The Prognostic Impact of Macroscopic Serosal Change on Resectable Advanced Gastric Cancer

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Abstract

Background: Advanced gastric cancer sometimes causes macroscopic serosal change (MSC) due to direct invasion or inflammation. However, the prognostic significance of MSC remains unclear.

Methods: We retrospectively reviewed the clinical records of 1410 patients who had been diagnosed with deeper-than-pathological-T2 gastric cancer and undergone R0 gastrectomy with lymph node dissection between January 2000 and December 2012 at the National Cancer Center Hospital, Japan.

Results: MSC was not found in 108 of the 506 patients with pathological T4a (21.3%), whereas it was detected in 250 of the 904 patients with pathological T2-T3 (27.7%). The sensitivity, specificity and accuracy for diagnosing pathological serosa exposed (SE) by MSC were 78.7%, 72.3% and 74.6%, respectively. The MSC-positive cases had a worse 5-year overall survival (OS) than the MSC-negative cases in pT3 (72.9% vs. 84.3%, p=0.001), pT4a (56.2% vs. 73.4%, p=0.001), pStageIIB (76.0% vs. 88.4%, p=0.005), pStageIIIA (63.4% vs. 75.6%, p=0.019), pStageIIIB (53.6% vs. 69.2%, p=0.029) and pStage IIIC (27.6% vs. 50.0%, p=0.062). A multivariate analysis showed that MSC was a significant independent predictor for the OS (hazard ratio [HR], 1.587) along with the tumor depth (HR, 7.742), nodal status (HR, 5.783) and age (HR, 2.382). Peritoneal recurrence rates were higher in the MSC-positive cases than in the MSC-negative cases at each pT stage.

Conclusions: MSC was an important prognostic factor in patients with resectable locally advanced gastric cancer. MSC should be considered when predicting the patient prognosis.

Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide [1]. Generally, the Union for International Cancer Control (UICC) tumour-node-metastasis (TNM) classification[2], which consists of the depth of tumor invasion, number of regional nodal metastasis and distant metastasis, is the standard staging system of gastric cancer. The accurate determination of the invasive depth and lymph node metastasis and the optimization of the pT and pN categories are critical for determining the extent of disease, guiding treatment planning and predicting outcomes[3]. Pathological serosal invasion is a particularly important prognostic factor in gastric cancer[4], as tumor cells exposed to the serosa can easily spread to the peritoneal cavity. The peritoneum is the most frequent site of distant metastasis in gastric cancer.

During operations, surgeons can diagnose tumor invasion exposed to the serosa based on changes in the color or irregularities at the serosal surface of the primary tumor. Such macroscopic serosal change (MSC) is usually consistent with pathological serosa exposed (SE), although it is sometimes indicative of pathological subserosa (SS). Conversely, macroscopic SS sometimes transforms to pathological SE. MSC is therefore related to the tumor progression but might reflect different reactions, such as inflammation.

Several previous studies have shown that patients with macroscopic serosal invasion had a worse prognosis than those without such invasion [5, 6]. However, they only showed that patients with pathologically negative but surgically positive serosal invasion had a similar survival to those with pathologically positive serosal invasion. They did not examine the recurrence pattern or deeply discuss the role of MSC. Furthermore, those studies ignored the combination of such findings with nodal metastasis when evaluating the survival impact of MSC. The prognostic value must be evaluated after adjusting for other key prognosticators in a multivariate analysis or by stratifying by the same TNM stage. Bando et al[7] also reported that macroscopic serosal changes predicts peritoneal recurrence of gastric cancer. However, their study has only about one-third the number of patients compared to our study, but also includes D3 dissection, and includes about 32% of R2 resections.

Given the above, we examined the prognostic impact of MSC using latest TNM classification with a focus on peritoneal recurrence in patients with locally advanced gastric cancer which could be radical resection.

