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ORIGINAL ARTICLE

# Gastrectomy for invasive micropapillary carcinoma is associated with poorer disease-free and disease-specific survival

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## Abstract

**Background** Invasive micropapillary carcinoma (IMPC) is a relatively rare subtype of gastric adenocarcinoma and has aggressive histopathologic characteristics, including lymphatic and vascular invasion. However, the associated long-term survival outcomes remain unclear. This study aimed to compare the clinicopathological characteristics and prognosis of gastric adenocarcinoma with and without IMPC using propensity score-matched (PSM) analysis.

**Methods** Patients with gastric adenocarcinoma who underwent gastrectomy between 2006 and 2015 were included in the analysis. PSM analysis was performed to compensate for the background heterogeneity between the groups. The primary endpoint was disease-free survival (DFS) after gastrectomy, and the secondary endpoints were disease-specific survival (DSS) and recurrence pattern.

**Results** Of 882 patients who underwent gastrectomy for gastric adenocarcinoma, with a follow-up duration greater than 36 months, 35 were diagnosed as having gastric adenocarcinoma with IMPC. After PSM, 70 patients, including 35 with IMPC and 35 without IMPC, were selected. Gastric adenocarcinoma with IMPC is characterized by lymphatic invasion (94% versus 69%, $p=0.012$). Patients with IMPC had significantly poorer DFS than those without IMPC, with 3-year DFS rates of 62.2% and 93.4% ($p=0.003$), respectively. Furthermore, a significant difference was also observed in DSS ($p=0.016$); patients with IMPC more frequently developed liver metastasis (20%) than those without IMPC (3%, $p=0.006$).

**Conclusions** Resected gastric carcinoma with IMPC was associated with poorer DFS and DSS; furthermore, an increased rate of lymphatic invasion and liver metastasis was noted than in cases without IMPC.

**Keywords** Invasive micropapillary carcinoma · Gastric carcinoma · Liver metastasis · Prognosis · Propensity score matching

## Introduction

Invasive micropapillary carcinoma (IMPC) was first reported as a rare subtype of invasive ductal carcinoma of the breast [1]. Previous studies demonstrated that this rare histological subtype frequently had aggressive characteristics with marked lymph-vascular invasion and poor prognosis [2].

Gastric carcinoma with IMPC has also been shown to be more frequently associated with lymph-vascular invasion, lymph node metastasis, and aggressive biological behavior [3–11]. However, little is known of the impact of IMPC on long-term survival in patients with gastric carcinoma who have undergone gastrectomy. In addition, immunological examination of the metastasis pattern is limited and not clear.

In this retrospective study, we compared the clinicopathological characteristics and survival outcomes of patients with and without IMPC using propensity score-matched analysis. Furthermore, the immunological examination was performed for the unique recurrence pattern.

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## Materials and methods

This retrospective analysis was approved by the Ethics Committee for Human Research of the Hiroshima City Asa Citizens Hospital and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained for surgery and all patients were given the option of opting out.

The primary endpoint was disease-free survival (DFS) after gastrectomy, and the secondary endpoints were disease-specific survival (DSS) and recurrence pattern.

### Patient selection

We retrospectively recruited 882 patients with gastric adenocarcinoma who were diagnosed and treated with curative gastrectomy clinically at the Hiroshima City Asa Citizens Hospital between January 2006 and November 2015. The time at which surgery was performed was considered the beginning of the follow-up period. The following features of the patients were extracted from the database for analysis: age at diagnosis, sex, tumor location, macroscopic type, histological type, pathological tumor invasion depth (pT), the number of pathological metastatic lymph nodes (pN), maximum size of tumor, presence of peritoneal lavage cytology (Cy), pathological Stage (pStage), lymphatic invasion, venous invasion, the method of surgical resection, site of recurrence, and survival periods.

