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Original Article

Clinicopathological Analysis of 17 Surgically Resected Pulmonary Pleomorphic Carcinoma Cases

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Objectives: To determine the outcomes and prognostic factors associated with pulmonary resection of pulmonary pleomorphic carcinoma (PPC).
Methods: During 2008–2017, 17 patients underwent pulmonary resection for primary PPC at the Saitama Cancer Center, Japan. We investigated clinicopathological characteristics and outcomes of these cases. Overall survival (OS) and disease-free survival (DFS) rates were determined using Kaplan–Meier method and compared using log-rank test. Univariate analysis was performed to identify prognostic factors.
Results: The 5-year OS and DFS rates were 27.2% and 51.0%, respectively. The median follow-up period was 30.8±24.9 (3.6–92.8) months after pulmonary resections. Patients with disease-free interval (DFI) <1 year of resection had poorer prognosis than those without (p = 0.001). Patients with N2 status and adenocarcinoma components had significantly poorer disease-free prognosis than their counterparts (p = 0.021 and p = 0.019, respectively). Univariate analysis revealed that DFI <1 year was an unfavorable prognostic factor for OS (p = 0.005); N2 pathological status and presence of adenocarcinoma components were unfavorable prognostic factors for DFS (p = 0.038 and p = 0.036, respectively).
Conclusion: PPC patients with an adenocarcinoma component and N2 pathological status may have an earlier relapse and poorer prognosis than their counterparts. Further assessment of cases may help clarify the predictors of PPC.

Keywords: pleomorphic carcinoma, lung cancer, prognostic factor

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Introduction

Pulmonary pleomorphic carcinoma (PPC) was first proposed as a distinct histological entity in the World Health Organization's (WHO) 1999 classification. It is defined as "a poorly differentiated non-small cell carcinoma (namely squamous cell carcinoma, adenocarcinoma, or large cell carcinoma), containing at least ≧10% spindle and/or giant cells or a carcinoma consisting of only spindle or giant cells."[1)] It was estimated that sarcomatoid carcinomas account for only 0.1%–0.4% of all lung cancers.[2)] Moreover, by definition, in small biopsy samples, sarcomatoid elements may be described, but their

definitive diagnosis as pleomorphic carcinoma may not be possible. Therefore, many previous cohort studies have not described PPC. The main characteristics of PPC that have been previously reported are as follows: it is predominantly found in men and in heavy smokers, and the tumor diameter is larger than that in other lung cancers[3]; the malignant potential is high; the metastasis tends to be more efficient than in other cancers; and the local invasion tendency is strong.[4] These features contribute to its poor prognosis.

In this retrospective study from a single institution, we reviewed clinicopathological features of 17 patients who underwent pulmonary resection for PPC and examined the outcomes and prognostic factors affecting the survival of these patients after pulmonary resection.

Materials and Methods

Patients

From January 2008 to December 2017, 1421 patients underwent pulmonary resection for primary lung cancer at the Saitama Cancer Center Hospital, of whom 17 who underwent pulmonary resection for primary PPC were included in the study. This study was approved by the institutional review board in July 2019 (approval number: 954).

All available clinical information such as age, sex, smoking history, Brinkman Index, and maximum standardized uptake value (SUV max) of whole-body scan using 2-deoxy-2-(18F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-computed tomography (CT) was obtained from patients' medical records. Tumors were classified and staged according to the 8th edition of Union for International Cancer Control (UICC) TNM classification of malignant tumors.[5] PPC was diagnosed according to the 2015 WHO classification.[1]

Statistical Analyses

Statistical calculations were conducted using the statistical software program IBM SPSS Statistics version 25 (IBM SPSS, Armonk, NY, USA). The overall survival (OS) and disease-free survival (DFS) rates were statistically analyzed using the Kaplan–Meier estimated survival curves. Differences between the survival curves were analyzed using the log-rank test. Hazard ratios (HRs) in the patient subsets were calculated using the Cox proportional hazards model. Differences with $p < 0.05$ were considered significant.

