

Figure 1 Algorithm for the management of perforation related to endoscopic submucosal dissection.

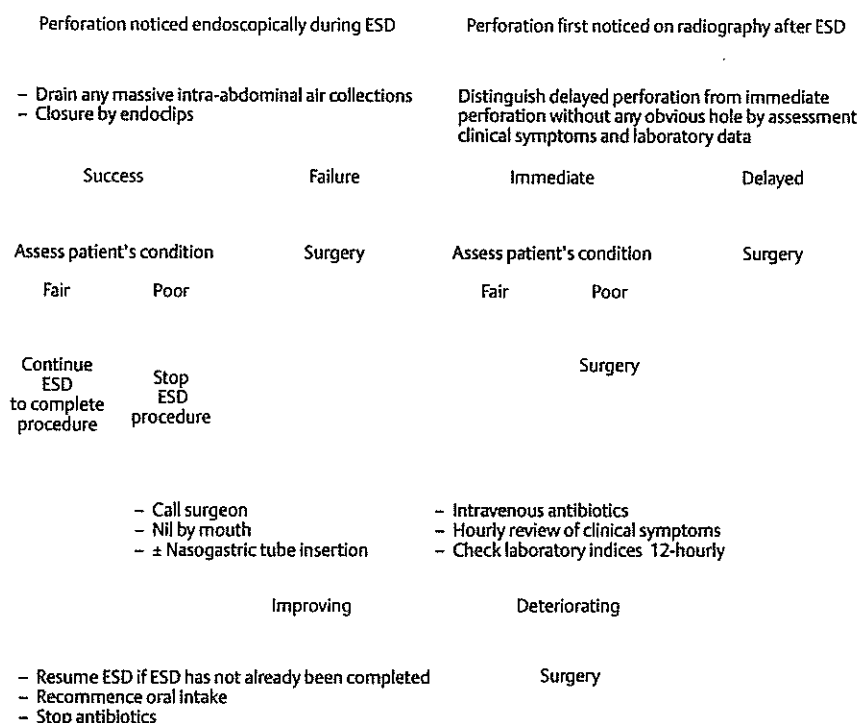


Table 1 Demographic characteristics of the 27 patients who developed a perforation during endoscopic submucosal dissection procedures and the clinicopathological features of their tumors

Mean age (range), years	65 (54–76)
Sex, male/female	23/4
Site of the tumor, n	
Esophagus	4
Stomach (cardia/body/antrum)	14 (1/13/0)
Colon (cecum/ascending/transverse/sigmoid)	7 (2/2/2/1)
Rectum	2
Mean tumor size (range), mm	28.6 (8–50)
Depth of tumor, n	
Adenoma	2
Mucosa	16
Submucosa	9
Submucosal fibrosis, n	
Present	7
Absent	20
Vessel infiltration, n	
Present	3
Absent	24

clinical observation and by monitoring of laboratory indices and did not undergo immediate endoscopy for endoclippping. The results for these three patients the morning after ESD were: mean body temperature 37.0°C (range 36.8–37.2°C); mean white blood cell count $9.7 \times 10^3/\text{mm}^3$ (range $8.5 - 11.5 \times 10^3/\text{mm}^3$); and mean C-reactive protein 1.2 mg/dl (range 0.9–1.4 mg/dl). They did not have any abdominal symptoms. The clinical course was uneventful in these patients, who were started on a nil-by-

mouth regime, peripheral fluid replacement, and intravenous antibiotic therapy. Second-look endoscopies in these patients, performed 3 days, 5 days, and 5 days post-ESD, revealed no defect on the ESD ulcer bases, which were well covered by exudate, and oral feeding was restarted.

The short-term outcomes after perforation are summarized in Table 2. Of the 27 patients, 21 (78%) showed air in the peritoneum, retroperitoneum, mediastinum, or in all three sites. All the patients were successfully managed by conservative treatments without any deterioration in their clinical condition and were discharged from the ward after a mean time of 12.1 days after ESD. Three representative cases are illustrated in Figures 2–4.

Among the 27 patients who had perforations, nine lesions (four esophageal, five gastric) were diagnosed histologically as being potentially associated with nodal metastases (due for example to submucosal massive invasive carcinoma or carcinoma with vessel infiltration). Seven of these patients received additional treatments such as chemoradiotherapy or gastrectomy/esophagectomy with lymphadenectomy. Open surgery revealed no dissemination of tumor cells into the intramediastinal or abdominal space in any patient. The other two patients were followed up without receiving additional treatment and in both cases the cancer eventually recurred: one gastric submucosal invasive carcinoma recurred locally as advanced carcinoma 32 months after ESD, and one esophageal intramucosal carcinoma with vessel infiltration recurred in the regional lymph node 18 months after ESD. It was considered that there was no relationship between recurrence and perforation. The other 18 neoplasms that had a low probability of nodal metastasis have not recurred after a median follow-up period of 36 months (range 9–52 months).

Table 2 Short-term outcomes after perforation

Air accumulation, n	
None	6
Peritoneum	15
Retroperitoneum	1
Mediastinum	4
All three sites	1
Mean duration of intravenous antibiotic treatment (range), days	6.7 (1–12)
Mean duration of nil-by-mouth regime (range), days	5.3 (2–8)
Mean maximum body temperature (range), °C	37.3 (36.5–38.9)
Mean maximum WBC count (range), cells × 10 ³ /mm ³	9.7 (4.7–16.8)
Mean maximum CRP (range), mg/dl	5.0 (0.19–14)
Time from ESD to discharge from the ward (range), days	12.1 (7–18)

CRP, C-reactive protein; ESD, endoscopic submucosal dissection; WBC, white blood cell.