### Tissues and pathological criteria

The gastric carcinomas were evaluated according to the 14th Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association [12]. The macroscopic types of the gastric carcinomas were classified according to Japanese Society for Gastroenterology endoscopic criteria as Type 0, and Type 1–5 (Bormann 1–5). All surgically resected specimens were fixed in 20% formalin for at least 3 h, serially cut into 5–7-mm-thick slices, and embedded in paraffin. The tumor areas on these slices were pathologically evaluated by staining with hematoxylin and eosin as the routine staining method. Furthermore, lymphovascular involvement was evaluated by immunostaining if the presence of IMPC was suspected, and D2-40 (DAKO Cytomation, Glostrup, Denmark) stain and Elastica van Gieson (EVG) stain were used. The presence of the IMPC component was histopathologically evaluated in all the stained slices. IMPC was defined as a carcinoma composed of small clusters of tumor cells within stromal spaces that mimic vascular channels (Fig. 1). IMPC in gastric carcinoma is usually a minor component of the entire lesion. The proportion of IMPC in each tumor was also evaluated, and a case was determined as IMPC-positive when the micropapillary component accounted for at least 5% of each tumor. Three pathologists (M.K., S.K., and H.M.) who were blinded to patient outcomes independently evaluated the pathologic indicators. In the case of discrepancies, the slides were reviewed again by all pathologists using a multiheaded microscope to achieve a diagnostic consensus. The histological type around the IMPC component was divided into the following categories: papillary (pap) and tubular (tub) adenocarcinoma, which are of the intestinal type, and poorly differentiated

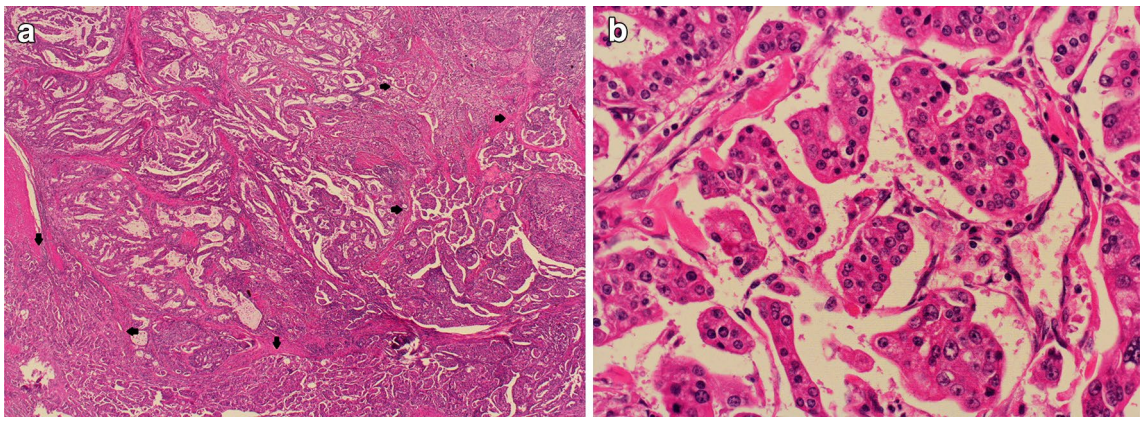


**Fig. 1** Histological findings of invasive micropapillary carcinoma in gastric adenocarcinoma cases. **a** Invasive micropapillary carcinoma (arrow) in the background of papillary adenocarcinoma with poorly adenocarcinoma by conventional histological examination with hematoxylin and eosin staining (original magnification, ×4). **b** Small clusters of tumor cells were observed surrounded by lacunar-like clear spaces (original magnification, ×40)

adenocarcinoma (por), mucinous (muc) adenocarcinoma, and signet-ring cell carcinoma (sig), which are of the diffuse type.

### Treatment

Patients underwent standard gastrectomy based on Japanese gastric cancer guidelines [13]. Distal or total gastrectomy with D2 lymph node (LN) dissection was performed for patients with advanced cancer. In case early gastric cancer was suspected, distal or total gastrectomy with D1 plus LN dissection was performed. Patients with advanced cancer received adjuvant chemotherapy with oral S1 (tegafur/gimeracil/oteracil) for 12 months. The treatment strategy after recurrence was decided at the discretion of the physicians.