Results

Clinical features, preoperative treatment, and surgical results

The clinical features of patients with PPC, preoperative treatment, and surgical results are shown in **Table 1**. In all, 17 patients with PPC underwent pulmonary resection. Patients were aged 71.5 ± 5.1 years at the time of the pulmonary resection. All patients were men and heavy smokers with an average Brinkman index 1126.8 ± 517.8. The mean serum carcinoembryonic antigen and cytokeratin-19 fragment levels were 3.74 ± 2.0 ng/mL and 2.39 ± 2.7 ng/mL, respectively. The mean SUV max of PET-CT were 15.8 ± 7.8. In total, 14 patients underwent lobectomy, whereas two required wedge resection and one patient needed pneumonectomy. In all, 14 patients underwent systemic nodal dissection 2a. The clinical TNM stage at the time of surgery was stage I in six patients (IA2: 2, IA3: 2, IB: 2), stage II in six (IIA: 3, IIB: 3), stage III in four (IIIA: 3, IIIB: 1), and stage IVA in one. Prior to pulmonary resection, the stage IIIB patient received chemoradiotherapy and the stage IVA patient underwent adrenalectomy for metastatic adrenal tumor, in addition to chemotherapy.

Pathological features and postoperative course

Pathological findings and clinical course after surgery in the 17 patients are shown in **Table 2**. The mean maximum tumor size was 5.5 ± 3.0 cm. The tumor status was pT1 in two patients, pT2 in six, pT3 in five, and pT4 in four. The nodal status was pN0 in eleven patients, pN1 in three, and pN2 in three. The pathological stage according to the TNM classification was stage I in five patients (IA2: 1, IB: 4), stage IIB in four, stage III in seven (IIIA: 5, IIIB: 2), and stage IVA in one. A histological examination revealed identifiable epithelial components in 15 of the 17 tumors (seven adenocarcinomas, six squamous cell carcinomas, one large cell carcinoma, and one adenosquamous carcinoma) and sarcomatous elements in 16 of the 17 tumors (seven spindle cells, four spindle and giant cells, three spindle and pleomorphic cells, and one spindle and round cells). Lymphatic permeation factor (ly-factor) and vascular invasion factor (v-factor) were observed in 6 cases and 12 cases, respectively. Three cases demonstrated driver mutations (one each in epidermal growth factor receptor [EGFR], KRAS, and mesenchymal to epithelial transition factor 14 [MET 14]). Seven patients received postoperative chemotherapy (three cases of treatment with tegafur and uracil and four cases of

Table 1 Clinical features of the patients with PPC, preoperative treatment, and surgical results

Case	Age	Sex	Brinkman Index	CEA	CYFRA	Tumor location	SUVmax of primary lesion	c-Stage	Preoperative Therapy	Operation	LND
1	73	M	960	6.1	2.4	RU	NP	III A	–	Lob	2a-2
2	68	M	1920	2.1	1.8	RU	26.2	II A	–	Lob	2a-2
3	74	M	1560	1.8	2.1	RM	15.2	I B	–	Lob	1a
4	66	M	800	3.7	1.2	RU	20.5	III B	CRTx	Pn	2a-2
5	74	M	1000	3.5	0.7	LL	2.7	IV A	Adrenectomy, CTx	Wed	0
6	69	M	1020	4.0	2.4	RL	7.4	I A3	–	Lob	2a-2
7	79	M	1160	4.4	3.0	RU	8.9	II B	–	Lob	2a-2
8	81	M	640	5.6	1.2	LU	13.9	I B	–	Lob	2a-2
9	63	M	825	1.6	2.3	LL	14.9	II B	–	Lob	2a-2
10	79	M	800	7.3	13.0	RL	18.5	II A	–	Lob	2a-1
11	68	M	780	1.4	0.3	RU	35.6	I A2	–	Lob	2a-2
12	73	M	1650	1.8	1.5	LL	7.3	I A3	–	Wed	0
13	72	M	676	8.0	1.2	RL	9.9	I A2	–	Lob	2a-2
14	66	M	900	4.7	2.3	RU	19.4	III A	–	Lob	2a-2
15	69	M	1150	3.3	2.3	LL	19.4	II B	–	Lob	2a-2
16	74	M	2640	1.8	2.0	LU	13.3	II A	–	Lob	2a-2
17	65	M	675	2.4	0.9	RL	19.2	III A	–	Lob	2a-2