Discussion

Traditionally, it is believed that all perforations should be treated by open or laparoscopic salvage surgery, with closure of the perforation and an intensive intra-abdominal lavage with a large volume of physiologic saline. However, this study demonstrates that it might be possible to treat iatrogenic perforations caused by ESD (in the esophagus, stomach, and colorectum) nonsurgically. From the few case series reported previously that have described the successful nonsurgical management of perforations caused by therapeutic endoscopy, it has emerged that the therapeutic approach and the prognosis after perforation depends in general on the adequacy of cleansing of the gastrointestinal tract, the length of time between the perforation event and the diagnosis, the size and the characteristics of the perforation, and the presence of underlying disease [13–16]. With these factors in mind, perforation during ESD may be suitable for nonsurgical treatment and may carry a better prognosis for the following two reasons: firstly, ESD is mainly performed in patients who would tolerate open surgery with general anesthesia after overnight fasting and intensive cleansing of the target organs; and, secondly, the perforation is noticed as soon as it occurs and the size of the perforation is very small (i.e. less than 5 mm, a so-called “miniperforation”), and can easily be closed by a few endoclips.

However, the situation may be quite different with colonic perforations, and we should act with caution in such cases because perforations here may lead to severe peritonitis, with a lot of bacteria pouring into the peritoneal cavity. The main reason why we were able to manage all the perforations in our series, including the colonic perforations, without recourse to surgery could have been that we never performed ESD unless the preparation of the gastrointestinal tract was fairly good, and because we were able to achieve immediate and complete closure of the perforation by endoclips before large amounts of fluid had escaped into the peritoneum.

Three of our stomach perforations were first detected after ESD by the appearance of free air on a plain chest radiograph. The ESD had been completed in all three patients without any sign of perforation, the stomach wall extended well during ESD, and

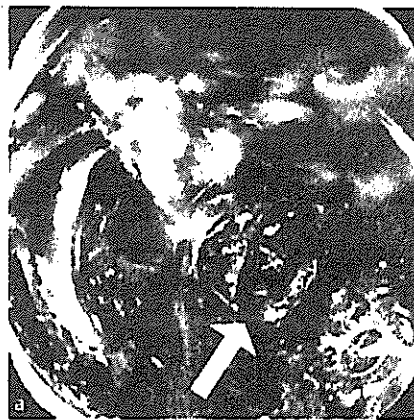


Figure 2 Endoscopic view of the mid-esophagus, showing a perforation (arrow) seen during submucosal dissection (a), and the view after closure of the perforation by endoclips (b). The chest radiograph showed pneumomediastinum and subcutaneous emphysema (c).

no perforation was noticed on careful observation of the post-procedure ulcer base after tumor resection. The mechanism leading to the appearance of the free air is unknown, but we speculate that the air might have passed through the small holes formed by an injection needle that had been placed too deeply or through tiny muscle tears occurring during the submucosal dissection which were not seen endoscopically. These small holes may close spontaneously after the deflation of air from the stomach and they could be managed without mechanical closure of



Figure 3 Endoscopic view of the gastric body, showing a perforation (arrow) that occurred during the mucosal incision (a), and the view after closure of the perforation by endoclips (b). The abdominal radiograph showed pneumoperitoneum (c).

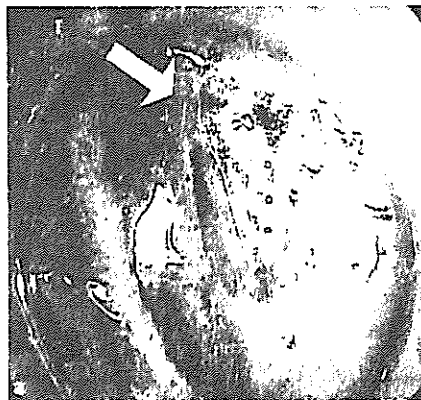
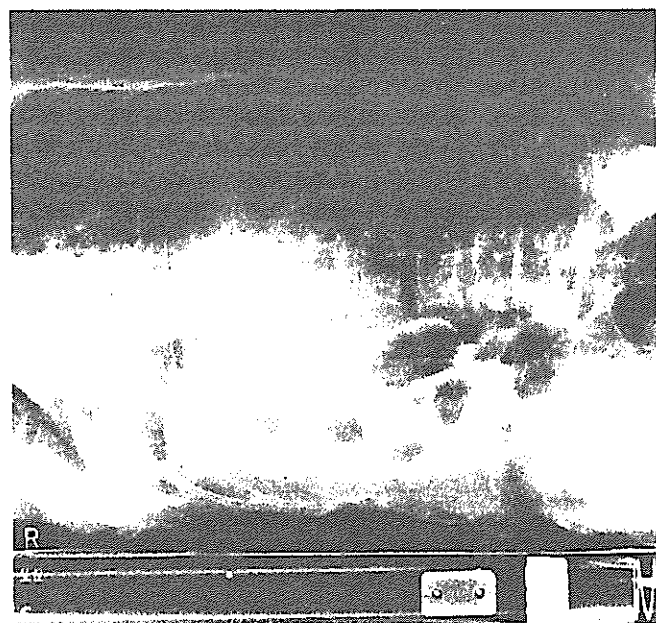
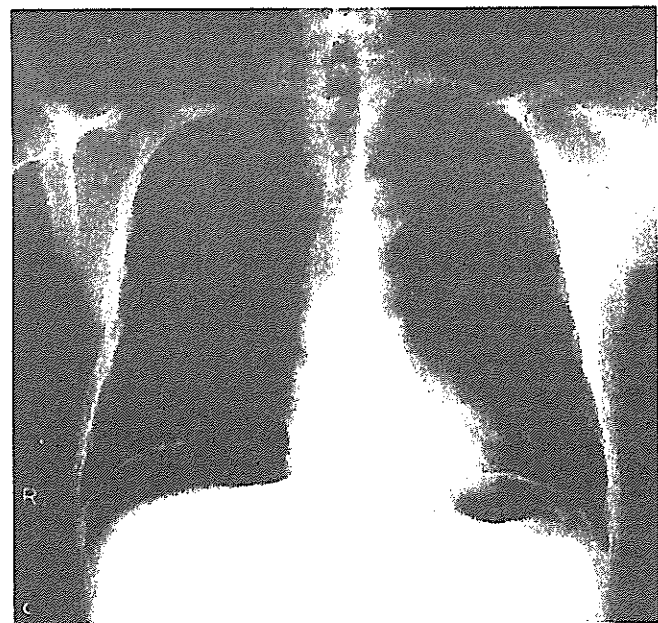