### Follow-up

Follow-up data in the database were collected semiannually during routine follow-ups. All the patients were assessed at intervals for local control and distant metastases by physical examination, contrast computed tomography (CT) of the chest and abdominal cavity, and blood tests. In principle, these results were recorded at follow-up visits every 3 months during the first 3 years, every 6 months during the next 2 years, and annually thereafter when considered necessary. Endoscopy was performed within 1 year of surgery, and once every year thereafter. Patients in whom recurrence was suspected underwent contrast CT, enhanced magnetic resonance imaging of the liver, and/or positron emission tomography. Recurrence was diagnosed pathologically by biopsy and/or radiologically.

### Statistical analysis

All data were presented as median values and associated ranges. Clinicopathological analyses were performed using a Chi square test, Fisher's exact test, *t* test, Mann–Whitney *U* test. DFS was defined as the interval between surgery and relapse or death. DSS was decided as the interval between surgery and death related to gastric carcinoma. The durations of DFS and DSS were analyzed using the Kaplan–Meier method, and differences in the DFS and DSS of IMPC and non-IMPC patients were assessed using log-rank tests. A value of $p < 0.05$ indicated a statistically significant difference.

To reduce the effect of treatment selection bias and potential confounding in this observational study, rigorous adjustment for significant differences in the baseline characteristics of the patients was performed with propensity score matching. The propensity score was estimated using a logistic regression model that adjusted for patient characteristics and tumor factors chosen for their potential association with the outcome of interest based on clinical knowledge. Adjusted confounders were age, sex, tumor location, macroscopic and histological type, maximum size of tumor, and pathological tumor invasion depth; both groups were matched using 1:1-optimal-matching and replacement.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

## Results

### Clinicopathological characteristics of gastric carcinoma with and without IMPC component

Of the 882 patients who underwent gastrectomy for gastric cancer, 35 (4.0%) had an IMPC component. Immunostaining for lymphovascular invasion was conducted in 10 cases. The proportion of the IMPC component ranged from 5 to 75%, and this comprised less than 20% of the tumor in 24 (69%) patients. The IMPC components of some patients were located at the invasive front; however, some were scattered in the submucosa.

Table 1 shows a comparison of the patient demographics and clinicopathological factors in cases of resected gastric carcinoma. There were significant differences in the histological type ($p < 0.001$), pathological depth of tumor invasion ($p < 0.001$), lymphatic invasion ($p < 0.001$), venous invasion ($p < 0.001$), rate of lymph node metastasis ($p = 0.008$), positive rate of peritoneal lavage cytology ($p = 0.009$), and tumor recurrence ($p < 0.001$) between the patients with and without IMPC.

### Propensity score-matched analysis

Table 2 shows the clinicopathological and tumor factors of the 35 patients with IMPC and 35 without IMPC after propensity score matching. Analysis of heterogeneity after matching between the two groups revealed an almost equal distribution of age, sex, tumor location, macroscopic type, size of tumor, histological type, and pathological depth of invasion.

### Pathological factors and clinical outcomes after propensity score-matched analysis

Table 3 demonstrates the pathological factors and clinical outcomes in the patients with and without IMPC after propensity score matching. Chemotherapy was administered to

