Table 1
Prognostic analyses for overall survival and disease-free survival in patients with invasive ductal carcinoma of the pancreas ($n = 170$).

Parameter	n	%	Overall survival			Disease-free survival		
			HR	95% CI	P	HR	95% CI	P
(a) Univariate analysis								
Age ⩾ 65	80	47.1	1.077	0.775–1.498	0.657	1.114	0.808–1.535	0.510
Sex, male	107	62.9	0.876	0.625–1.227	0.442	0.960	0.689–1.339	0.811
ECOG PS ⩾ 1	28	16.5	1.975	1.266–3.081	0.003*	1.403	0.909–2.166	0.126
Absence of adjuvant chemotherapy	110	64.7	1.715	1.186–2.481	0.004*	1.501	1.061–2.123	0.022*
CEA ⩾ 3.4 ng/ml	88	51.8	1.419	1.019–1.975	0.038*	1.584	1.147–2.186	0.005*
CA19-9 ⩾ 111.5 U/ml	85	50.0	0.904	0.648–1.260	0.550	1.026	0.743–1.417	0.877
Tumour differentiation, moderate/poor	126	74.1	1.248	0.857–1.817	0.248	1.514	1.042–2.199	0.030*
Tumour size ⩾ 3.0 cm	81	47.6	1.615	1.160–2.248	0.005*	1.596	1.156–2.203	0.004*
Serosal invasion (+)	46	27.1	0.865	0.591–1.266	0.457	1.164	0.811–1.671	0.411
Retroperitoneal invasion (+)	145	85.3	1.174	0.724–1.904	0.516	1.060	0.668–1.682	0.805
Portal vein invasion (+)	40	23.5	1.479	1.014–2.156	0.042*	1.186	0.818–1.722	0.368
Ly, moderate to severe	46	27.1	1.634	1.130–2.365	0.009*	1.620	1.135–2.312	0.008*
V, moderate to severe	103	60.6	1.779	1.254–2.524	0.001*	1.636	1.168–2.292	0.004*
Ne, moderate to severe	106	62.4	1.812	1.270–2.583	0.001*	1.637	1.164–2.302	0.005*
Lymph node involvement (+)	141	82.9	1.505	0.968–2.341	0.069	1.554	1.002–2.409	0.049*
Pathological stage IIB/III/IV	143	84.1	1.414	0.903–2.214	0.130	1.463	0.937–2.284	0.094
Peripheral CD204%^{high}	85	50.0	1.777	1.272–2.484	0.001*	1.570	1.135–2.172	0.006*
Plx-inv (+)	91	53.5	1.612	1.147–2.264	0.006*	1.785	1.280–2.489	0.001*
Plx-inv distance ⩾ 2500 μm	56	32.9	1.949	1.368–2.777	<0.001*	2.274	1.597–3.238	<0.001*
Plx-inv CD204%^{high}	48	28.2	1.779	1.247–2.539	0.001*	1.904	1.341–2.705	<0.001*
(b) Multivariate analysis								
Absence of adjuvant chemotherapy	110	64.7	1.741	1.143–2.651	0.010*	1.559	1.042–2.332	0.031*
CEA ⩾ 3.4 ng/ml	88	51.8	1.437	1.011–2.041	0.043*	1.602	1.139–2.253	0.007*
Tumour size ⩾ 3.0 cm	81	47.6	1.610	1.147–2.262	0.006*	1.616	1.160–2.250	0.005*
Ly, moderate to severe	46	27.1	1.254	0.839–1.876	0.270	1.151	0.775–1.709	0.487
V, moderate to severe	103	60.6	1.505	1.010–2.242	0.045*	1.291	0.879–1.897	0.192
Peripheral CD204%^{high}	85	50.0	2.167	1.522–3.086	<0.001*	1.831	1.297–2.583	0.001*
Plx-inv CD204%^{high}	48	28.2	2.008	1.362–2.962	<0.001*	2.046	1.400–2.991	<0.001*