CEA: carcinoembryonic antigen; CYFRA: cytokeratin-19 fragment; SUVmax: maximum standardized uptake value; LND: lymph node dissection; M: male; RU: right upper lobe; RM: right middle lobe; RL: right lower lobe; LU: left upper lobe; LL: left lower lobe; NP: not performed; CRTx: chemoradio therapy; CTx: chemotherapy; Lob: lobectomy; Pn: pneumonectomy; PPC: pulmonary pleomorphic carcinoma; Wed: wedge resection

Table 2 Pathological features and postoperative course

Case	Tumor size (cm)	pT	pN	p-Stage	Sarcomatous elements	Epitherial components	ly-factor	v-factor	Ddriver mutation	Adjuvant therapy	DFI (months)	Recurrent site	OS (months)	Outcome
1	3.5	2a	1	II B	S	Sq	1	1	–	–	54.6	–	54.6	Dead
2	5.4	3	0	II B	S	Ad	0	0	–	–	15.2	BRA	22.9	Dead
3	3.8	2a	0	I B	S	Sq	0	1	–	UFT-E	41.6	–	41.6	Dead
4	10.0	4	1	III A	S + P	Sq	1	1	–	–	4.3	–	4.3	Dead
5	1.4	1b	0	IV A	–*	La	0	0	EGFR	CDDP + DOC	92.8	–	92.8	Alive
6	2.9	3	2	III B	S + P	Ad	1	0	–	–	8.0	PLE	14.6	Dead
7	3.2	2a	0	I B	S	Ad	0	0	–	–	5.6	ADR	10.1	Dead
8	4.2	2a	2	III A	S	Ad	0	1	–	–	2.0	PLE, OTH	6.0	Dead
9	9.6	3	0	II B	S + R	Ad > Sq	1	1	–	CDDP + DOC	2.9	LYM	6.2	Dead
10	6.9	3	0	II B	S + P	Sq	1	1	–	–	40.1	–	60.9	Alive
11	3.9	2a	0	I B	S + G	–	0	1	–	UFT-E	42.5	–	62.6	Alive
12	1.4	1b	0	I A2	S + G	Ad	0	0	–	–	30.8	–	30.8	Dead
13	3.2	2a	0	I B	S + P	AdSq	0	1	–	UFT-E	3.5	OSS, HEP	4.6	Dead
14	9.8	4	0	III A	S + G	Sq	0	1	–	–	2.6	HEP	3.6	Dead
15	6.0	3	2	III B	S	Ad	1	1	MET	CDDP + GEM	4.5	PUL	32.9	Alive
16	9.0	4	1	III A	S	Sq	0	1	–	CDDP + DOC	21.0	–	30.6	Alive
17	10.0	4	0	III A	S + G	–	0	1	–	–	16.2	–	25.3	Alive

*Findings of lung lesions. This lesion is after spontaneous regression and chemotherapy. Spindle cells only in adrenal lesions. Ad: adenocarcinoma; ADR: adrenals; AdSq: adenosquamous carcinoma; BRA: brain; CDDP: cisplatin; DOC: docetaxel; DFI: disease-free interval; G: giant cell; GEM: gemcitabine; HEP: hepatic; La: large cell carcinoma; LYM: lymph nodes; OS: overall survival; OSS: osseous; P: pleomorphic cell; PLE: pleura; PUL: pulmonary; R: round cell; S: spindle cell; Sq: squamous cell carcinoma; UFT: tegafur/uracil.