**Table 1** Clinicopathological factors of 35 patients with IMPC and 847 patients without IMPC of gastric carcinoma

| | Gastric carcinoma with IMPC ($n=35$) | Gastric carcinoma without IMPC ($n=847$) | $p$ value |
|---|---|---|---|
| Age, years | | | |
| Median, range | 73, 45–87 | 71, 33–95 | 0.368 |
| Gender | | | |
| Female, *n* (%) | 10 (29) | 258 (30) | 1.000 |
| Male, *n* (%) | 25 (71) | 589 (70) | |
| Location of gastric tumor | | | |
| Upper, *n* (%) | 12 (34) | 194 (23) | 0.151 |
| Middle, lower, *n* (%) | 23 (66) | 553 (77) | |
| Macroscopic type[a] | | | |
| Type 0, 1, 2, *n* (%) | 19 (54) | 552 (65) | 0.208 |
| Type 3, 4, 5, *n* (%) | 16 (46) | 295 (35) | |
| Size of tumor, mm | | | |
| Median, range | 56, 22–138 | 45, 3–280 | 0.261 |
| Histological type[b] | | | |
| Por, sig, muc, *n* (%) | 4 (11) | 375 (44) | < 0.001* |
| Tub, pap, *n* (%) | 31 (89) | 472 (56) | |
| Surgical resection | | | |
| Total gastrectomy, *n* (%) | 9 (26) | 173 (20) | 0.521 |
| Others, *n* (%) | 26 (74) | 674 (80) | |
| Pathological depth of tumor invasion[c] | | | |
| T1, *n* (%) | 3 (9) | 414 (49) | < 0.001* |
| T2, 3, 4, *n* (%) | 32 (91) | 433 (51) | |
| Lymphatic invasion | | | |
| Negative, *n* (%) | 2 (6) | 374 (44) | < 0.001* |
| Positive, *n* (%) | 33 (94) | 473 (56) | |
| Venous invasion | | | |
| Negative, *n* (%) | 0 | 366 (43) | < 0.001* |
| Positive, *n* (%) | 35 (100) | 481 (57) | |
| Lymph node metastasis | | | |
| Negative, *n* (%) | 12 (34) | 488 (58) | 0.008* |
| Positive, *n* (%) | 23 (66) | 359 (42) | |
| Peritoneal lavage cytology | | | |
| Negative, *n* (%) | 27 (77) | 776 (92) | 0.009* |
| Positive, *n* (%) | 8 (23) | 71 (8) | |
| Primary site of recurrence | | | |
| Liver, *n* (%) | 7 (20) | 15 (2) | < 0.001* |
| Others, *n* (%) | 6 (17) | 128 (15) | |
| No, *n* (%) | 22 (63) | 704 (83) | |

T1: M, SM; T2: MP; T3: SS; T4: SE, SI

*IMPC* invasive micropapillary carcinoma, *tub* tubular adenocarcinoma; well differentiated, moderately differentiated adenocarcinoma, *pap* papillary adenocarcinoma, *muc* mucinous adenocarcinoma, *por* poorly differentiated adenocarcinoma, solid type and non-solid type, *sig* Signet-ring cell carcinoma

* indicates a statistically significant difference as a value of $p < 0.05$

[a]The macroscopic type of resected gastric cancers was classified according to the Japanese Society for Gastroenterology endoscopic criteria as Type 0, and Types 1–5

[b]The gastric cancers were evaluated according to the Japanese Gastric Cancer Association, 14th Japanese classification of gastric carcinoma

[c]The gastric cancers were evaluated according to the Japanese Gastric Cancer Association, 14th Japanese classification of gastric carcinoma

**Table 2** Clinicopathological and tumor factors for patients of 35 patients with IMPC and 35 patients without IMPC after propensity score matching