* $P < 0.05$. Prognostic analyses were carried out using Cox regression model. HR, hazard ratio; 95% CI, 95% confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; Ly, lymphatic invasion; V, vessel invasion; Ne, intrapancreatic neural invasion, Peripheral CD204%^{high}, percentage of CD204-positive cells area at the periphery ⩾ 3.34; Plx-inv, extrapancreatic nerve plexus invasion; Plx-inv CD204%^{high}, percentage of CD204-positive cells area at plx-inv ⩾ 0.57.

liver metastasis, peritoneal dissemination, locoregional recurrence and distant lymph node metastasis. Peritoneal dissemination was defined as marked peritoneal nodules, increased ascites or malignant ascites as confirmed by cytology. Locoregional recurrence was defined as tumour in a dissected space or metastasis in regional lymph nodes according to the 7th edition of the UICC classification [26]. Distant lymph node metastasis was defined as marked lymph node swelling apart from the regional space.

2.6. Statistical analysis

Uni- and multivariate analyses for OS, DFS and time to each type of recurrence were performed using a Cox regression model. Factors showing values of $P < 0.05$ for both OS and DFS in univariate analyses were included in multivariate analyses. Pearson's correlation coefficient r was used to evaluate the correlation among covariates. The observation period was until March 2013, and the median duration was 17.6 months [95% confidence interval (CI), 14.5–20.6]. OS was defined as the time from surgery to death or the date censored at last follow-up. DFS was calculated as the time from surgery to tumour relapse or death or the date censored at last follow-up. Survival curves were drawn using the Kaplan–Meier method, and the differences between patient groups were analysed by log-rank test. P-values were two-sided, with the significance level at $P < 0.05$. Statistical analyses were performed using SPSS version 19.0 software (SPSS, Chicago, IL).

3. Results

3.1. Distribution of CD204%

CD204 accumulation at the primary tumour was measured in all 170 patients, and median CD204% at the tumour periphery was 3.34% [range, 0.16–14.04%]. Plx-inv was observed in 91 patients (53.5%). CD204-positive cells and the measured area at plx-inv are shown in Fig. 1a and b, and CD204-positive cells and the measured area at the tumour periphery are shown in Fig. 1c and d. Median CD204% at plx-inv was 0.57% [range,