Methods

Patients

We retrospectively reviewed the clinical records of 5957 patients who received gastrectomy with nodal dissection for gastric cancer between January 2000 and December 2012 at the National Cancer Center Hospital, Japan. The selection criteria were 1) received total gastrectomy/proximal gastrectomy/distal gastrectomy/pylorus-preserving gastrectomy (TG/PG/DG/PPG)and 2) diagnosed with primary gastric cancer of pT2-T4b/N0-N3b. The exclusion criteria were 1) main tumor location at the esophagogastric junction or esophagus, 2) a final diagnosis of stage IV (positive for peritoneal lavage cytology, para-aortic lymph node metastasis, or peritoneal dissemination), 3) R1 or R2 resection, 4) a history of neoadjuvant chemotherapy, 5) a history of other malignant disease, 6) received other organ resection except splenectomy for the primary tumor, 7) received thoracotomy for the primary tumor, 8) tumors diagnosed as special pathological type (such as adenosquamous carcinoma; n = 3, endocrine carcinoma; n = 19, hepatoid adenocarcinoma; n = 1, others; n = 7) and 9) unknown intraoperative MSC. The patients were followed until their death or for five years, whichever came first. MSC was judged during surgery with findings of color and morphological differences between tumoral and normal surface of the serosa by experienced gastric surgeons and was recorded prospectively.

Postoperative therapy and follow-up

Based on the results of the ACTS-GC trial in Japan[8], S-1 has been the standard postoperative chemotherapy regimen since 2007. Therefore, postoperative adjuvant chemotherapy with S-1 was principally administered when the final tumor stage was consistent with the ACTS-GC criteria after 2007. Before 2007, S-1 was administered only for patients who participated in the ASCTS-GC trial and were allocated to the S-1 group. Outpatient follow-up involved physical examination and blood tests including tumor markers, every 3 to 6 months for the first 2 years postoperatively. Chest and abdominal computed

tomography were performed every 6 months for the first 3 years, and then annually until 5 years postoperatively.

Clinical and pathological factors

The 8th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis classification of gastric carcinoma was used for the tumor staging[2]. We reviewed the following clinical and pathological factors: age, gender, surgical procedure, splenectomy (yes/no), main location of the tumor, maximum tumor diameter, macroscopic type according to the Borrmann classification, histological type, intraoperative macroscopic serosal change (+/-), pathological T factor, pathological N factor, pathological stage, and adjuvant chemotherapy (yes/no). The histopathological diagnosis was determined by experienced pathologists. Resected specimens were diagnosed according to the Japanese Classification of Gastric Carcinoma 15th edition[9] and the stages were determined according to the UICC classification 8th edition.

Statistical analyses

All statistical analyses were performed using the SPSS statistical software program (ver. 24; SPSS Inc., Chicago, IL, USA). The chi-squared test and Student's *t*-test were used for the statistical analyses. OS was defined as the period from the date of surgery to the date of death due to any cause. Data for patients who did not experience an event were censored on the date of final observation. Survival data were obtained from hospital records. The survival curves were calculated using the Kaplan-Meier method and were compared by the log-rank test. Cox's proportional hazard model was used to perform the univariate and multivariate analyses. A P value of 0.05 was defined as denoting statistical significance.

The study was conducted with the approval of the Institutional Review Board of the National Cancer Center (No. 2017-077).

Results

Patients

Among the 5957 patients who received gastrectomy during this period, a total of 1410 met the eligibility criteria and were enrolled in this study. The flow diagram of the patients registered for this study is shown in Fig. 1. The median follow-up period was 78.0 months (range: 1–197 months). Table 1 shows the background characteristics and pathological findings of the patients. MSC-positive tumors had more advanced stage than MSC-negative tumors, thus total gastrectomy and splenectomy were more frequently selected in patients with MSC-positive tumors than those with MSC-negative disease.

Accuracy of the macroscopic diagnosis of serosal invasion

Table 2 shows the relationship between the intraoperative macroscopic diagnosis and pathological diagnosis. MSC was not found in 108 of the 506 patients who were diagnosed with pathological T4a or

T4b (21.3%), whereas it was detected in 250 of the 904 patients who were diagnosed with pathological T2-T3 disease (27.7%). The sensitivity, specificity and accuracy for diagnosing pathological SE based on MSC were 78.7%, 72.3% and 74.6%. The proportions of overestimation (MSC-positive but pathological T2 or T3) were 5.1% (33 of 648) in pT2 and 33.4% (217 of 648) in pT3. The proportions of underestimation (MSC-negative but pathological T4a or T4b) were 14.2% (108 of 762) in pT4a and 0% (0 of 762) in pT4b.

The Overall Survival

The overall survival (OS) was lower in MSC (+) patients than in MSC (-) patients at all T-stages, and the difference was significant in pT3 and pT4a (Fig. 2). The OS was also inferior in MSC (+) patients compared with MSC (-) patients in pStage IIB-IIIC (Fig. 3) to a significant degree, except for pStage IIIC.

