When the multivariable analysis was performed on the entire cohort without PSM analysis, the independent prognostic factors related to OS were CA 19-9 greater than or equal to 100 and LN metastasis.

The incidence of IPMN has increased with the development of cross-sectional imaging, and the rate of high-grade dysplasia or invasive IPMN has reached 23%[2,8]. As the prevalence increases, there have been developments in treatment strategies and guidelines, most predominantly focused on identifying patients before developing the malignant disease. Currently, there are no established guidelines for administering AT to patients who have undergone pancreatic resection for invasive IPMN. Therefore, most oncologists still adhere to the guidelines for PDAC treatment. Although the genetic background of invasive IPMN has not been clearly identified, it shows a more indolent pattern than that of PDAC[20,21]. Koh and colleagues compared the pathological characteristics of invasive IPMN and PDAC in a meta-analysis. The invasive IPMN group showed a lower rate of T3 or T4 tumours and a substantially lower rate of lymph node metastasis. In addition, they found that infiltration of surrounding tissues,

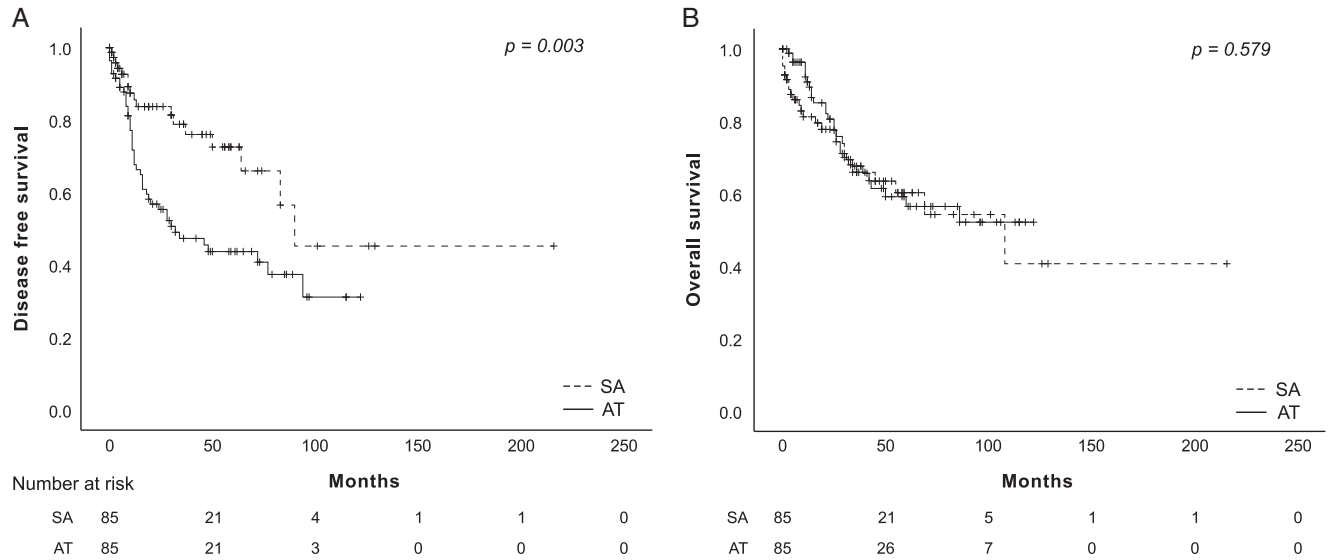

Figure 2. (A) Overall survival, overall cohort, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P=0.579$. (B) Disease-free survival, overall cohort, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P=0.003$. AT, adjuvant therapy; PSM, propensity score-matched; SA, surgery alone.