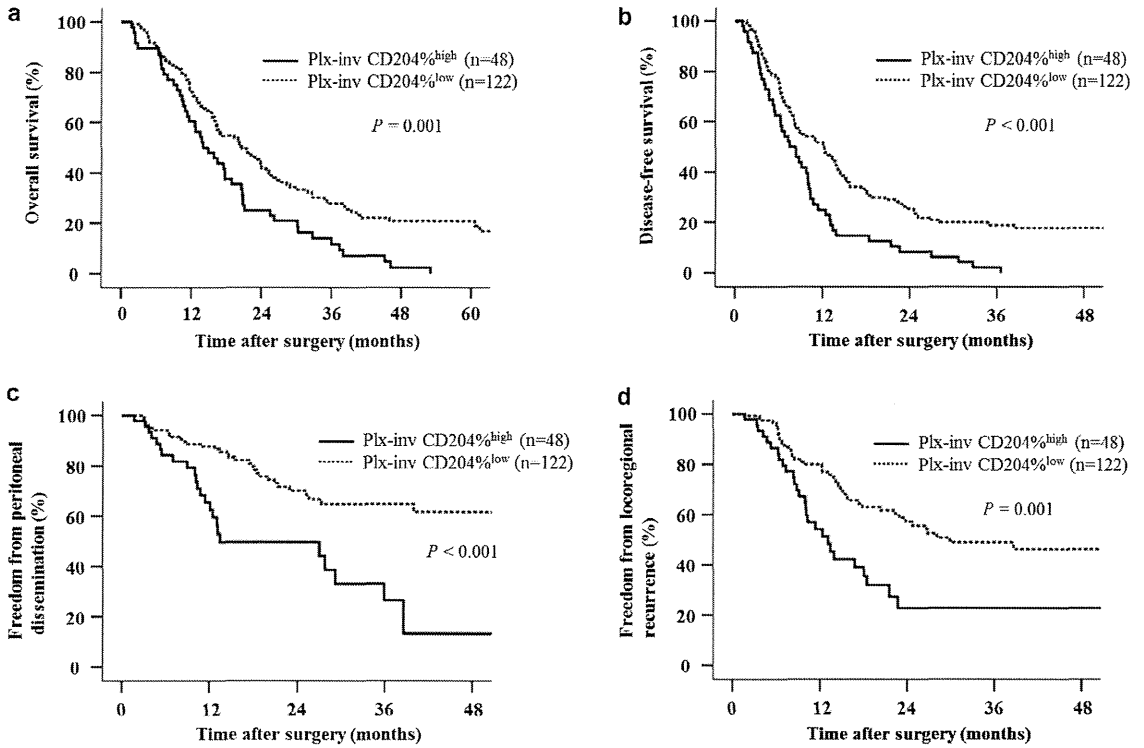

Fig. 2. (a) Kaplan–Meier curve for overall survival stratified by the level of CD204-positive cell area as a percentage at extrapancreatic nerve plexus invasion (plx-inv CD204%). (b) Kaplan–Meier curve for disease-free survival stratified by the level of CD204-positive cell area as a percentage at extrapancreatic nerve plexus invasion (plx-inv CD204%). (c) Kaplan–Meier curve for peritoneal dissemination-free survival stratified by the level of CD204-positive cell area as a percentage at extrapancreatic nerve plexus invasion (plx-inv CD204%). (d) Kaplan–Meier curve for locoregional recurrence-free survival stratified by the level of CD204-positive cell area as a percentage at extrapancreatic nerve plexus invasion (plx-inv CD204%).

0.00–7.76%]. Forty-eight patients with CD204% at plx-inv $\geqslant$0.57% were categorised as plx-inv CD204%^{high}. There were 43 patients with CD204% at plx-inv <0.57% and 79 patients without plx-inv, who were categorised as plx-inv CD204%^{low}.

3.2. Prognostic analyses of clinicopathological factors

The median OS and DFS were 17.8 months [95% CI, 14.7–20.9] and 9.8 months [95% CI, 7.9–11.6], respectively. Univariate analysis identified absence of adjuvant chemotherapy, CEA $\geqslant$ 3.4 ng/ml, tumour size $\geqslant$ 3.0 cm, moderate to severe ly, v and ne, peripheral CD204%^{high}, plx-inv, plx-inv distance $\geqslant$ 2500 μm and plx-inv CD204%^{high} as candidates for correlation with both shorter OS and shorter DFS ($P < 0.05$) (Table 1a). Strong correlations were observed between plx-inv CD204%^{high} and the following covariates: moderate to severe ne, $r = 0.299$, $P < 0.001$; plx-inv, $r = 0.584$, $P < 0.001$; and plx-inv distance $\geqslant$ 2500 μm, $r = 0.534$, $P < 0.001$. Therefore, these covariates were excluded from the multivariate analysis. Multivariate analysis revealed absence of adjuvant chemotherapy (hazard ratio [HR], 1.741; $P = 0.010$), CEA $\geqslant$ 3.4 ng/ml (HR, 1.437; $P = 0.043$), tumour size $\geqslant$ 3.0 cm (HR, 1.610; $P = 0.006$), moderate to severe v (HR, 1.505; $P = 0.045$), peripheral CD204%^{high} (HR, 2.167; $P < 0.001$), and plx-inv CD204%^{high} (HR, 2.008; $P < 0.001$) as independent risk factors for shorter OS (Table 1b). In terms of DFS, absence of adjuvant chemotherapy (HR, 1.559; $P = 0.031$), CEA $\geqslant$ 3.4 ng/ml (HR, 1.602; $P = 0.007$), tumour size $\geqslant$ 3.0 cm (HR, 1.616; $P = 0.005$), peripheral CD204%^{high} (HR, 1.831; $P = 0.001$) and plx-inv CD204%^{high} (HR, 2.046; $P < 0.001$) represented independent risk factors for shorter DFS (Table 1b). OS and DFS curves according to the level of plx-inv CD204% are shown in Fig. 2a and b.

