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Oncologic Outcome With Use of Sodium Hyaluronate–Carboxymethylcellulose Barrier in Gastric Cancer

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Hyaluronan is a component of an anti-adhesive barrier and has been implicated in tumor growth and metastasis. We aimed to determine whether this anti-adhesive barrier was associated with rates of postoperative complications and duration of survival in patients with gastric cancer. We identified 415 consecutive patients with gastric cancer who underwent gastrectomy. Information about patients' demographics, medical history, surgical procedures, postoperative complications, disease stage, histology, and survival was collected from medical records. One hundred and ninety-six patients received intraoperative placement of an anti-adhesive barrier composed of hyaluronan–carboxymethylcellulose (HA-CMC) (HA-CMC group), and 219 did not (control group). The incidence of postoperative complications was significantly increased in the control group (22.8%) compared with the HA-CMC group (13.3%). However, there was no significant difference in overall survival between the HA-CMC and control groups. Our study suggests that the anti-adhesive barrier does not affect oncologic outcome, nor does it increase postoperative complications in patients undergoing surgery for gastric cancer.

Key words: Hyaluronan – Survival – Adhesion – Prevention

Postoperative adhesions between adjacent tissues are a source of many complications including small bowel obstruction, difficult and dangerous reoperations, and infertility. Gastrectomy is associated with a high risk of bowel obstruction (incidence, 11.7%–38.5%).[1,2] Several clinical studies have reported that the use of anti-adhesive barrier composed of hyaluronan–carboxymethylcellulose

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(HA-CMC) significantly reduces the incidence and severity of adhesions after gastrointestinal surgery.[3–5]

Concerns exist about whether HA-CMC may increase tumor growth because its chemical composition includes hyaluronan, a component of the extracellular matrix known to enhance cell migration, differentiation, and proliferation.[6] Hyaluronan has been implicated in tumor growth, invasion, and metastasis in several *in vitro* and animal cancer models.[7–11] Thus, the use of HA-CMC in cancer surgery appears to have the potential to increase metastatic capability and reduce survival time.

In studies of human patients with colorectal and gynecologic cancer, no association has been found between the use of HA-CMC and cancer outcomes.[12–14] The impact of HA-CMC on survival outcomes in patients with gastric cancer has not been fully investigated. We conducted a retrospective review of patients who had gastrectomy for gastric cancer with the aim of determining whether the use of the HA-CMC barrier was associated with patients' disease-free survival, overall survival, and immediate complication rates.

Patients and Methods

Patients

We reviewed the medical records of all consecutive patients identified through our cancer registry at the Mie University Hospital between January 1992 and December 2008. We have been able to use HA-CMC (Seprafilm, Cambridge, MA) in all open gastrectomies since January 2001.

Variable and data collection

We determined HA-CMC barrier use from information recorded in operating room billing sheets and operative reports. Patients without documentation of receiving the HA-CMC barrier according to one of these sources were considered not to have received it. The adhesion barrier was placed at the discretion of the surgeon.

From patients' medical records, we extracted information on demographic characteristics, surgical procedures, disease stage, histology, immediate postoperative complications (*i.e.*, within 30 days after surgery), and survival. Disease stage and histology were examined according to the Japanese Classification of Gastric Carcinoma.[15] The complications were those commonly encountered in postoperative gastric cancer patients: documented infection, anastomotic failure, early postoperative small bowel obstruction (EPSBO), and death. EPSBO was as defined by Ellozy *et al*[16]: patients were judged to have EPSBO if, within the first 30 days, (1) they developed signs, symptoms, and X-ray evidence of return of bowel function, or (2) mechanical intestinal obstruction was definitively confirmed by laparotomy or contrast study. Documented infection was based on an identified source by clinical examination, imaging, or culture. Furthermore, we also examined the incidence of PSBO during follow-up.