| | Gastric adenocarcinoma with IMPC ($n=35$) | Gastric adenocarcinoma without IMPC ($n=35$) | $p$ value |
|---|---|---|---|
| Age, years | | | |
| 70≤, *n* (%) | 23 (66) | 23 (66) | 1.000 |
| <70, *n* (%) | 12 (34) | 12 (34) | |
| Gender | | | |
| Female, *n* (%) | 10 (29) | 9 (26) | 1.000 |
| Male, *n* (%) | 25 (71) | 26 (74) | |
| Location of tumor | | | |
| Upper, *n* (%) | 12 (34) | 14 (40) | 0.805 |
| Middle, lower, *n* (%) | 23 (66) | 21 (60) | |
| Macroscopic type[a] | | | |
| Type 0, 1, 2, *n* (%) | 19 (54) | 19 (54) | 1.000 |
| Type 3, 4, 5, *n* (%) | 16 (46) | 16 (46) | |
| Size of tumor, mm | | | |
| 50≤, *n* (%) | 23 (66) | 23 (66) | 1.000 |
| <50, *n* (%) | 12 (34) | 12 (34) | |
| Histological type[b] | | | |
| Por, sig, muc, *n* (%) | 4 (11) | 2 (6) | 0.673 |
| Tub, pap, *n* (%) | 31 (89) | 33 (94) | |
| Pathological depth of tumor invasion[c] | | | |
| T1, *n* (%) | 3 (9) | 5 (14) | 0.710 |
| T2, 3, 4, *n* (%) | 32 (91) | 30 (86) | |

T1: M, SM; T2: MP; T3: SS; T4: SE, SI

*IMPC* invasive micropapillary carcinoma, *tub* tubular adenocarcinoma; well differentiated, moderately differentiated adenocarcinoma, *pap* papillary adenocarcinoma, *muc* mucinous adenocarcinoma, *por* poorly differentiated adenocarcinoma, solid type and non-solid type, *sig* signet-ring cell carcinoma

[a]The macroscopic type of resected gastric cancers was classified according to the Japanese Society for Gastroenterology endoscopic criteria as Type 0, and Types 1–5

[b]The gastric cancers were evaluated according to the Japanese Gastric Cancer Association, 14th Japanese classification of gastric carcinoma

[c]The gastric cancers were evaluated according to the Japanese Gastric Cancer Association, 14th Japanese classification of gastric carcinoma

22 patients with IMPC (67%) in contrast to the 14 patients without IMPC (40%, $p=0.094$). No significant difference was observed in the rate of lymph node metastasis ($p=0.465$), positive rate of peritoneal lavage cytology ($p=0.084$), and venous invasion ($p=0.114$). However, the patients with IMPC had a higher incidence of lymphatic invasion (94%) than those without IMPC (69%, $p=0.012$).

## Survival analysis and recurrence after propensity score-matched analysis

The incidence of recurrence after gastrectomy in patients with IMPC (37%) was significantly higher than that in patients without IMPC (6%, $p=0.002$); moreover, patients with IMPC more frequently developed metastasis in the liver (20%) as a primary site of recurrence than patients without IMPC (3%, $p=0.006$). In terms of the primary site of recurrence apart from the liver, in the IMPC patients, five cases of lymph node metastasis and one of peritoneum metastasis were observed. Two patients without IMPC had peritoneum metastasis. Furthermore, the recurrent pattern of liver metastasis was a single lesion in six patients (86%), two of whom had lymph node metastasis, simultaneously. Furthermore, for liver metastasis cases, immunohistostaining of MUC1, epithelial membrane antigen (EMA), CD31, and CD10 were performed; however, no significant findings were found (Table 4).

As shown in Fig. 2, the 3-year DFS rates after gastrectomy in patients with and without IMPC were 62.2% and 93.4%, respectively. There was a significant difference in the 3-year DFS rates between the two groups ($p=0.003$). Furthermore, the 3-year DSS rates were 61.8% in the IMPC patients and 92.4% in the matched patients without IMPC ($p=0.016$, Fig. 3).