A univariate analysis showed that the MSC, age, tumor diameter, tumor depth, nodal status, lymphatic invasion and vascular invasion were significantly associated with the OS. In the multivariate analysis, the MSC, age, pathological tumor depth and nodal status remained statistically significant (Table 3).

Recurrence patterns

There were significant differences in the rate of recurrence between MSC (+) and MSC (-) patients (40.6% vs. 14.1%, respectively; p < 0.001). The most predominant site was the peritoneum, followed by the lymph nodes in both groups. Peritoneal recurrence rates were higher in the MSC (+) group than in the MSC (-) group at each pT stage (Table 4), with statistical significance noted for pT2 (9.1% vs. 0.5%; p = 0.004) and pT4a/b (30.7% vs. 16.9%; p = 0.015).

Discussion

We explored the prognostic significance of MSC in patients with advanced gastric cancer. Even after stratification by T stage or final stage using the Eighth TNM Classification, the patients with MSC had a poorer prognosis than the patients without MSC, except for those with early stage disease. Furthermore, MSC was an independent prognostic factor for OS. These results suggest that MSC can be used to further stratify patients of identical T stage and final TNM stage. Therefore, MSC has utility for predicting the prognosis of patients with advanced gastric cancer.

Several studies have shown that MSC has a poor prognosis. Wang *et al*. [10] reported that pT3 MSC (+) patients had a similar prognosis to pT4a patients. Sang *et al*. [6] showed that pT2-3 MSC (+) patients had a similar survival rate to pT4a MSC (−) patients. However, in those studies, the effects of MSC on the final pathological stage, the combination of T stage and lymph node metastasis, were not evaluated. Bando *et al*. [7] reported that the magnitude of serosal changes predicted peritoneal recurrence of gastric cancer; they also showed that pT2 patients with marked macroscopic serosal invasion had a poorer prognosis than pT3 and pT4 patients with little or no macroscopic serosal invasion. However, that study involved only about one-third the number of patients as compared to our present study. In addition, this study also included patients who underwent D3 (para-aortic) lymph node dissection, and the R2 resection

rate was 32%. In contrast, our study involved strict eligibility to accurately verify the impact of MSC on the patients with resectable advanced gastric cancer.

Intraoperative MSC is determined based on the color of, and morphological differences between, the tumoral and adjacent normal surface of the serosa. In this study, MSC was found in pT2 and pT3 tumors, suggesting that it reflects not only the tumor itself but also reactions to it, such as inflammation. In pT4 cases, MSC may be negative when the tumor shows only slight invasion of the serosa without inflammation. Therefore, MSC-positive cases may have either a substantial tumor volume at the serosal surface or accompanying inflammation. Recently, it has been known that inflammatory reactions play important roles in the growth of tumors. Both cancer cells and the surrounding stromal and inflammatory cells engage in well-orchestrated reciprocal interactions to form an inflammatory tumor microenvironment that promotes tumor growth, angiogenesis, and metastasis [11, 12]. Our study showed that the rate of peritoneal recurrence was higher in MSC-positive than -negative pT2–T4 patients with negative lavage cytology (Table 4). This means that tumor cells can directly invade the serosa or cause serosal changes indirectly, such as by inducing inflammation, which can in turn cause peritoneal changes at distant sites even if intraoperative lavage cytologic analysis yielded a negative result. Previous studies also showed that the invasion area of the tumors at the serosal surface, and the magnitude of serosal change, are risk factors for peritoneal metastasis and prognosis [13, 7].

Most important finding in our present study is that not only MSC is an independent prognostic factor, similar to pT and pN, but also that MSC further stratifies the prognosis in patients with late-stage gastric cancer after stratifying by final TNM stage. This may lead to more efficacious postoperative adjuvant therapies, including switching from single to dual agents. Also, confirmation of the presence of MSC by staging laparoscopy may influence the selection of treatments such as preoperative chemotherapy in the future.