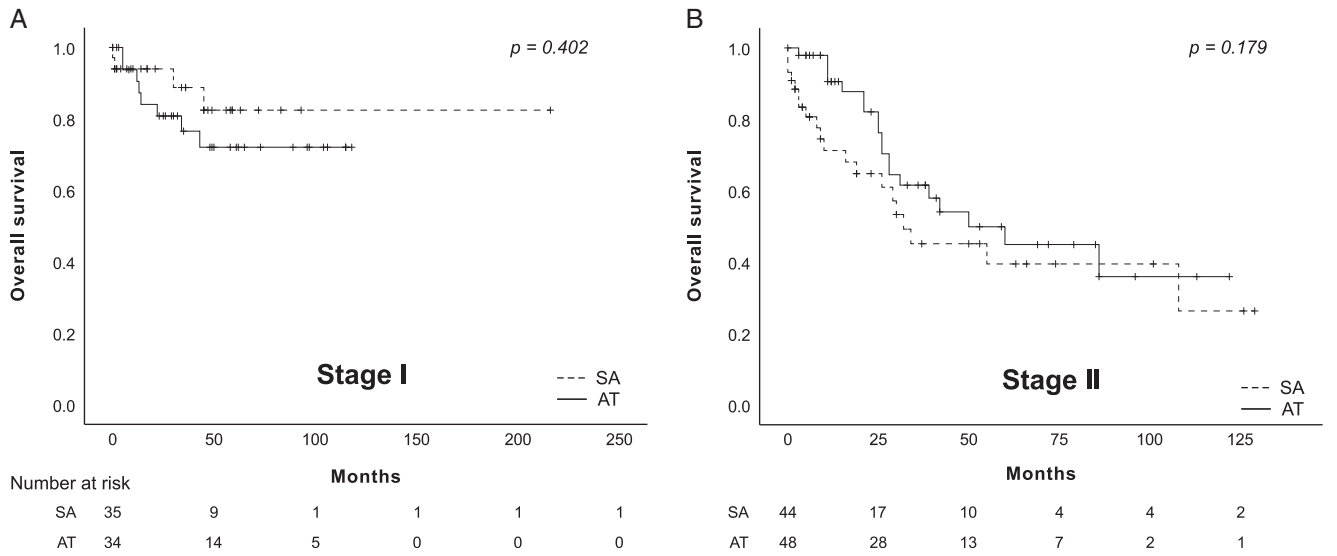

Figure 3. (A) Overall survival, stage I group, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P = 0.402$. (B) Overall survival, stage II group, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P = 0.179$. AT, adjuvant therapy; PSM, propensity score-matched; SA, surgery alone.

such as LVI or PNI, is relatively infrequent and is related to R status[22]. A recent meta-analysis also reported that invasive IPMN was associated with better tumour differentiation[23]. According to a recent study, in a stage-matched analysis of OS and DFS between invasive IPMN and PDAC, the invasive IPMN group showed a better survival rate in stage I and II groups[11]. Therefore, a different AT strategy from PDAC in invasive IPMN after pancreatic resection is urgently needed.

Looking at the results of previous studies, some groups claim survival benefits when AT is administered to the LN+ group, while others point out that the effects of AT are unclear (Table 4). Therefore, it can be explained that it is not appropriate to perform AT unconditionally in patients with resected invasive IPMN according to the PDAC guidelines. Invasive IPMN has a more indolent pattern than PDAC, and the evidence for its anticancer effect in the LN+ group is unclear. Moreover, the problem with recent studies is that there is no clear standard for selecting a therapeutic agent and implementing additional radiotherapy due to the absence of clear guidelines. In most cases, these studies were based on small-scale data. However, McMillan *et al.*[16] found a survival benefit of AT in stage II or higher, LN+ group, or poorly differentiated group in a study based on the National Cancer Database (NCDB). However, detailed information on AT was not provided. Furthermore, Mungo *et al.*[24] also reported a survival benefit in the LN+ group for 492 patients using NCDB, but there is also no detailed information about AT. This study