Figure 4 Endoscopic view of the transverse colon, showing a perforation (arrow) that occurred during sub-mucosal dissection (a), and the view after closure of the perforation using endoclips (b). The chest radiograph showed pneumoperitoneum (c).



the perforation. Although these cases were clearly distinguishable from delayed perforation, which is considered to be a different entity, by the unremarkable nature of the clinical symptoms and laboratory indices, patients with free air whose features are indistinguishable from those of delayed perforation should usually be sent for surgery without delay because the perforation would otherwise remain unsealed for a prolonged period and because an additional endoscopic attempt to close the defect may worsen the prognosis.

We make it a rule to perform radiography routinely the morning after ESD in all standard cases without a recognized perforation during ESD in order to check for air accumulation and other abnormalities. The reason why we do not obtain radiographs immediately after ESD is that patients undergoing ESD for upper gastrointestinal neoplasia are in a drowsy state for a few hours because of the sedation. However, it may be preferable to obtain radiographs as soon as possible after ESD in order to distinguish immediate perforation without a hole from delayed perforation,

at least in patients undergoing ESD in the colorectum, whose procedure is usually performed without sedation.

On the other hand, we encountered six perforations (three in the stomach, two in the colon, and one in the rectum) without any radiographic evidence of air accumulation. These cases might have been misdiagnosed and overtreated, but a muscle tear was obvious in these cases and extraluminal fat or extraluminal space was observed endoscopically through the small hole (1 mm or less) in the muscle layer. We speculate that the perforation might have occurred into the omental sac or subserosal/intrapelvic fat tissues and that immediate closure prevented radiographically obvious air accumulation in these cases.

Although we were able to successfully treat all the perforations that occurred during ESD using endoscopic clips and conservative treatments, there must be limitations to the use of nonsurgical management, and there are prerequisites for a successful outcome. The first is that the perforation is small enough that it can be closed by endoclips (i.e. less than 1 cm) [16,22]. The second is that the contents of the gastrointestinal tract are as clean as possible, and that the amount of material escaping into the abdomen or mediastinum is minimized. The third prerequisite is that the perforation is completely sealed by expert interventional endoscopists, and the fourth is that there should be no deterioration in clinical symptoms and laboratory indices, which should be intensively monitored by experienced surgeons. If even one of these conditions is not fulfilled, the patient should be sent for surgery without delay.

In summary, this study demonstrates that when the perforation is very small and immediate closure of the perforation is achieved by endoclips, nonsurgical management of ESD-related perforation using intensive conservative treatments is a feasible option. However, intensive monitoring is essential for at least the first few days, and it is imperative that we do not delay surgery to the point where the patient's clinical condition has begun to deteriorate.

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Competing interests: None

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Submucosal Injection of Normal Saline may Prevent Tissue Damage From Argon Plasma Coagulation: An Experimental Study Using Resected Porcine Esophagus, Stomach, and Colon

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Abstract: Argon plasma coagulation (APC) is considered to be a safe thermocoagulation technique, but some reports show perforation and deformity during and after APC. In this study, we investigated the usefulness of prior submucosal injection for APC. APC over the mucosa was performed on fresh resected porcine esophagus, stomach, and colon with prior submucosal injection of normal saline (injection group) and without it (control group). The depth of tissue damage increased linearly with pulse duration up to the shallower submucosal layer in both groups. After that, tissue damage in the injection group remained confined to the shallower submucosal layer under any condition, whereas that in the control group continued to extend. The tissue damages of the injection groups were significantly ($P < 0.05$) shallower than those of the control groups that reached the deeper submucosal layer in all the organs. Submucosal injection of normal saline before the application of APC may limit tissue damage and prevent perforation and deformity.