On the other hand, there was no marked difference in survival between MSC (+) and MSC (−) pStage IB and IIA patients. The stage IB group included only T2N0 cases, and the stage IIA group included T3N0 and T2N1 cases. MSC was not associated with peritoneal metastasis when pT2 and pT3 patients had no nodal metastasis. Peritoneal dissemination is established by detachment cancer cells from the gastric serosa and attachment to, and growth at, the peritoneum. And another mechanism of peritoneal dissemination is the release of tumor cells via lymphatic channels [14]. Pathologically serosa-negative (T2 or T3) tumor is thought to occur peritoneal dissemination from tumors with some degree of lymph node metastases.

Although the Kaplan–Meier curves of MSC (+) and MSC (−) stage IIIC patients were clearly dissociable, the difference in OS was not significant. This is likely because of the small number of MSC (−) cases included in the stage IIIC group (n = 20). In other words, cases having pT3 or pT4 tumor with extensive lymph node metastasis (7 ≤ N) classified as pStage IIIC almost show MSC (+). Accurate verification of the impact of MSC on Stage IIIC will require further cases.

This study had several limitations. First, it used a retrospective design and included patients treated at only a single cancer center. Therefore, a multicenter, prospective study is required to validate the present results. Second limitation is that the MSC-positive rate may be different in other hospitals. Sang et al. [6] reported the diagnostic accuracy for MSC to be 82.1%, with 87.1% sensitivity and 81.1% specificity. Our results showed a diagnostic accuracy of 74.6%, sensitivity of 78.7% and specificity of 72.3%. Although the difference was not large, there are some discrepancies for diagnosing MSC, depending on the institution and country.

Conclusion

MSC was an independent prognostic factor for the OS. Physicians should consider both MSC and the pathological stage when predicting the more accurate prognosis.

Abbreviations

MSC
macroscopic serosal change, OS:overall survival, SE:serosa exposed, HR:hazard ratio, UICC:Union for International Cancer Control, TNM:tumor node metastasis, SS:subserosa, TG:total gastrectomy, DG:distal gastrectomy, PG:proximal gastrectomy, PPG:pylorus preserving gastrectomy.

Declarations

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.
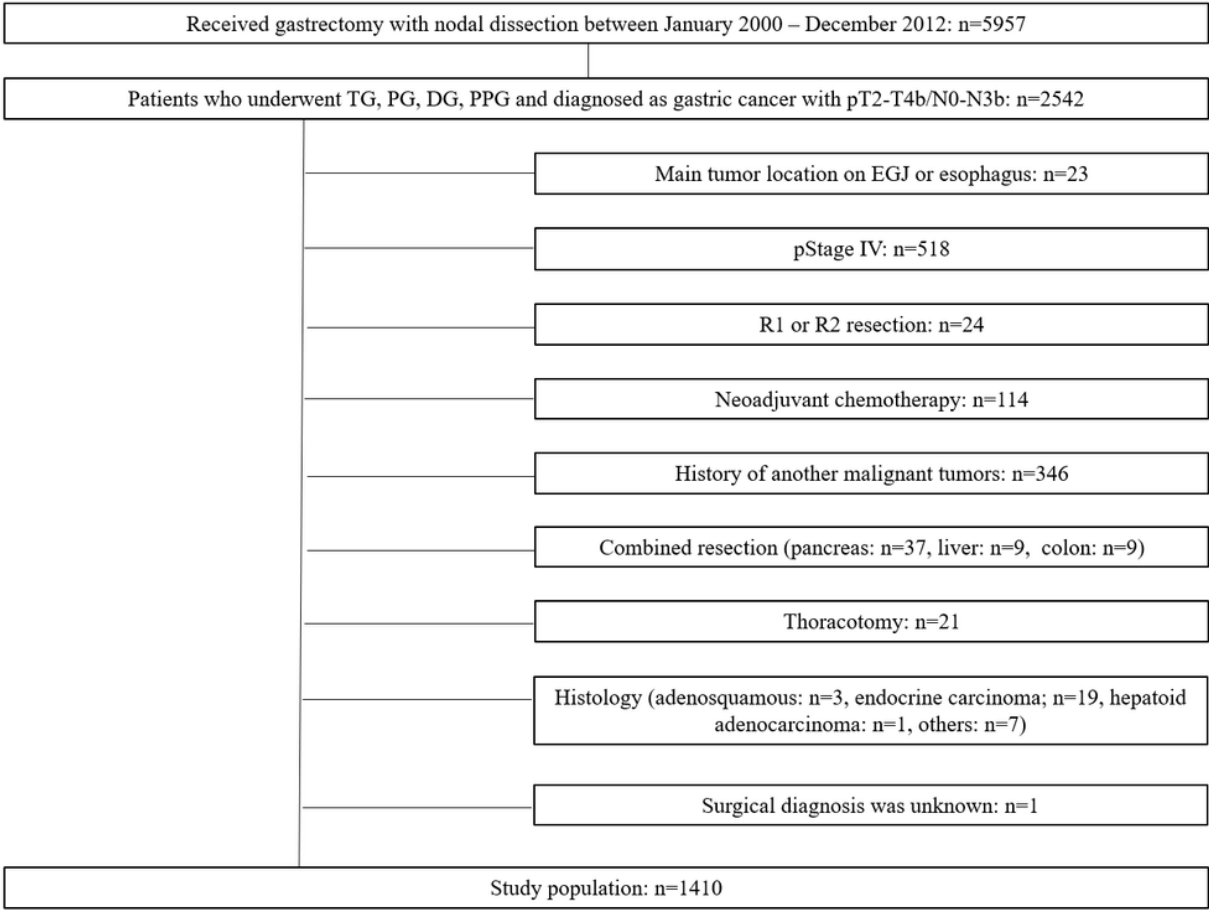
Figures