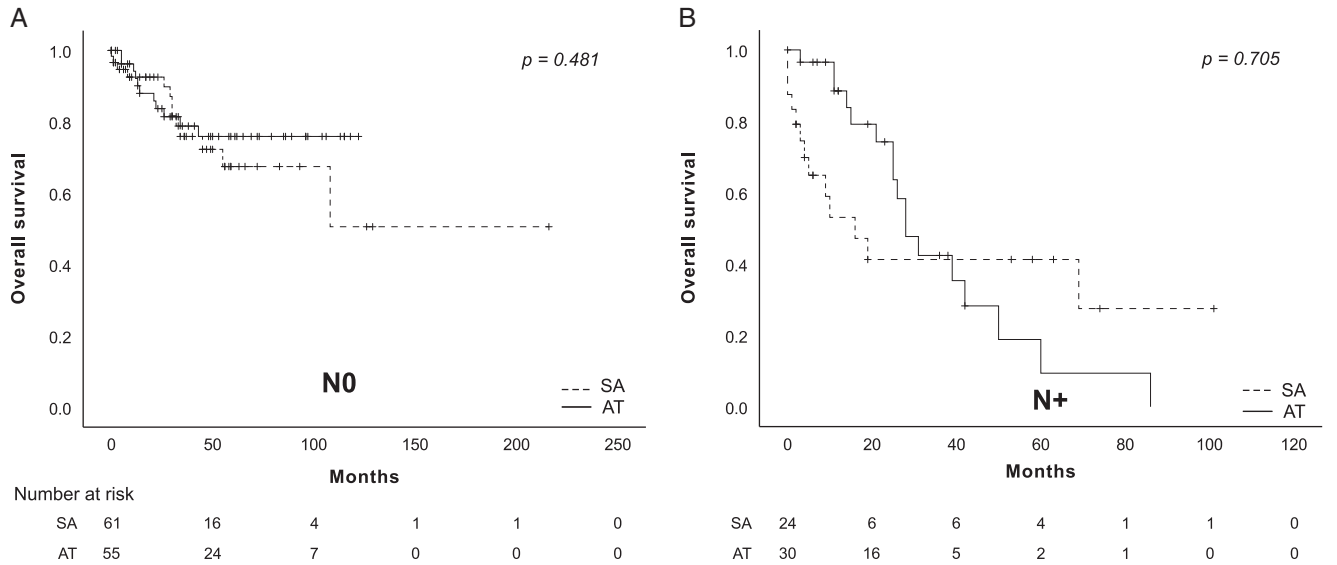

Figure 4. (A) Overall survival, N0 group, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P = 0.481$. (B) Overall survival, N+ group, after PSM analysis; surgery alone group vs. adjuvant therapy group, $P = 0.705$. AT, adjuvant therapy; PSM, propensity score-matched; SA, surgery alone.

Table 3

Multivariate analysis of clinicopathological factors influencing overall survival in invasive IPMN (before PSM).

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.022 (0.999 – 1.045)	0.057		
CA 19-9 ≥ 100	2.764 (1.727 – 4.424)	< 0.001	2.058 (1.247 – 3.395)	0.005
AJCC stage				
I	1.000			
II	4.395 (2.613 – 7.391)	< 0.001		
III	3.816 (1.509 – 9.648)	0.005		
N stage I/II	4.697 (3.049 – 7.236)	< 0.001	4.038 (2.408 – 6.772)	< 0.001
R1 or R2	1.836 (1.154 – 2.921)	0.010	1.630 (0.940 – 2.825)	0.082
LVI	1.612 (1.058 – 2.456)	0.026		
PNI	2.802 (1.804 – 4.352)	< 0.001		
Adjuvant therapy	1.573 (1.025 – 2.412)	0.038		

AJCC, American Joint Committee on Cancer; CA19-9, cancer antigen 19-9; HR, hazard ratio; IPMN, intraductal papillary mucinous neoplasm; LVI, lymphovascular invasion; PNI, perineural invasion; PSM, propensity score-matched.

attempted to derive convincing results by performing PSM analysis on 289 patients by recruiting the most significant number of cases among studies excluding NCDB data.