**Table 3** Pathological factors and clinical outcome for patients with IMPC and 35 patients without IMPC after propensity score matching

| | Gastric adenocarcinoma with IMPC ($n=35$) | Gastric adenocarcinoma without IMPC ($n=35$) | $p$ value |
|---|---|---|---|
| Lymphatic invasion | | | |
| Negative, $n$ (%) | 2 (6) | 11 (31) | 0.012* |
| Positive, $n$ (%) | 33 (94) | 24 (69) | |
| Venous invasion | | | |
| Negative, $n$ (%) | 0 | 4 (11) | 0.114 |
| Positive, $n$ (%) | 35 (100) | 31 (89) | |
| Lymph node metastasis | | | |
| Negative, $n$ (%) | 12 (34) | 16 (46) | 0.465 |
| Positive, $n$ (%) | 23 (66) | 19 (54) | |
| Peritoneal lavage cytology | | | |
| Negative, $n$ (%) | 27 (77) | 33 (94) | 0.084 |
| Positive, $n$ (%) | 8 (23) | 2 (6) | |
| Primary site of recurrence[a] | | | |
| Liver, $n$ (%) | 7 (20) | 1 (3) | 0.006* |
| Others, $n$ (%) | 6 (17) | 1 (3) | |
| Lymph node | 5 | 0 | |
| Peritoneum | 1 | 1 | |
| No, $n$ (%) | 22 (63) | 33 (94) | |

*IMPC* invasive micropapillary carcinoma

* indicates a statistically significant difference as a value of $p < 0.05$

[a]The site that recurrence was first confirmed

## Discussion

Invasive micropapillary carcinoma has been recently reported to be an aggressive variant of carcinoma with a high incidence of lymph node metastasis and poor clinical outcomes, not only in the breast but also in various other organs, including the gastrointestinal tract [1, 3]. However, survival outcomes in gastric adenocarcinoma patients with IMPC have not been clarified. Previous studies found that IMPC patients account for only 0.07–13.40% of gastric adenocarcinoma patients; however, IMPC patients share common histopathological findings, such as high incidence of lymphatic and venous invasion, with gastric adenocarcinoma patients [4–11]. In the present study, IMPC was identified in 4% of gastric adenocarcinoma cases; pure IMPC tumors were not observed. Furthermore, despite the small size of IMPC lesions, they were associated with a high frequency of lymphatic invasion, and minor IMPC components were sometimes detected at the leading front of cancer invasion, which is unlike other carcinomas. It is believed that IMPC morphology along with the peculiar inverted structure of pseudopapillary clusters in the empty space may be responsible for IMPC-related stromal and lymphatic invasion; therefore, the presence of even small IMPC lesions can indicate tumor aggressiveness [4].

Few studies have reported poor prognoses in gastric adenocarcinoma cases with IMPC. These studies reported 3-year overall survival rates of 45–59% and 3-year DFS rates of 40–62% in IMPC patients [4–8]. In two of the above-stated reports, significant differences were demonstrated in the DFS rates of patients with IMPC of the stomach and stage-matched controls. The 3-year DFS rate of patients with IMPC was 40.5%, whereas that of stage-matched patients without IMPC was 72.6% ($p=0.02$) [5]. Furthermore, the overall survival of patients with IMPC was significantly shorter than that of patients with conventional adenocarcinoma when using matching ($p=0.031$) [6]. Although we analyzed our data using a more detailed propensity score matching methodology than Zhang et al., our prognostic results were similar. In the present study, we found a significant difference in 3-year DFS and DSS rates between patients with gastric IMPC and controls using propensity score-matched analysis; this analysis not only included location, size, and type of tumor but also pathological invasion depth as the tumor-related factors that seem to affect prognoses. A review article on a large-scale trial focusing on breast cancer showed that IMPC is an unfavorable prognostic factor for relapse-free survival and DSS compared with invasive ductal carcinoma without IMPC [14].