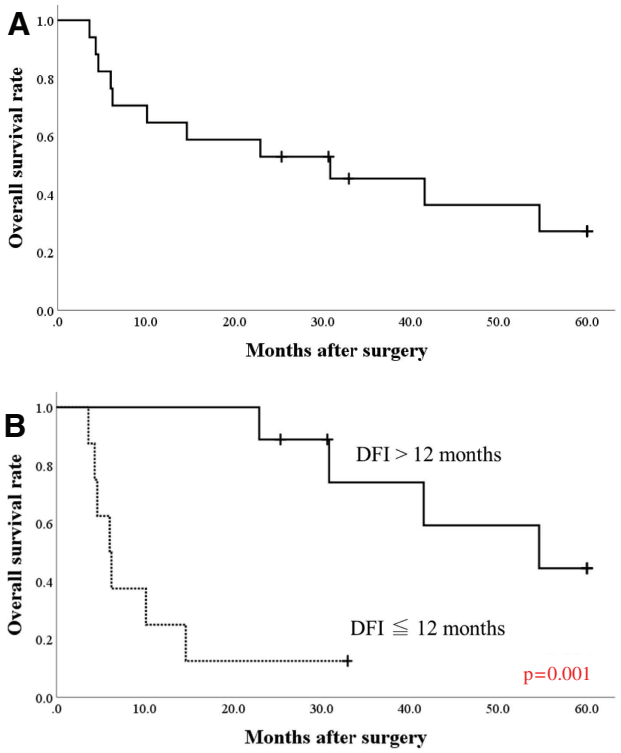

Fig. 1 (**A**) OS curve of pulmonary pleomorphic carcinoma. (**B**) OS curves for patients with a DFI <1 year (bold line) and with a DFI >1 year (dashed line) (log-rank test, p = 0.001). DFI: Disease-free survival interval; OS: overall survival

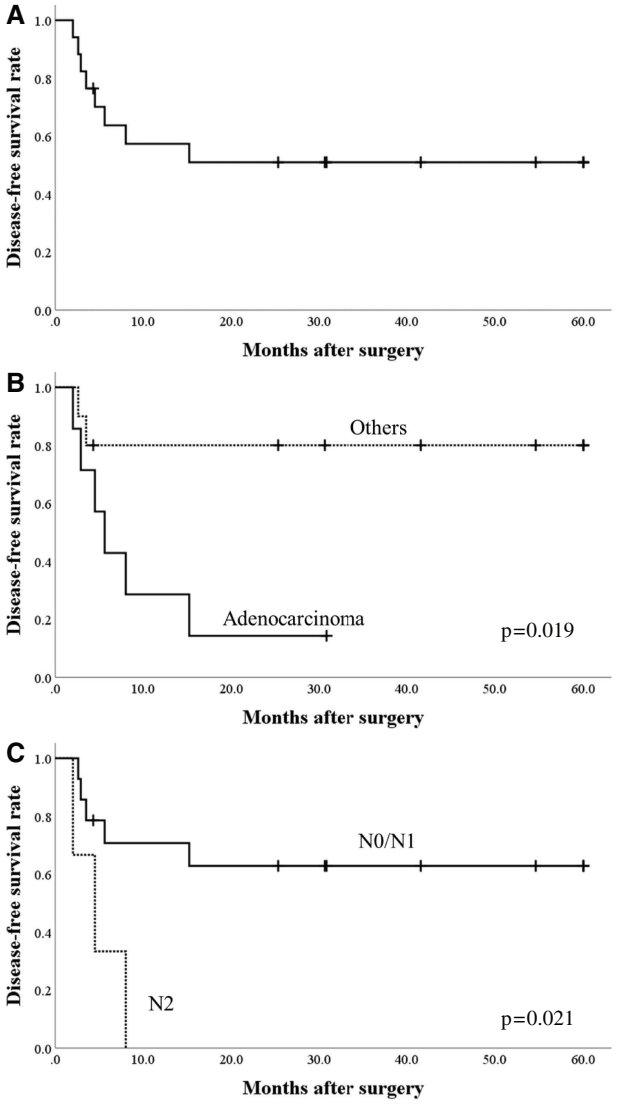

Fig. 2 (**A**) DFS curve of pulmonary pleomorphic carcinoma. (**B**) Disease-free survival curves for patients with an adenocarcinoma component (bold line) and those with other epithelial components (dashed line) (log-rank test, p = 0.019). (**C**) Disease-free survival curves for patients with N0/1 status (bold line) and those with N2 status (log-rank test, p = 0.021). DFS: disease-free survival

platinum-based chemotherapy). There was no local recurrence, but 8 out of 17 cases had distant metastases after surgery. The median disease-free interval (DFI) was 15.2 months (2.0–92.8). Three pathological N2 patients had recurrence early, within 8 months after surgery; and all had adenocarcinoma components. While six patients are still alive and cancer-free, the remaining 11 patients were followed up until death. Five deaths were related to cancer and six were due to other causes. The median follow-up period of patients after the pulmonary resection was 25.3 months (3.6–92.8).

Results of the Kaplan–Meier curves for survival

The Kaplan–Meier curves for OS and DFS are shown in **Figs. 1** and **2**, respectively. The 3- and 5-year OS rates after surgery for PPC were 45.4% and 27.2%, respectively. The median survival time following pulmonary resection was 30.8 months (**Fig. 1A**). The 5-year DFS rate after surgery was 51.0% (**Fig. 2A**).