AT is performed regardless of stage in patients with PDAC according to current guidelines; however, in this study, it was found that AT was not beneficial in stage I, II, and N + groups in resected invasive IPMN. In the N + group in this study, there were no differences in stages between the SA and AT groups, and LVI showed a higher ratio in the AT group, but there were no differences in OS (Fig. 4A). In addition, the recurrence rate was significantly higher in the group that underwent AT in both the N0 and N + groups; therefore, the adverse effect of AT was also considered (Supplementary Table, Supplemental Digital Content 2, http://links.lww.com/JS9/A689). The initial hypothesis suggests that despite the similarity in conditions between the SA and AT groups, the patients who receive anticancer treatment in clinical practice are often more advanced in their illness, and this may not be adequately reflected in a retrospective study. Second, although there is no definitive evidence, the cause of the high recurrence rate observed in the group that received AT may be related to the increased risk of malignancy associated with both primary and secondary immunosuppression, as compared with the general population. AT exhibits both immunosuppressive and cancer-killing effects, and if it is not effective in destroying invasive IPMN, only the immunosuppressive effect remains, which could be contributing to the high recurrence rate after surgery. In addition, according to Shockley *et al*.[25], genetic and metabolic changes, along with other disruptions to the cellular microenvironment, including immune alterations and inflammation, can contribute to tumorigenesis. Furthermore, Roth *et al*.[26] have demonstrated that alterations in the microenvironment caused by immunosuppression are linked to the advancement of IPMN to an invasive form, which provides important insights for improving the effectiveness of immunotherapies in enhancing the body's natural antitumor immune response.

This study has several limitations. First, due to the retrospective nature of data collection and the absence of a

Table 4

Literature review reporting the effects of AT on resected invasive IPMN.

	Type of study	No. patients	Regimen of adjuvant therapy	Benefit from AT
Swartz *et al.* [13]	Retrospective	70 (SA vs. AT, 30 vs. 40)	5-FU, $n=40$ Additional radiotherapy, $n=40$	< OS > LN + group (RR = 0.43, $P=0.047$)
Caponi *et al.* [15]	Retrospective	64 (SA vs. AT, 31 vs. 33)	Gemcitabine, $n=23$ Additional radiotherapy, $n=10$	< DFS, OS > LN + group (7.5 vs. 16.5 months; $P=0.04$)
McMillan *et al.* [16]	Retrospective	1220 (SA vs. AT, 679 vs. 541)	No details	< OS > Stage II (30.42 vs. 22.83 months; $P=0.039$) Stage III/IV (17.41 vs. 11.40 months; $P<.0001$) LN + group (19.38 vs. 12.19 months, $P<0.001$) Poorly differentiated (15.51 vs. 9.56 months, $P=0.002$)
Marchegiani *et al.* [17]	Retrospective	102 (SA vs. AT, 83 vs. 19)	Gemcitabine, $n=15$ Gemcitabine + oxaliplatin, $n=2$ 5-FU + oxaliplatin, $n=2$ Additional radiotherapy, $n=5$	< DSS > LN + group (5-years-DSS 76 vs. 35.8%, $P=0.01$) Tubular carcinoma (5-years-DSS 88.9 vs. 53%, $P=0.03$)
Mungo *et al.* [24]	Retrospective	492 (SA vs. AT, 267 vs. 225)	NS	LN + group (HR, 0.05; 95% CI 0.32 – 0.79)
Turrini *et al.* [14]	Retrospective	98 (SA vs. AT, 61 vs. 37)	5-FU and/or Gemcitabine, $n=7$ Chemoradiation 45 Gy over 5 weeks, $n=30$	No benefit from adjuvant therapy
Rodrigues *et al.* [18]	Retrospective	103 (SA vs. AT, 69 vs. 34)	Gemcitabine, $n=34$ Gemcitabine-capecitabine, $n=2$ 5-FU, $n=2$ Additional radiotherapy, $n=19$	No benefit from adjuvant therapy
Choi *et al.* [11]	Retrospective	67 (SA vs. AT, 38 vs. 25) External validation 34 (SA vs. AT, 24 vs. 10)	Gemcitabine, $n=16$ Gemcitabine-capecitabine $n=10$ 5-FU, $n=2$ Additional radiotherapy, $n=3$	No benefit from adjuvant therapy