Key Words: argon plasma coagulation, submucosal injection, normal saline, depth control, endoscopic application, the gastrointestinal tract

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Argon plasma coagulation (APC) has been available in flexible endoscopy since 1991 and applied to the treatment of various conditions, such as hemorrhages, malignant and benign tumors, tissue ingrowth and overgrowth of stents, angiodysplasias, dysplasia, etc.¹ The advantages of APC have been controllable depth of coagulation (0.5 to 3 mm)^{2,3} and a low rate of perforation, reported to be less than 0.3% in clinical practice.¹ Adverse effects of APC are extremely low in comparison with laser therapy,⁴ but it is desirable to gain more accurate depth control to prevent deep ulceration, stricture due to tissue damage, and, of course, perforation. In our own experiments with the exposed submucosal layer with prior submucosal injection of normal saline, that is, a model of artificial mucosal defect made immediately after endoscopic mucosal resection, APC caused only subtle superficial damage on the submucosal layer.⁵ This result indicated that submucosal injection of normal saline can control tissue damage up to the shallower submucosal layer, even if APC was applied over the mucosal surface. To confirm our speculation, we performed this study using fresh resected porcine esophagus, stomach, and colon.

MATERIALS AND METHODS

Porcine esophagus, stomach, and colon used for this study were obtained within 2 hours after resection. Five milliliters of normal saline was injected into the submucosal layer at separate sites of esophagus, stomach, and colon, using a disposable syringe and a 23-gauge needle, and then the application of APC over the mucosa was performed. In the stomach, 3 parts (the lower, middle, and upper thirds) were each independently examined because the thickness of the gastric wall and its proportion varied among different parts of the organ.⁶

The equipment for application of APC consisted of a high-frequency generator (Erbotom ICC 200), an automatically regulated argon source (APC 300), and a flexible APC applicator, 2.3 mm in diameter. All of them were products of ERBE Elektromedizin, Tübingen,

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Germany. The power and argon gas flow were set at 40 or 60 W and 1 or 2 L/min, respectively, for the stomach, and 40 or 60 W and 1 L/min, respectively, for the esophagus and the colon, typical settings used in clinical procedures. Pulse duration was adjusted as follows: 2, 4, 8, and 20 seconds for the esophagus and the stomach; 2, 4, and 8 seconds for the colon. A pulse duration of 20 seconds was not examined in the colon, because the thinner wall had been perforated with this pulse duration in a pilot study. We determined that pulse duration up to 8 seconds was sufficient to detect the difference in tissue injury in the colon. As distances of 2 mm or less between a probe and tissue are necessary to produce a coagulation arc, a fixed distance of 2 mm at a 90-degree angle was used. For the controls, the application of APC over the mucosa without prior submucosal injection was also examined with the same instrument settings.

After the application of APC, the specimens were cut on the points of coagulation, fixed with formalin, and embedded in paraffin. A histologic section was made from each block and stained with hematoxylin eosin and examined microscopically for tissue damage. The depth of damage was categorized as follows: m, up to the mucosa; mm, up to the muscularis mucosae; sm shallow, up to the shallow submucosal layer; sm deep, up to the deep submucosal layer; mp shallow, up to the shallow proper muscle layer; mp deep, up to the deep proper muscle layer. In the case of the esophagus, the category m was further divided into ep, up to the mucosal epithelium and lpm, up to the lamina propria mucosae. For the stomach and the colon, the added category ss, up to the subserosal layer, was included to indicate the deepest structural damage. Each category was scored on a scale from 1 to 7, with the shallowest (ep or m) ranked as 1 and the deepest (mp deep or ss) ranked as 7. Four trials of coagulation were performed at different parts of the same organs or compartments under each condition and mean scores were compared between the injection groups and the control groups. Statistical analyses between the 2 groups under each condition were performed by using the Mann-Whitney *U* test and a *P* value < 0.05 was considered as a significant difference.

RESULTS

Coagulation arc was produced consistently under all the examined conditions and coagulation damage was observed on the applied areas. Figures 1A to E show the depth of tissue damage under each condition in the individual organs. Figure 2 shows the representative histologic findings of the applied areas under the maximum power (60 W), the highest argon gas flow (1 or 2 L/min), and the longest pulse duration (8 or 20 sec) in each organ. The depth of tissue damage increased as pulse duration increased in both the injection group and the control group, until tissue damage extended to the shallower submucosal layer. However, after that, tissue damage in the injection group was limited to only the shallower submucosal layer, even though pulse duration

increased in all the organs. In contrast, tissue damage in the control group increased linearly until maximally reaching the deeper submucosal layer in the gastric middle and upper thirds, and reaching the proper muscle layer in the esophagus, the gastric lower third, and the colon. The depths of tissue damage of the injection groups were significantly ($P < 0.05$) shallower than those of the corresponding control groups where tissue damage extended to the deeper submucosal layer in all the organs.

DISCUSSION

Previous experimental studies of APC suggested that deep tissue destruction leading to perforation was rare⁷⁻⁹ and the clinical experiences with regard to endoscopic applications also supported the rarity of perforation.^{1,10} However, those studies indicated that tissue damage to the proper muscle layer could occur, which might lead to stricture or deformity of the gastrointestinal tract and could also cause functional disturbance of the sphincter or in the peristaltic movement. Furthermore, in some reports, there is the possibility of severe complication caused by APC.^{11,12} In the present study, we could limit tissue damage to the shallower submucosal layer in all the applied organs with whatever instrument settings were used, and thus, submucosal injection of normal saline may become an essential preparation for endoscopies. In fact, tissue damage up to the shallower submucosal layer is sufficient to treat most lesions indicated for the application of APC. Although the small intestine was not examined under the same settings in this study, prior submucosal injection may also be beneficial, because the wall is thinner and the risks of proper muscle injury or perforation are higher than for the other organs in the gastrointestinal tract.