Salient findings from the OS curve: We set a cutoff value of DFI at 1 year calculated by using the receiver operating characteristic curve. The cumulative 5-year OS rate in patients with a DFI <1 year was 12.5%, whereas that in patients with a DFI >1 year was 44.4% (p = 0.001, **Fig. 1B**). There was a significant difference between the two cohorts. The median survival interval was 6.0 months in patients with a DFI <1 year and 54.6 months those with a DFI >1 year.

Salient findings from the DFS curve: Survival rates were worse in groups with adenocarcinoma components than in those with other components. The 5-year survival rate was 14.3% and 80.0% in patients with

adenocarcinoma components and those with other components, respectively (p = 0.019, **Fig. 2B**). The median survival interval was 5.6 months in patients with adenocarcinoma components. Moreover, survival rates were worse in the groups with N2 pathological status than in their counterparts. The 5-year DFS rate was 0% and 62.9% in the group with the N2 pathological status and in that with N0 or N1 status, respectively (p = 0.021, **Fig. 2C**). The median survival interval was 4.5 months in patients with the N2 pathological status.

Results of univariate analysis performed to identify predictors of the OS and DFS

Results of the univariate analysis are shown in **Table 3**. Univariate analysis identified the DFI within 1 year as an unfavorable prognostic factor for OS (p = 0.005). The HR of PPC relapse within 1 year compared to PPC relapse in more than 1 year was 0.095 (95% confidence interval [CI]: 0.018–0.049). Moreover, the N2 pathological status and presence of adenocarcinoma components were poor prognostic factors for DFS (p = 0.038 and p = 0.036).

Discussion

In the present study, we reviewed data of 17 patients with PPC who underwent pulmonary resection at a single institution. PPC is a relatively rare form of lung cancer with poor prognosis. There are few reports on the number of cases, and its outcomes and prognostic factors are not elucidated. Fishback et al.[6] reported that the 5-year OS rate was 10%, but in recent studies, the 5-year OS rate was reported to be 33%–80%.[7-10] In addition, the 5-year DFS was reported as 33.6%–63.3%.[9-11] Our results are similar to those of past reports but less than those reported recently.

Additionally, various reports on prognostic factors for PPC were reported, but there is no unified opinion. Previously, most examined were based on the patient background (sex, age, smoking history, etc.) and pathological findings (pathological stage, lymph node metastasis, tumor size, etc.).[6-11] In this study, DFI within 1 year was detected as a poor prognostic factor for OS, and the N2 pathological status and presence of adenocarcinoma components were identified as poor prognostic factors for DFS. We could not identify significant differences in the survival curves for tumor size, stage, and v-factor that were previously reported to have poor prognosis. Okuda et al.[12] reported that the epithelial component of adenocarcinoma was a good prognostic factor for progression-free survival (PFS), whereas v-factor and lymph node metastasis were poor prognostic factors. In this report, lymph node metastasis was identified as a poor prognostic factor for DFS, whereas the epithelial component of adenocarcinoma was identified as a poor prognostic factor for DFS. In addition, five of seven early recurrence cases within the first year had adenocarcinoma components. Moreover, all three cases had N2 status and presence of adenocarcinoma components. We believe that this may contribute to a poor prognosis of DFS in cases with adenocarcinoma components, but we could not explain in details why the cases with adenocarcinoma components had poor prognosis. The other details of clinicopathological examination such as ly-factor and v-factor were not significant in this study.

The SUV max and SUV average were higher in PPC than in other histological types of non-small-cell lung carcinomas (NSCLCs).[13] Similar results were found in our study. Recently, Kaminuma et al.[11] reported that a high concentration of FDG PET-CT is a prognostic factor of OS and DFS and that FDG accumulation reflects tumor malignancy. However, in our study, SUV max values were not extracted as shown to be prognostic predictors. Since SUV may become an indicator of malignancy and prognostic predictor, it is necessary to study this in the future.