3.3. Time to relapse according to site of recurrence

Median times to tumour relapse were 7.3 months [95% CI, 5.5–9.1] for liver metastasis (71 patients, 41.8%), 12.1 months [9.2–15.0] for peritoneal dissemination (57 patients, 33.5%), 10.0 months [7.1–13.0] for locoregional recurrence (76 patients, 44.7%) and 8.8 months [4.0–13.6] for distant lymph node recurrence (46 patients, 27.1%). Multivariate analyses showed that absence of adjuvant chemotherapy (HR, 1.924; $P = 0.030$) and moderate to severe ly (HR, 2.634; $P < 0.001$) correlated with early relapse to liver metastasis (Table 2). Peripheral CD204%^{high} was a predictor of peritoneal dissemination (HR, 1.815; $P = 0.031$)

(Table 2). Plx-inv CD204%^{high} was independently associated with peritoneal dissemination (HR, 2.886; $P < 0.001$) and locoregional recurrence (HR, 2.483; $P < 0.001$) (Table 2 and Fig. 2c and d).

3.4. Prognostic analyses stratified by presence of adjuvant chemotherapy

Adjuvant chemotherapy represented an independent prognostic factor for OS and DFS as a definitive therapeutic modality (Table 1, Fig. 3a and b). Multivariate analyses to test prognostic factors with adjuvant chemotherapy were re-examined and revealed that only plx-inv CD204%^{high} was associated with both shorter OS (HR, 2.624; $P = 0.011$) and shorter DFS (HR, 2.257; $P = 0.038$) in patients with plx-inv who underwent postoperative adjuvant chemotherapy (Table 3).

4. Discussion

The present study demonstrated that the accumulation of CD204-positive cells, representing M2 macrophages, at plx-inv of pancreatic IDC was an independent predictor of shorter OS and DFS in patients who underwent curative pancreaticoduodenectomy for pancreatic IDC. The prognostic impact of plx-inv CD204%^{high} was maintained in patients who received adjuvant chemotherapy. Infiltration of M2 macrophages at plx-inv of pancreatic IDC was revealed as a key factor to explain the aggressiveness of pancreatic IDC for the first time in this study.

Peritoneal dissemination has long been considered a poor prognostic factor for patients with pancreatic IDC [27–29]. Patients with plx-inv CD204%^{high} showed early relapse to the peritoneal cavity in this study. The interaction between M2 macrophages and tumour cells at plx-inv was suggested to play a crucial role in peritoneal recurrence, which led to poor survival. From the perspective of surgical anatomy, nerve fibres of the plexus pancreaticus capitalis might provide a convenient pathway for infiltrating tumour cells. As recent experimental study showed that macrophages around nerves were recruited in response to cytokine secreted by invading tumour cells and increased migration of tumour cells [15], M2 macrophages might promote the invasiveness of tumour cells at plx-inv, leading tumour cells to disperse into the peritoneal space and resulting in peritoneal dissemination. This speculation warrants further studies to observe the distribution of M2 macrophages in metastatic sites of pancreatic IDC and to test the role of M2 macrophages in metastatic tumour models.

Immunophysiologically, neural injury leads to the accumulation of macrophages in the peripheral nerve system, although few macrophages exist in intact nerves [30]. Ceyhan et al. reported that neuritis was caused by the invasion of malignant tumour cells into the pancreas

Table 2
Multivariate analysis for early relapse according to the sites of recurrence in patients with invasive ductal carcinoma of the pancreas ($n = 170$).