Differences in tissue damage without prior injection may originate mainly from differences in the wall thickness and in the proportions of the wall components. Among the organs examined in this study, the deepest tissue damage was observed in the colon under the same conditions as applied to the other tissues, probably because the colonic wall, including the mucosa and the submucosa, is much thinner than that of the other organs. Among the parts of the stomach, the deepest tissue damage was observed in the upper third at a 2-second pulse duration, which may also be caused by the thinness of the mucosal wall. On the other hand, the increment of tissue damage that occurred as pulse duration lengthened was the least in the upper third of the stomach, which may be due to the thickest submucosal layer acting to absorb heat, much like the submucosal injection of normal saline in the porcine model.

Notably, this study showed that depth of injury in the control group barely reached the proper muscle layer. This may mean that perforation will not occur even in the control group. However, this study was carried out with resected materials and we did not examine the thermal effects for the nearby tissue without coagulation in this study. Another study using a living animal and

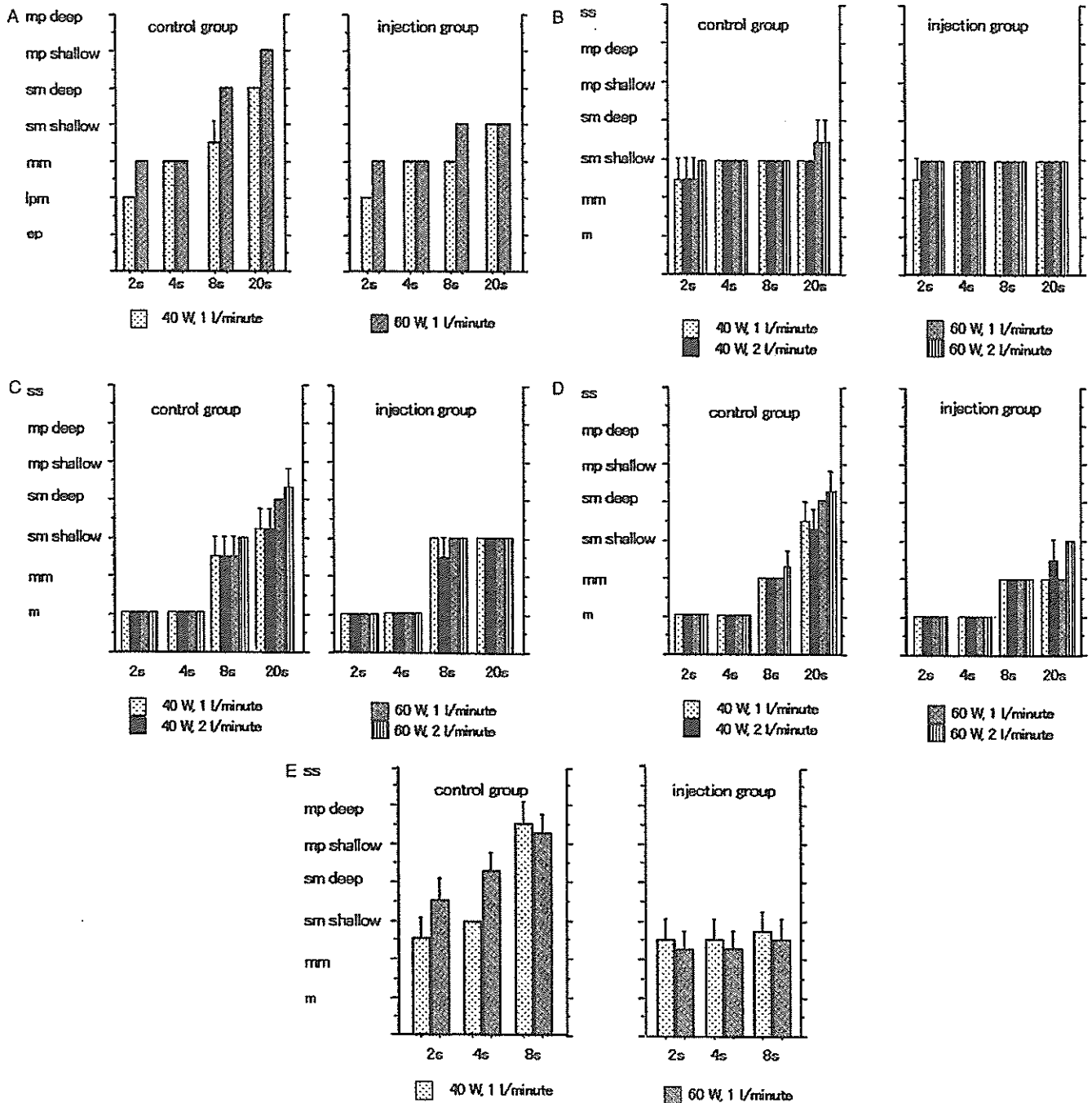


FIGURE 1. Correlation between the depth of tissue damage and pulse duration. The mean depth of the 4 observations is indicated as bars with a standard deviation in each condition. *m, the mucosal layer; ep, the epithelial layer; lpm, the lamina propria mucosae layer; mm, the muscularis mucosae layer; sm, the submucosal layer; mp, proper muscle layer. A, Esophagus. B, Gastric upper third. C, Gastric middle third. D, Gastric lower third. E, Colon.