Statistical analysis

Two-sample t test or χ^2 tests were used to compare patient characteristics, procedures, histopathologic characteristics, and postoperative complication rates between patients receiving or not receiving the HA-CMC barrier. The cumulative incidence of early and overall PSBO was calculated by the Kaplan–Meier method, and curves were compared by means of the log-rank test. Analysis of the cumulative incidence of overall PSBO included only patients for whom disease-free status could be confirmed; that is, patients were excluded if they did not receive curative resection, or had disease recurrence during follow-up. Disease-free and overall survival curves were also constructed by Kaplan–Meier estimation and compared by the log-rank test. The disease-free survival analysis included only patients for whom disease-free interval could be confirmed; that is, patients were excluded if they did not complete curative resection. All patients were included in the overall survival analysis. A significance level of 0.05 was used for each statistical test.

Results

We identified 415 consecutive patients operated on at our institution from 1992 to 2008 who were diagnosed with gastric cancer. One hundred and ninety-six patients received the HA-CMC barrier and 219 did not. Demographic and histopathologic characteristics are shown in Table 1. Age, sex, comorbidity, surgical history, disease stage, and histology were comparable between the 2 groups. In the HA-CMC group, all patients received the 2 sheets of Seprafilm under the midline incision. The estimated rates of curative resection for the HA-CMC and control groups were 75.5% and 74.9%, respectively.

All patients underwent gastrectomy for gastric cancer. As for operative data, there were no

Table 1 Patient demographic and histopathologic characteristics[a]

Characteristic	HA-CMC group (n = 196)	Control group (n = 219)	*P* value
Sex			
Male	135 (68.9%)	147 (67.1%)	0.7522
Female	61 (31.1%)	72 (32.9%)	
Age at diagnosis	64.9 (11.5)	63.0 (11.3)	0.0752
History of abdominal operation			
Yes	23 (11.7%)	36 (16.4%)	0.2052
No	173 (88.3%)	183 (83.6%)	
Comorbidity			
Yes	77 (39.3%)	71 (32.4%)	0.1520
No	119 (60.7%)	148 (67.6%)	
Stage			
I	92 (46.9%)	113 (51.8%)	0.5591
II	39 (19.9%)	33 (15.1%)	
III	39 (19.9%)	46 (21.1%)	
IV	26 (13.3%)	26 (12.0%)	
Histology			
Well differentiated	48 (24.5%)	66 (30.1%)	0.3503
Moderately differentiated	56 (28.6%)	63 (28.8%)	
Poorly differentiated	87 (44.4%)	88 (40.2%)	
Mucinous	5 (2.5%)	2 (0.9%)	

[a]Values are n (%) or mean (standard deviation).

significant differences between the groups in the type of gastrectomy, mean operative time, or mean blood loss (Table 2).

The incidence of immediate postoperative complications in the HA-CMC group was significantly reduced compared with that in the control group (Table 3). No patients had died within 30 days after surgery. There were no detectable differences between the groups for wound infection, intra-abdominal abscess, or leakage. However, the incidence of EPSBO in the HA-CMC group was significantly reduced compared with that in the control group.

The mean patient follow-up was 59.4 months. Patients who did not receive curative resection (n = 103) or experienced disease recurrence during follow-up (n = 47) were excluded from the analysis of the cumulative incidence of overall PSBO. As a result, there were 128 and 137 patients in the HA-CMC and control groups, respectively. The cumulative incidence was slightly, but not significantly, lower in the HA-CMC group (3.0% versus 5.1% at 1 year, and 4.7% versus 7.9% at 5 years; $P = 0.3636$) (Fig. 1).

Table 2 Operative characteristics[a]

Characteristic	HA-CMC group (n = 196)	Control group (n = 219)	*P* value
Operation time (min)	281.7 (62.5)	290.7 (64.7)	0.1350
Blood loss (g)	361.2 (278.1)	392.4 (229.4)	0.1931
Total gastrectomy (%)	82 (42.5)	93 (41.8)	0.9209
Partial gastrectomy (%)	114 (57.5)	126 (58.2)	

[a]Values are n (%) or mean (standard deviation).