Parameter	Liver metastasis ($n = 71$)				Peritoneal dissemination ($n = 57$)				Locoregional recurrence ($n = 76$)				Distant lymph node metastasis (n = 46)			
	n	%	HR	95% CI	*P*	*n*	%	HR	95% CI	*P*	*n*	%	HR	95% CI	*P*	*n*	%	HR	95% CI	*P*
Absence of adjuvant chemotherapy	50	70.4	1.924	1.065–3.476	0.030*	34	59.6	1.107	0.602–2.036	0.743	52	68.4	1.734	0.995–3.022	0.052	32	69.6	1.660	0.794–3.471	0.178
CEA ⩾ 3.4 ng/ml	40	56.3	1.347	0.819–2.215	0.241	23	40.4	0.934	0.531–1.640	0.811	36	47.4	1.238	0.773–1.985	0.374	26	56.5	1.516	0.810–2.839	0.193
Tumour size ⩾ 3.0 cm	38	53.5	1.492	0.925–2.405	0.101	22	38.6	0.968	0.558–1.681	0.909	34	44.7	1.114	0.698–1.780	0.650	23	50.0	1.327	0.732–2.407	0.351
Ly, moderate to severe	28	39.4	2.634	1.574–4.408	<0.001*	14	24.6	0.839	0.436–1.617	0.601	21	27.6	0.878	0.501–1.539	0.649	17	37.0	1.909	0.993–3.671	0.053
V, moderate to severe	46	64.8	1.146	0.660–1.988	0.629	30	52.6	1.126	0.618–2.052	0.698	47	61.8	1.323	0.774–2.261	0.306	29	63.0	1.133	0.560–2.292	0.729
Peripheral CD204%^{high}	37	52.1	1.517	0.931–2.472	0.095	30	52.6	1.815	1.055–3.124	0.031*	36	47.4	1.501	0.933–2.417	0.094	21	45.7	1.305	0.706–2.412	0.396
Plx-inv CD204%^{high}	18	25.4	0.916	0.518–1.619	0.763	24	42.1	2.886	1.615–5.159	<0.001*	28	36.8	2.483	1.485–4.151	<0.001*	15	32.6	1.564	0.795–3.073	0.195

* $P < 0.05$. Multivariate analysis was carried out using Cox regression hazard model. HR, hazard ratio; 95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; Ly, lymphatic invasion; V, vessel invasion; Peripheral CD204%^{high}, percentage of CD204-positive cells area at the periphery ⩾ 3.34; Plx-inv CD204%^{high}, percentage of CD204-positive cells area at extrapancreatic nerve plexus invasion ⩾ 0.57.

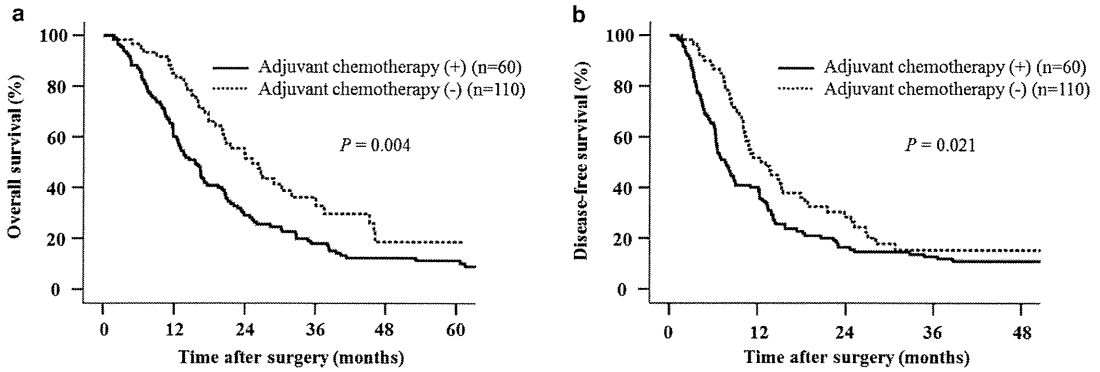

Fig. 3. (a) Kaplan–Meier curve for overall survival stratified by the presence of adjuvant chemotherapy. (b) Kaplan–Meier curve for disease-free survival stratified by the presence of adjuvant chemotherapy.

Table 3
Multivariate analysis for overall survival and disease-free survival in patients who received adjuvant chemotherapy ($n = 60$).