Figure 1

Study flow for the 5957 patients who underwent gastrectomy for gastric cancer between January 2000 and December 2012.
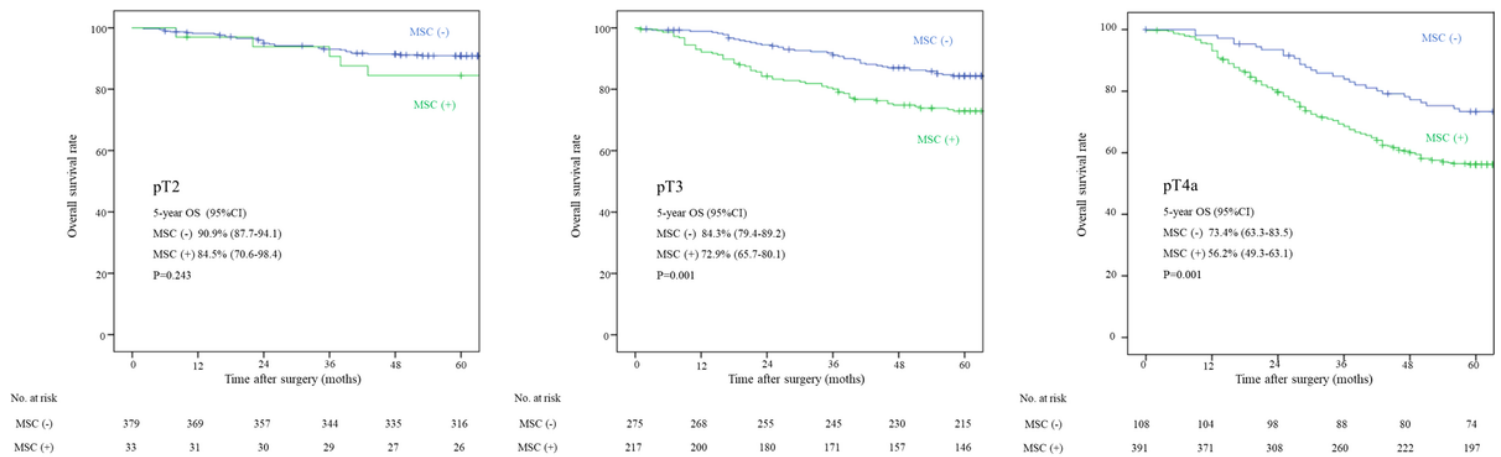
Figure 2