Table 3 Postoperative complications occurring within 30 days[a]

	HA-CMC group (n = 196)	Control group (n = 219)	*P* value
Overall	26 (13.3%)	50 (22.8%)	0.0154
Wound infection	8 (4.1%)	19 (8.7%)	0.0725
Intra-abdominal infection	10 (5.1%)	10 (4.6%)	0.8223
EPSBO	3 (1.5%)	12 (5.5%)	0.0357
Leakage	7 (3.6%)	7 (3.2%)	0.9999

[a]Values are n (%).

In the overall survival analysis, all evaluated patients were included. There was no significant difference in the overall survival curves between the HA-CMC and control groups (Fig. 2, $P = 0.1682$). The 5-year overall survival estimates were 73.0% and 69.4%, respectively. Furthermore, we performed a subgroup analysis to examine curability status. Among the 312 patients who underwent curative resection (R0), 5-year overall survival was 86.7% and 79.2% for the HA-CMC and control groups, respectively (Fig. 3a). Among the 103 patients who underwent noncurative resection (R1 and R2), 5-year overall survival was 30.2% and 27.5% for the HA-CMC and control groups, respectively (Fig. 3b). There was no detectable difference in overall survival curves with regard to HA-CMC barrier

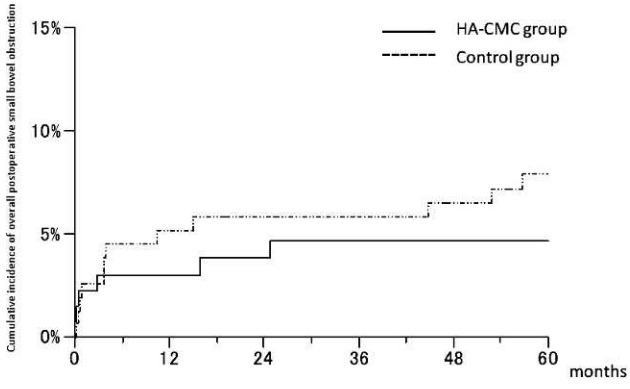

Fig. 1 Cumulative incidence of overall postoperative small bowel obstruction in patients with gastric cancer, comparing those receiving (n = 128) versus not receiving (n = 137) an HA-CMC barrier ($P = 0.3636$, log-rank test).

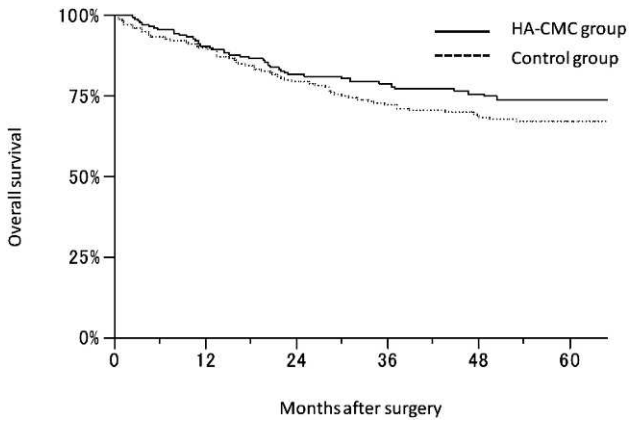

Fig. 2 Overall survival in patients with gastric cancer, comparing those receiving (n = 196) and those not receiving (n = 219) an HA-CMC barrier ($P = 0.4531$, log-rank test).

use when patients were stratified according to their curability status (Fig. 3a and 3b).