The specific recurrence pattern associated with IMPC has not yet been clarified. A report describing a case of pure IMPC with metastasis indicated the possibility of metastasis to the lymph nodes and liver with strongly positive MUC1 [15].The 2009 annual report of the Japanese Gastric

**Table 4** Clinicopathological factors for IMPC patients with recurrence of liver metastasis

| Factors | With IMPC ($N=7$) |
|---|---|
| Age, years | |
| Median, range | 74, 62–81 |
| Gender | |
| Female, *n* (%) | 3 (43) |
| Male, *n* (%) | 4 (57) |
| Gastric tumor | |
| Pathological metastatic lymph node | |
| Positive, *n* (%) | 6 (86) |
| Peritoneal lavage cytology | |
| Positive, *n* (%) | 3 (43) |
| Lymphatic invasion | |
| Positive, *n* (%) | 7 (100) |
| Venous invasion | |
| Positive, *n* (%) | 7 (100) |
| Immunohistostaining | |
| Ki67 | |
| Positive, *n* (%) | 4 (57) |
| CD31 | |
| Positive, *n* (%) | 0 |
| CD10 | |
| Positive, *n* (%) | 2 (29) |
| EMA | |
| Positive, *n* (%) | 2 (29) |
| MUC1 | |
| Positive, *n* (%) | 1 (14) |
| Metastatic liver tumor | |
| Time to recurrence from gastric resection, months | |
| Median, range | 6.0, 2–12.6 |
| Recurrent pattern of liver metastasis | |
| Single, *n* (%) | 6 (86) |
| Multiple, *n* (%) | 1 (14) |
| Sub-Site of recurrence with liver metastasis[a] | |
| Liver alone, *n* | 4 |
| Liver and lymph node, *n* | 2 |
| Liver and lung and lymph node, *n* | 1 |
| Liver and peritoneum, *n* | 0 |
| Site of recurrence in terminal stage[b] | |
| Liver alone, *n* | 1 |
| Liver and multi-organs excluding peritoneum, *n* | 3 |
| Liver and multi-organs including peritoneum, *n* | 3 |

*IMPC* invasive micropapillary carcinoma

[a]Another recurrence site that occurred at the same time when the liver recurrence was first confirmed

[b]Expansion of the site of recurrence at the final or terminal stage

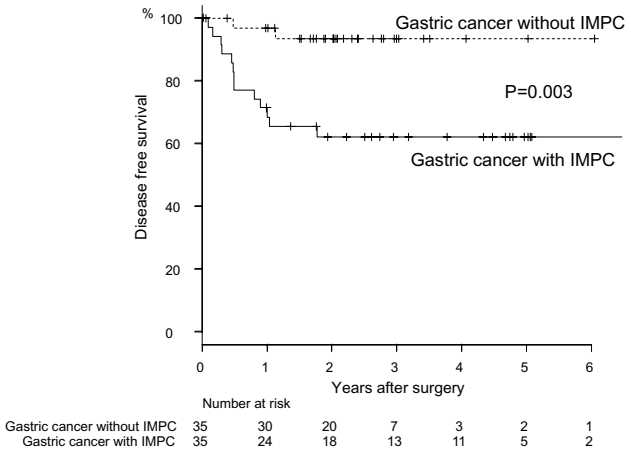


**Fig. 2** Disease-free survival. The 3-year disease-free survival (DFS) rates were 62.2% for patients with IMPC and 93.4% for those without IMPC; the DFS rates differed between patients with and without IMPC, statistically ($p=0.003$)

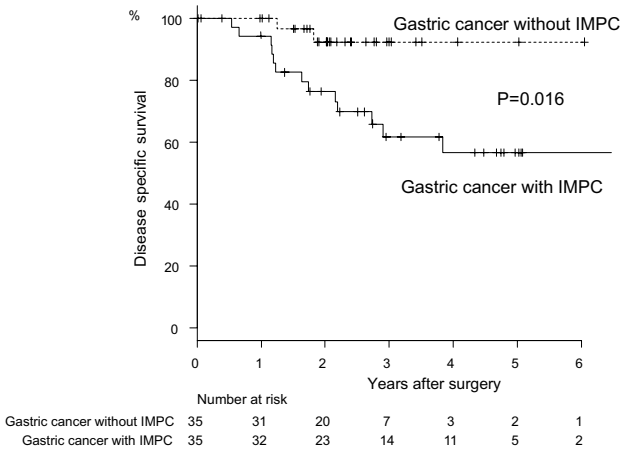


**Fig. 3** Disease-specific survival. The 3-year disease-specific survival (DSS) rates were 61.8% for patients with IMPC and 92.4% for patients without IMPC; the DSS rates differ between patients with and without IMPC ($p=0.016$)