The 5-year survival rate in pT2–T4a according to MSC positivity. (A) The 5-year survival rates were slightly lower in patients with MSC (+) than MSC (−) T2 tumors (84.5% vs. 90.9%, P=0.243). (B and C) The 5-year survival rates were significantly lower in patients with MSC (+) than MSC (-) tumors of pT3 (72.9% vs. 84.3%, P=0.001) and pT4 (56.2% vs. 73.4%, P =0.001).
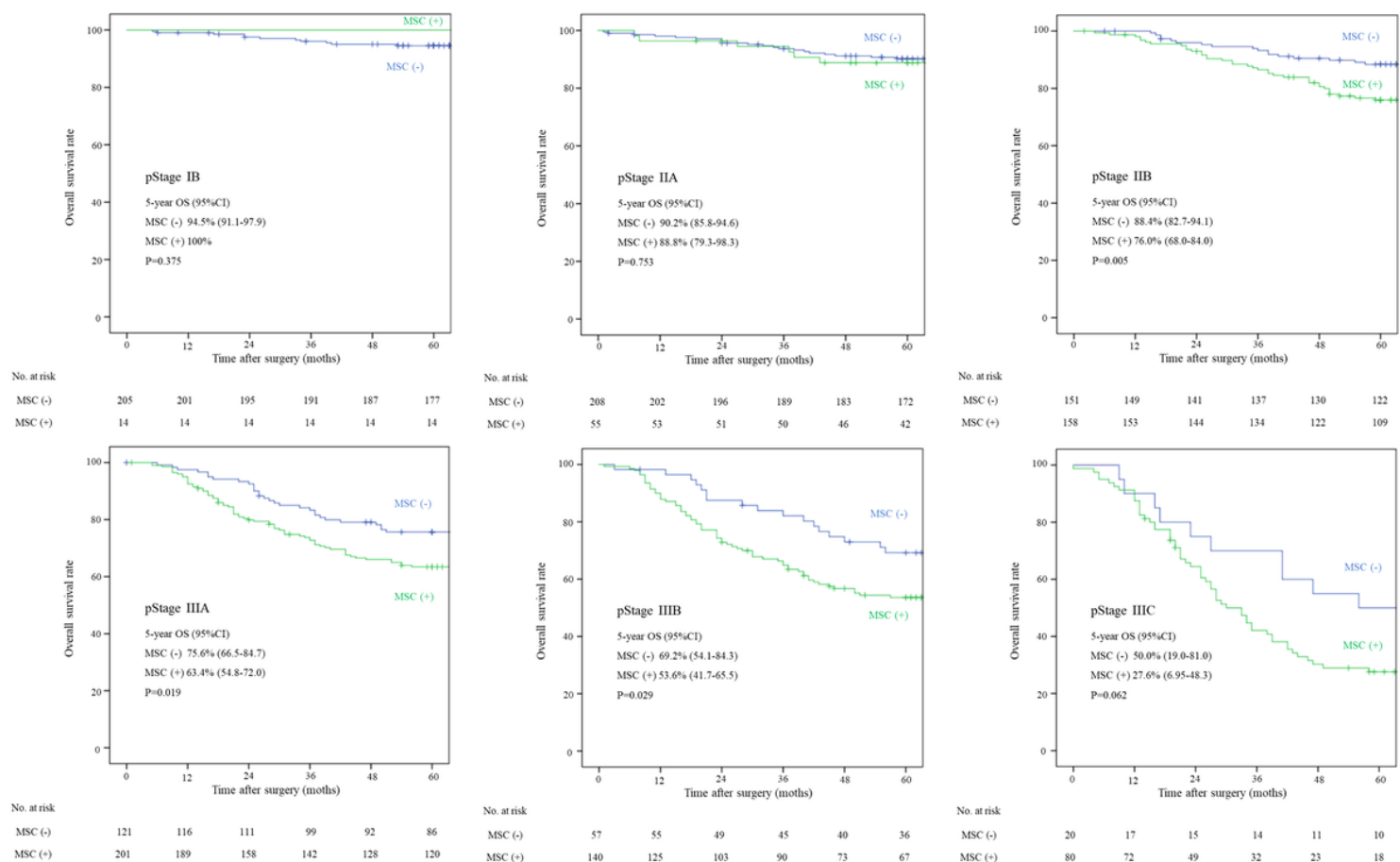
Figure 3

The 5-year survival rate in pStageIB−IIIC according to MSC positivity. (A and B) The 5-year survival rates were similar in patients with MSC (+) than MSC (−) tumors of pStageIB and IIA. (C-F) The 5-year survival rates were lower in patients with MSC (+) than MSC (-) tumors of pStageIIB (76.0% vs. 88.4%, P=0.005), pStageIIIA (63.4% vs. 75.6%, P=0.019), pStageIIIB (41.7% vs. 69.2%, P=0.029) and pStageIIIC (27.6% vs. 50.0%, P=0.062).

Supplementary Files

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