observation of at least a few days after the application of APC is necessary to examine the safety of long-time application of APC. In fact, we occasionally experience an unexpected extension of tissue destruction in clinical practice, which caused deeper and larger ulceration or severer deformity. On the other hand, too little tissue

destruction may result in insufficient therapeutic effects. The extent of tissue damage in a living body may be influenced by various factors; for example, blood flow, inflammation as host factors, or the volume of inflated air and also the technical factors of the applied angle or distance between an applicator and tissue. Submucosal

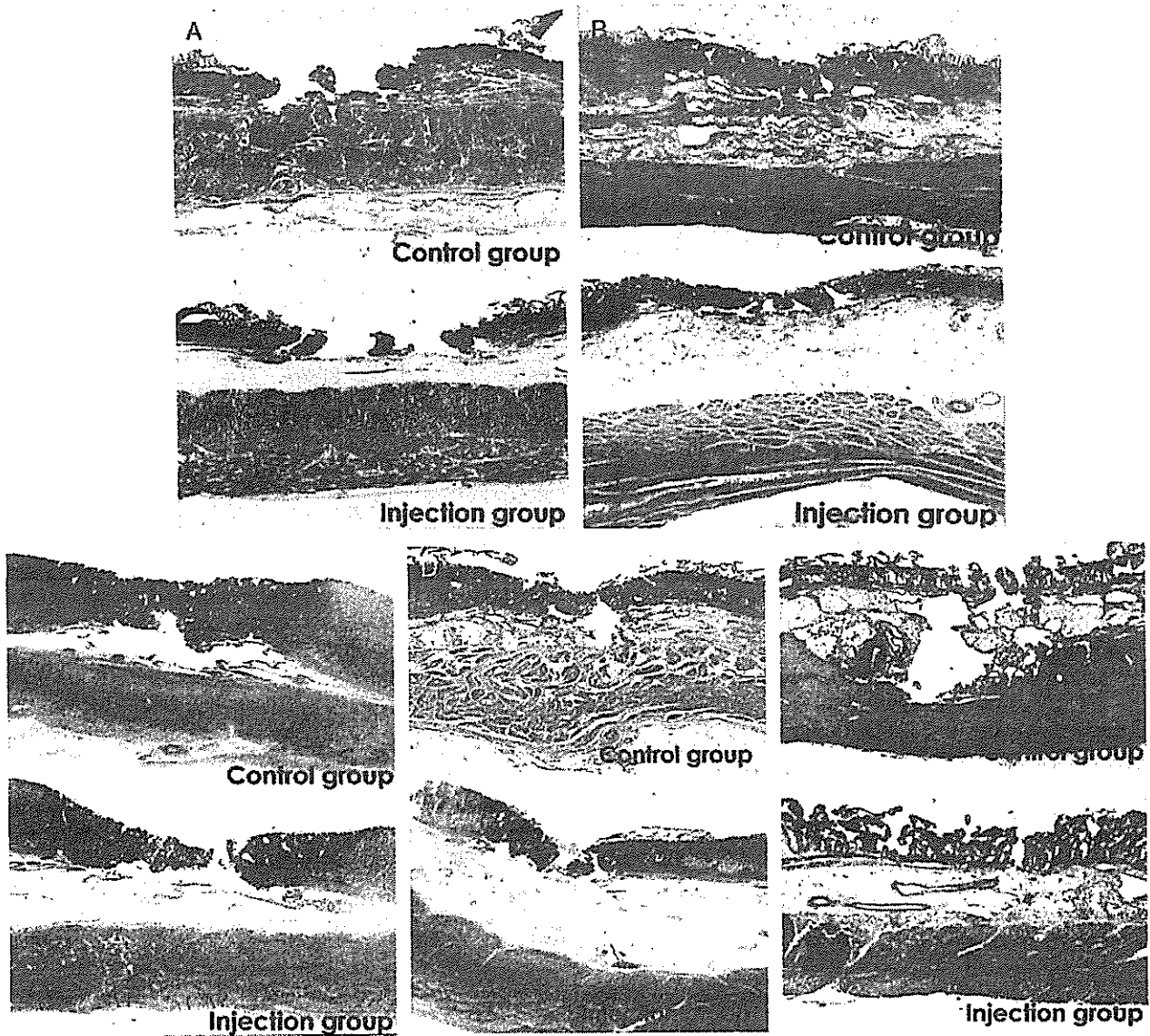


FIGURE 2. Histologic section showing tissue damage under the maximum values of watts, rate of argon gas flow, and pulse duration in the control group (top) and the injection group (bottom). Tissues were stained with hematoxylin eosin; original magnification $\times 10$ (esophagus and stomach), $\times 20$ (colon). A, Esophagus (60 W, 1 L/min, 20 sec). B, Gastric upper third (60 W, 2 L/min, 20 sec). C, Gastric middle third (60 W, 2 L/min, 20 sec). D, Gastric lower third (60 W, 2 L/min, 20 sec). E, Colon (60 W, 1 L/min, 8 sec).

injection of normal saline may prove very useful to obtain sufficient results at any encountered situation, without the fear of extensive damage into the proper muscle layer.