AT, adjuvant therapy; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; IPMN, intraductal papillary mucinous neoplasm; OS, overall survival; RR, relative risk; SA, surgery alone.

standardized protocol for AT administration, it was difficult to confirm the exact number of cycles of AT drug administered. As a result, this factor could potentially confound the analysis of survival rates. Moreover, we attempted to obtain a substantial amount of retrospective data, which in turn led to a relatively lengthy observational period. Second, the proportion of patients with stage III or IV disease was low due to the characteristics of invasive IPMN; therefore, a subgroup analysis of the usefulness of AT could not be performed at the corresponding stage. Third, invasive IPMN is a heterogeneous disease with three histological types: colloid, tubular, and oncocytic. Survival analysis could not be performed by dividing into tubular type, which is known to be relatively similar to PDAC and has a poor prognosis, and colloid and oncocytic types, which are known to have a relatively good prognosis, are considered an essential limitation of this study.

In conclusion, AT may not be recommended to be performed in stage I and II groups, unlike PDAC in this retrospective international multicenter study. However, insufficient research on the appropriate therapeutic agents for invasive IPMN is also considered to have contributed to these results. Going forward, it is imperative to conduct a randomized controlled trial of FOLFIRINOX on resected invasive IPMN based on the consensus reached in this study. Alternatively, efforts can be made to identify new target drugs and explore the feasibility of conducting clinical trials for them. Therefore, more studies based on larger study populations, such as well-designed nationwide multicenter collaborative randomized controlled trial, are warranted to validate the present observations and investigate the potential effect of AT on resected invasive IPMN.

Ethical approval

This study was approved by the Institutional Review Board of the Yonsei University College of Medicine (registration date: December 20, 2020; registration number:4-2020-1243).

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Author contribution

Conceptualization, Pejman Radkani and Chang Moo Kang; Investigation, Joon Seong Park, Hyung Sun Kim, Sung Hoon Choi, Jin Ho Lee, Jae Uk Chong, Yuichi Nagakawa, Byoung UK Park, Emily Winslow, Thomas Fishbein, Jason Hawksworth and Keita Wada; Methodology, Yoshiharu Nakamura, Hiroki Sunagawa, Bobby VM Dasari, Cheng-Ming Peng, Lee Lip Seng, Heiner Wolters and Unenbat Gurbadam, Resources, Hyung Sun Kim, Sung Hoon Choi, Yuichi Nagakawa, Keita Wada, Yoshiharu Nakamura, Hiroki Sunagawa, Bobby VM Dasari, Cheng-Ming Peng, Lee Lip Seng, Heiner Wolters, Unenbat Gurbadam, Munseok Choi and Shin-E Wang; Supervision, Pejman Radkani and Chang Moo Kang; Writing – original draft, Munseok Choi and Shin-E Wang; Writing – review & editing, Pejman Radkani and Chang Moo Kang. The author(s) read and approved the final manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinical Research information Service.
2. Unique Identifying number or registration ID: KCT0008256.
3. Hyperlink to the registration (must be publicly accessible): https://cris.nih.go.kr/cris/search/listDetail.do?searchWord=KCT0008256&search_yn=Y.

Guarantor

Chang Moo Kang.

Data statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

Provenance and peer review

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