Patients who did not receive curative resection were excluded from the disease-free survival analysis. Among the 312 patients who underwent curative surgery, peritoneal recurrence was observed in 43 patients (11.8%), including 26 patients (13.3%) in the control group and 17 patients (10.2%) in the HA-CMC group, which was not a significant difference between these 2 groups ($P = 0.3645$). Among the patients with serosal invasion (n = 78; HA-CMC group, n = 25; control group, n = 53) peritoneal recurrence was observed in 27 patients, including 8 patients (32%) in the HA-CMC group and 19 patients (36%) in the control group, which was not a significant difference between these 2 groups ($P = 0.8031$). There were no significant differences in disease-free survival between the HA-CMC and control groups (Fig. 4, $P = 0.5287$). The 5-year disease-free survival estimates were 86.5% in the HA-CMC group and 83.3% in the control.

Discussion

We believe our study to be the first to examine whether use of an HA-CMC barrier affects long-term cancer survival in patients with gastric cancer. The data presented in this study suggest that anti-adhesive barrier composed of HA-CMC does not reduce the overall and disease-free survival time in patients undergoing open surgery for gastric cancer. Among patients who received noncurative resection, there was also no significant difference in overall survival time between those receiving and those not receiving the HA-CMC barrier.

The theoretical concerns regarding the safety of HA-CMC in the oncologic setting arises from conflicting *in vitro* and *in vivo* data. Tan *et al* have demonstrated that sodium hyaluronate enhances tumor proliferation and motility in colorectal tumor cell lines. They have also identified higher tumor growth in the peritoneal cavity of experimental animals treated with sodium hyaluronate as compared with untreated controls.[9] They have suggested that sodium hyaluronate may enhance intraperitoneal tumor growth. Conversely, other authors have concluded that HA-CMC barrier placement does not influence tumor spread in animal models of colon cancer.[10,11]

Anti-adhesive barrier composed of HA-CMC is effective at reducing adhesions that are due to benign colorectal and gynecologic procedures.[3,4,17,18] However, there have been few studies

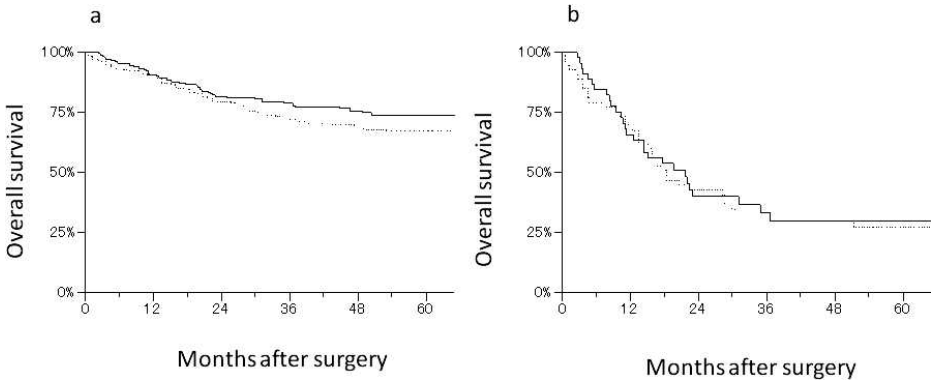

Fig. 3 Overall survival, stratified according to curability status. (a) Curative resection, comparing those receiving (n = 148) and those not receiving (n = 164) an HA-CMC barrier ($P = 0.1017$, log-rank test). (b) Noncurative resection, comparing those receiving (n = 48) and those not receiving (n = 55) an HA-CMC barrier ($P = 0.7400$, log-rank test).

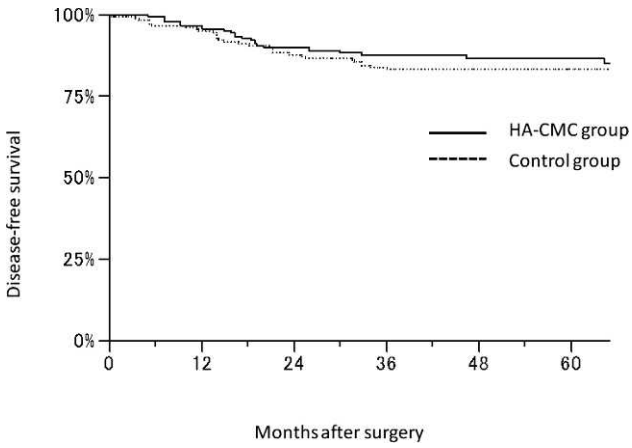

Fig. 4 Disease-free survival in patients with gastric cancer, comparing those receiving (n = 148) and those not receiving (n = 164) an HA-CMC barrier ($P = 0.9286$, log-rank test).