The changes of power and argon plasma flow caused only minor differences on tissue damage (Fig. 1), suggesting that the most important parameter affecting tissue damage is pulse duration under the generally applied conditions. Although we tried only 2 power settings, 40 and 60 W, and 2 argon plasma flow rates, 1 and 2 L/min, the results of this study suggest that the lower settings of 40 W and 1 L/min may be recommended. We should choose an argon gas flow rate of 1 L/min,

especially in a narrow space, such as the esophagus and in the small and large intestines.

Although we used normal saline as the injection fluid in this study, additional use of epinephrine or substitution of hypertonic saline or glucose solutions might be preferred in, for example, the case of hemostasis. This study suggests that there are numerous means to optimize the submucosal injection solutions to obtain the desired results. Further experimental and clinical studies will be needed to elucidate the advantage of other fluids compared with normal saline.

In conclusion, submucosal injection of normal saline before the application of APC in the gastrointestinal

tract may limit tissue damage to the shallower submucosal layer. We believe that the procedure could prevent wall deformity or perforation, especially in the organs with a thin wall such as the small and large intestines. Saline submucosal injection should be tested to determine whether it can become the standard preparation before the application of APC in humans.

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Original Contribution

Prospective Cohort Study of the Risk of Prostate Cancer among Rotating-Shift Workers: Findings from the Japan Collaborative Cohort Study

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Shift workers have been reported to have an increased risk of some cancers. However, the risk of prostate cancer in shift workers is not known to have been examined previously. This study prospectively examined the association between shift work and risk of prostate cancer incidence among 14,052 working men in Japan enrolled in a large-scale prospective cohort. A baseline survey was conducted between 1988 and 1990. Subjects were asked to indicate the most regular work schedule they had undertaken previously: day work, rotating-shift work, or fixed-night work. During 111,974 person-years, 31 cases of prostate cancer were recorded. The Cox proportional hazards model was used to estimate the risk, with adjustments for age, family history of prostate cancer, study area surveyed, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status. Compared with day workers, rotating-shift workers were significantly at risk for prostate cancer (relative risk = 3.0, 95% confidence interval: 1.2, 7.7), whereas fixed-night work was associated with a small and nonsignificant increase in risk. This report is the first known to reveal a significant relation between rotating-shift work and prostate cancer.

circadian rhythm; cohort studies; Japan; occupational exposure; prostatic neoplasms; work schedule tolerance

Abbreviations: CI, confidence interval; JACC, Japan Collaborative Cohort; RR, relative risk.

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workers and fixed-night workers compared with day workers (21). In the analysis, relative risks were adjusted for age only and for age, study area, and family history of prostate cancer. Relative risks were further adjusted for the lifestyle-related factors and the occupational and psychosocial factors listed in table 1. Missing values for adjusting variables were treated as an additional category. The assumptions for the Cox proportional hazards model were checked by using the goodness-of-fit testing approach and were found to be valid. Calculations were performed with Stata version 8.0 (Stata Corporation, College Station, Texas) and SPSS version 12.0 (SPSS, Inc., Chicago, Illinois) statistical software.

Approval

This study was approved by the Ethics Committee for Medical Care and Research, University of Occupational and Environmental Health, Japan, and the Ethical Board of the Nagoya University School of Medicine, Japan.

RESULTS

Table 1 shows the baseline characteristics of the study subjects according to type of work schedule. Of the 14,052 men, 11,269 (80.2 percent) reported day work, 982 (7.0 percent) reported fixed-night work, and 1,801 (12.8 percent) reported rotating-shift work. Compared with those who had engaged in day work, men who had performed rotating-shift work reported a higher prevalence of high body mass index (>23.9 kg/m²; 34.4 percent vs. 30.8 percent), sitting work (48.4 percent vs. 28.1 percent), and indoor work (44.5 percent vs. 38.6 percent) and a lower prevalence of office work (14.3 percent vs. 22.7 percent). The prevalences of family history of prostate cancer (0.8 percent vs. 0.3 percent), current smoking (55.4 percent vs. 53.8 percent), current alcohol drinking (75.6 percent vs. 78.0 percent), frequent stress (15.3 percent vs. 13.2 percent), higher educational level (higher than high school; 51.1 percent vs. 52.3 percent), and marriage (89.3 percent vs. 90.7 percent) revealed no differences in magnitude.

Table 2 shows the results of the Cox proportional hazards model analysis. Compared with that for the day workers, the age-adjusted relative risk for the rotating-shift workers revealed a significant increase (RR adjusted for age = 3.0, 95 percent CI: 1.2, 7.3). For the fixed-night workers, a slight increase was observed but was not significant (RR adjusted for age = 1.7, 95 percent CI: 0.5, 5.9). Adjustments for study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status did not significantly alter these results (rotating-shift work: RR adjusted for age, study area, and family history of prostate cancer = 2.5, 95 percent CI: 1.0, 6.2; RR adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status = 3.0, 95 percent CI: 1.2, 7.7 and fixed-night work: RR adjusted for age, study area, and family history of prostate cancer = 1.5, 95 percent

CI: 0.4, 5.3; RR adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status = 2.3, 95 percent CI: 0.6, 9.2).