PPC is generally regarded as resistant to both chemotherapy and radiotherapy, and refractory to treatment. The most effective treatment option is surgical resection. Currently, there is no evidence-based regimen because it is a rare pathological type. Postoperative adjuvant chemotherapy is often enforced with platinum combination therapy such as cisplatin (CDDP)+vinorelbine and carboplatin (CBDCA) + paclitaxel (PTX) therapy.[14,15] In this study, combination therapy of CDDP and docetaxel was administered in three cases and that of CDDP and gemcitabine was administered in one. One of them (Case 5, see **Tables 1** and **2**) obtained 96 months survival and a good prognosis, suggesting the importance of multimodal therapy.[16] Because this patient had spontaneous regression of the primary lesion after adrenalectomy, immunological mechanisms may have played a role in this case. In addition to traditional chemotherapy, therapeutic effects of new anticancer agents such as immune checkpoint inhibitors (ICIs) and molecular-targeted agents (MTAs) are expected to help in PPC. Kaira et al.[13] reported that vascular endothelial growth factor (VEGF) was elevated in lung pleomorphic cancer tissues, and

Table 3 Results of the univariate analysis for the overall survival and disease-free survival

Baseline and clinical features		OS				DFS		
		Patients	HR	95% CI	p-value	HR	95% CI	p value
Pathological stage	I/II	9	1.000			1.000		
	III/IV	8	0.950	0.273–3.306	0.935	1.465	0.365–5.887	0.590
Maximum diamater of tumor	<Mean (55.4 mm)	10	1.000			1.000		
	>Mean (55.4 mm)	7	1.185	0.350–4.010	0.924	2.106	0.500–8.873	0.310
Pathological N factor	N0/N1	14	1.000			1.000		
	N2	3	1.406	0.290–6.818	0.672	4.960	1.096–22.434	**0.038**
Sarcomatous elements	spindle cell only	7	1.000			1.000		
	others	10	0.931	0.281–3.087	0.907	0.743	0.185–2.984	0.676
Epithelial component	adenocarcinoma	7	1.000			1.000		
	others	10	0.332	0.082–1..347	0.123	0.178	0.035–0.895	**0.036**
Lymphatic permiation factor	−	11	1.000			1.000		
	+	6	0.951	0.276–3.270	0.936	1.240	0.293–5.246	0.770
Vascular invasion factor	−	5	1.000			1.000		
	+	12	0.813	0.235–2.808	0.743	0.948	0.225–4.001	0.942
Adjuvant chemotherapy	−	10	1.000			1.000		
	+	7	2.525	0.652–9.778	0.180	2.563	0.514–12.768	0.251
TDT (n = 16)	<Median (48.9 days)	11	1.000			1.000		
	>Median (48.9 days)	5	1.849	0.544–6.277	0.325	1.043	0.258–4.211	0.953
DFI	<12 months	8	1.000					
	>12 months	9	0.095	0.018–0.491	**0.005**			

DFI: disease-free interval; DFS: disease-free survival; HR: hazard ratio; OS: overall survival; TDT: tumor doubling time; 95% CI: 95% confidence interval

Tsubata et al.[17] reported an abundance of new blood vessels in lung pleomorphic carcinoma tissues compared to other non-small-cell lung cancer tissues. Zhao et al.[18] reported a significant correlation between high microvessel density in tumor tissue and high tumor reduction rate with bevacizumab-combined chemotherapy in advanced-stage NSCLC. Therefore, it is expected that therapeutic results in PPC will be improved using combination therapy with bevacizumab. Moreover, the effective use of other molecular-targeted therapeutic drugs in PPC such as EGFR-tyrosine kinase inhibitor (TKI) for EGFR gene mutation,[19] anaplastic lymphoma kinase (ALK)-TKI for ALK fusion gene positive case,[20] and ICI for cases with high expression of programmed cell death ligand 1 (PD-L1) has been reported.[21,22] Even in our study, one case each of positive EGFR, KRAS, and MET 14 skipping was reported. The results of multidisciplinary treatment, including new anticancer drugs such as ICI and MTA, will be revealed in future studies.

Conclusion

DFI within 1 year was an unfavorable prognostic factor for OS, and N2 pathological status and the presence of adenocarcinoma components were unfavorable prognostic factors for DFS. Therefore, PPC patients with an adenocarcinoma component and N2 pathological status may have an earlier relapse and poorer prognosis than their counterparts. Because this study was a single-center study with a small sample size, it was difficult to determinate the prognostic factors. Accumulation and analysis of cases in a multicenter collaborative research are required.

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Disclosure Statement

Y. Iijima and his co-authors have no conflicts of interests to declare.

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