concerning its safety in cancer patients. Oikonomakis and colleagues performed the first retrospective evaluation of short-term outcomes in patients with colorectal cancer who had received an HA-CMC barrier.[12] They reported that HA-CMC barrier did not adversely affect the short-term recurrence rate after curative resection. Our group has also performed prospective evaluation of long-term outcomes in patients with rectal cancer and has shown that use of the HA-CMC barrier had no effect on metastases or recurrence from rectal cancer.[13] Hayashi and colleagues reported no adverse effects of HA-CMC on the overall survival time in patients with gastric cancer, demonstrating similar overall survival rates in those patients receiving and those not receiving the HA-CMC barrier.[19] In their study, however, the follow-up period was less than 3 years, and patients with distant metastasis including peritoneal seeding were excluded. In contrast, patients in our study were followed for a mean of 5 years, and we also examined the impact of the HA-CMC barrier on outcome in patients who had noncurative resection. No differences were observed in disease-free or overall survival between the HA-CMC and control groups. After curative resection for gastric cancer, the peritoneum is the most common site of metastasis.[20] Serosal invasion has been reported to be a significant risk factor for peritoneal metastasis.[21,22] However, it is unclear whether the use of HA-CMC anti-adhesion barriers increases the peritoneal metastasis rate after curative surgery. Our study found no significant difference in the peritoneal metastasis rate between the HA-CMC and control groups, regardless of the depth of tumor invasion, indicating that the use of HA-CMC anti-adhesion barriers did not affect oncologic outcomes, regardless of whether patients underwent curative or noncurative resection.

In addition to survival, we assessed 30-day postoperative complication rates and the long-term incidence of PSBO. Our data showed that the incidence of postoperative complications was significantly reduced in patients who received the HA-CMC barrier compared with patients who did not. Becker and colleagues have demonstrated that the HA-CMC barrier seems safe in the setting of nonmalignant colorectal surgery.[4] Studies of adhesion barriers in the gastric-cancer literature are limited. One prospective study[19] examined the efficacy of the HA-CMC barrier and complications in patients undergoing surgery for gastric cancer. There was no significant difference between the HA-CMC group and the control group for early postoperative complications. The incidence of EPSBO was significantly reduced in the HA-CMC group compared with the control group, although there were no significant differences in other complications between those who received the HA-CMC barrier and those who did not. We included EPSBO in our analysis of early postoperative complications. This result was similar to other retrospective studies.[23,24] Therefore, it seems that HA-CMC is safe and effective for reducing the incidence of EPSBO. Although the incidence of EPSBO was significantly reduced in patients who received the HA-CMC barrier compared with the controls, the cumulative incidence of overall small bowel obstruction in the HA-CMC group was slightly but not significantly lower than that in the control group. This result was consistent with other studies.

The limitation of this study include its retrospective, single-center design, a potential bias in the selection of patients who underwent placement of HA-CMC anti-adhesion barriers, and potential error in the accuracy of documentation in the medical records. In spite of these limitations, we believe that if a survival difference had been detected between the HA-CMC and control groups, additional prospective study would be warranted. It would be more appropriate to compare the median overall survival times than the survival rates between groups, but such comparisons would require a much larger sample size.

Our data suggest that HA-CMC does not have a deleterious effect on disease-free and overall survival. Given similar results in other cancers and the

potential benefits with respect to adhesion prevention, the use of the HA-CMC barrier should be considered in patients with open gastrectomy for gastric cancer.

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