Parameter	n	%	Overall survival			Disease-free survival		
			HR	95% CI	P	HR	95% CI	P
CEA ⩾ 3.4 ng/ml	23	38.3	1.514	0.704–3.257	0.289	1.883	0.969–3.658	0.062
Tumour size ⩾ 3.0 cm	26	43.3	1.283	0.663–2.484	0.460	1.179	0.641–2.170	0.596
Ly, moderate to severe	21	35.0	1.775	0.833–3.782	0.137	1.475	0.667–3.263	0.337
V, moderate to severe	19	31.7	2.178	1.059–4.479	0.034*	1.476	0.769–2.833	0.242
Peripheral CD204%^{high}	32	53.3	1.206	0.601–2.420	0.598	0.890	0.472–1.679	0.719
Plx-inv CD204%^{high}	20	33.3	2.624	1.242–5.544	0.011*	2.257	1.045–4.879	0.038*

* $P < 0.05$. Multivariate analysis was carried out using Cox regression model. HR, hazard ratio; 95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; Ly, lymphatic invasion; V, vessel invasion; Peripheral CD204%^{high}, percentage of CD204-positive cells area at the periphery ⩾ 3.34; Plx-inv CD204%^{high}, percentage of CD204-positive cells area at extrapancreatic nerve plexus invasion ⩾ 0.57.

[31]. In our previous experimental study [12], neural invasion over a long distance could lead to severe neural damage. Additionally, the present study showed strong positive correlations among ne, plx-inv, long plx-inv distance and plx-inv CD204%^{high}. Taken together with the paracrine regulation between macrophages and tumour cells at plx-inv [14,15], severe neural invasion of tumour cells appears to recruit M2 macrophages due to neural damage. Moreover, the neural system was suggested as an expedient structure for interaction between tumour cells and M2 macrophages that promotes pancreatic cancer cell proliferation.

Adjuvant chemotherapy after complete resection of pancreatic IDC has been established as the definitive standard of care within the last decade [24,32,33]. In the present study, plx-inv CD204%^{high} was the only independent prognostic factor for poor OS and DFS in the group of patients with adjuvant chemotherapy. According to recent reports, immunoregulatory cytokines such as interleukin-6 and prostaglandin E2, which are present in the tumour microenvironment, are associated with chemoresistance and tumour-induced differentiation of tumour-promoting M2 macrophages [34,35]. Additional therapy to suppress M2 macrophages might thus prove effective, particularly against cases with plx-inv and high accumulation of M2 macrophages. Depletion of macrophages by zoledronic acid has been reported to enhance the effects of sorafenib in an *in vivo* model of metastatic liver cancer [36]. A phase II randomised controlled study of tasquinimod (oral quinolone-3-carboxamide) for metastatic castrate-resistant prostate cancer patients prolonged progression-free survival and confirmed the pharmacological efficacy of this agent for inhibiting S100A9 [37], which is a protein expressed in inflammatory cells that induces the maturation of macrophages [38]. Therefore, anti-M2 macrophage therapy may have potential as an innovative treatment for pancreatic IDC.

Limitations of this study include the retrospective manner of the investigation. Adjuvant chemotherapy was performed in 60 patients and was an independent factor predictive of OS and DFS, but the indication was influenced by time trends, and some degree of selection bias might have been present. Although OS and DFS for our patient cohort were comparable with the other previous studies [24,32,33], further investigation in patients with standardised adjuvant chemotherapy is needed. Moreover, since only resectable pancreatic cancer was studied, it is unknown whether the results can be extrapolated to the much higher numbers of unresectable cases.

In conclusion, pancreatic cancer patients with high accumulation of CD204-positive cells at plx-inv who underwent curative resection showed a high incidence

of recurrence in the form of peritoneal dissemination and locoregional recurrence and shorter OS and DFS. The impact of CD204-positive cells at plx-inv on OS and DFS was maintained in the setting of adjuvant chemotherapy. Increased infiltration of M2 macrophages at plx-inv may represent an important finding for detecting patients with aggressive IDC of the pancreas.

Conflict of interest statement

None declared.

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