Cancer Association nationwide registry revealed that the frequent causes of death in patients who had undergone gastrectomy were peritoneal metastasis ($n=1283$; 9.9%) followed by other diseases and local recurrence, including node metastasis. The frequency of liver metastasis was only 2.7% ($n=357$) [16]. However, in our IMPC patients, 20% of the cases showed high frequencies of recurrence in the liver. In particular, among three of the eight cases with positive peritoneal lavage cytology that involved liver metastasis recurrence, only one case showed peritoneal metastasis recurrence. Furthermore, the recurrence pattern of liver metastasis included a single lesion and simultaneous lymph node metastasis in about half of the cases; therefore, a

pathway of metastasis due to active lymph or vascular invasion was predicted.

Expression patterns of cell adhesion molecules in IMPC of the breast have been examined previously [17]. Down-regulation of major cell adhesion molecules may induce detachment of the tumor cells from the primary lesions due to weakening of cell-to-cell and cell-to-matrix adhesion, facilitating subsequent penetration into the lymph-vascular spaces in IMPC. Therefore, there is a possibility that progression of peritoneal dissemination is not induced; however, hematogenous and lymphogenous progressions may be accelerated. In fact, there was no significant difference in the metastatic frequency of dissected lymph nodes. However, with respect to recurrence pattern, 5 patients with IMPC had lymph node recurrence. Furthermore, all these patients had recurrence in the distant lymph nodes, which were not dissected. Therefore, we suspected that lymphatic invasion was aggressive.

In the previous study, CD31, MUC1, EMA, CD10, and Ki67 immunohistostaining were confirmed in cases with metastasis. However, the positivity rate varies across studies, and no consensus has been reached regarding this issue [6–8, 10, 11]. In our IMPC cases with liver metastasis, these immunostains were re-investigated. The high positivity for Ki67, one of the tumor growth factors, may be associated with liver metastasis in IMPC cases. These findings may suggest that the invasive image with IMPC is more active than the simple vascular invasive image. However, CD31 staining was negative, and thus, no consistent conclusion could be drawn. This might be attributable to the heterogeneity of gastric cancer tissue, which is considered to be different from that of solid cancers, such as breast cancer.

Chemotherapy is a very important factor when analyzing DSS and DFS. Chemotherapy was administered in more cases of IMPC; however, patients with IMPC showed a poor prognosis, even if the tumor was small. Therefore, if IMPC has a variable sensitivity to chemotherapy, it is possible that chemotherapy may not be useful for treating patients with IMPC.

The present study has several limitations. First, the components of gastric IMPC were rare; furthermore, the number of patients was too low for performing a rigorous pathological and statistical evaluation. Second, selection biases were unavoidable due to the use of retrospective data at a single center. Propensity score-matching analysis is increasingly being used in observational studies [18]; however, all biases cannot be offset with the use of this method. In fact, about 95% of patients without IMPC were excluded from the present study. Finally, immunostaining was not performed sufficiently, and needs to be incorporated in future studies along with genetic studies.

In conclusion, our data confirmed that IMPC was characterized by aggressive lymphatic invasion and short DFS and DSS, and that IMPC patients had high incidence of liver metastasis. The presence of the IMPC component in gastric carcinoma should be recognized as a risk factor for recurrence, particularly liver metastasis. Additional studies, especially large-scale prospective studies, should be performed for the establishment of more optimal management guidelines for this uncommon histological variant of gastric adenocarcinoma.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical standards** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study is a retrospective observational study, carried out by the opt-out method of our hospital website.

**Informed consent** For this type of study, formal consent is not required.

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