Table 3 shows the characteristics of the prostate cancer cases according to type of work schedule. Between day workers and rotating-shift workers, there were no differences in mean age at baseline (58.5 years vs. 59.3 years), mean number of years of follow-up (6.7 vs. 6.3), mean age at endpoint (65.2 years vs. 65.6 years), family history of prostate cancer (one case for each work schedule), and mean body mass index at baseline (22.8 kg/m² vs. 21.6 kg/m²).

DISCUSSION

We found a significant increase in prostate cancer risk among rotating-shift workers. This result supports the hypothesis that shift work is a risk factor for prostate cancer. To our knowledge, this is the first report to reveal the association of rotating-shift work with prostate cancer.

The melatonin pathway, which is closely linked to circadian rhythms, is most frequently implicated in the observed increase in tumor incidence among shift workers. Secretion of the hormone is low during daytime, increases soon after the onset of darkness, peaks in the middle of the night, and gradually falls until morning. The hormone has been reported to affect circadian rhythms and exhibit both hypnotic and antineoplastic effects (9). Several possible mechanisms have been proposed regarding tumor growth inhibition by melatonin. Melatonin may suppress tumor growth by down-regulating transcription, secretion, or activity of growth factors; it may stimulate the immune system through increased production of interleukin-2 and interleukin-4 by T-helper cells; lastly, it may protect DNA against oxidative damage by scavenging free radicals (9). Among shift workers, it has been proposed that an elevated risk of cancer may be due to a phase shift and reduced secretion of melatonin, resulting from a disruption in circadian rhythms (22–24). In terms of prostate cancer, previous studies showed that melatonin could directly inhibit proliferation of cultured prostate cancer cells (25). The melatonin pathway may therefore be relevant to prostate cancer incidence among shift workers.

The effect of sex hormones may be secondary to melatonin. Melatonin suppression is believed to increase the level of sex hormones (9, 24). Among female shift workers, increased levels of estradiol and low levels of melatonin have been reported (22). An interrelation between melatonin and testosterone has also been suggested for males (26), so high levels of testosterone due to low levels of melatonin could also be hypothesized in male shift workers. The growth and differentiation of the prostate is under androgen control (12); therefore, this pathway should attract attention as a relevant mechanism.

Decreased exposure to daylight is known to be a risk factor for prostate cancer (27, 28). This link was explained by decreased production of vitamin D due to reduced exposure to ultraviolet rays. The biologically active form of vitamin D, 1 α ,25-dihydroxyvitamin D₃, has been reported

TABLE 2. Relative risk of prostate cancer associated with work schedule, Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 1988–1997

Work schedule	No. of person-years	No. of cases	Age adjusted			Multivariate adjusted					
			RR*	95% CI*	p value	RR†	95% CI	p value	RR‡	95% CI	p value
Daytime	89,179	21	1.0			1.0			1.0		
Fixed night	8,272	3	1.7	0.5, 5.9	0.387	1.5	0.4, 5.3	0.534	2.3	0.6, 9.2	0.231
Rotating shift	14,523	7	3.0	1.2, 7.3	0.016	2.5	1.0, 6.2	0.043	3.0	1.2, 7.7	0.020

* RR, relative risk; CI, confidence interval.

† Adjusted for age, study area, and family history of prostate cancer.

‡ Adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status.

to inhibit proliferation of prostate cancer cells (29, 30). In shift work, daylight exposure is shortened, so elevated risk could be explained through this pathway. In our studies, however, rotating-shift workers, whose exposure to daylight is longer, had a higher risk compared with fixed-night workers, whose exposure is relatively shorter. Effects on circadian rhythms were suggested to be more serious for rotating-shift workers compared with fixed-night workers (31). Disrupting the circadian rhythm in rotating-shift workers may therefore have a greater effect on tumorigenesis than shortening exposure to daylight.

The scientific field of chronotoxicology examines the biologic cycle of susceptibility to chemical toxicity (32). The toxicity of many chemical agents was reported to vary with circadian change, and the possibility was suggested that susceptibility to chemical agents may increase at night in humans (4, 32). Occupational exposure to chemical agents such as cadmium and manganese is suspected to increase the risk of prostate cancer (33, 34), so these agents may have a stronger influence among shift workers. Exposure to these chemicals is considered rare, however. Thus, the relevance of chemical toxicity to this study is questionable.

Diet is also known to play a role in prostate cancer. A Western diet, which is relatively high in fat and meat, may contribute to higher prostate cancer risk (12). We examined confounding dietary factors, including meat, vege-

tables, fried foods, milk, and butter, but adjustment for these covariates did not alter the results (data not shown).

An association between prostate cancer and obesity has not been established in spite of repeated studies. However, obesity has been hypothesized to be a risk factor for prostate cancer because of the connections between body size and testosterone (35). Shift workers are known to be a high-risk group for obesity (4). In the current study population, rotating-shift workers showed a higher distribution of the highest body mass index compared with daytime workers (table 1). High body mass index among shift workers might confound the result. However, there was no significant difference in baseline body mass index between the prostate cancer cases in day work and in rotating-shift work (table 3). In addition, the significant association between rotating-shift work and prostate cancer was still observed after we adjusted for body mass index. Therefore, the effect of obesity, or at least body mass index at the time of the baseline survey, on the current study appears limited.

Limitations of our study

Important limitations of our study should be discussed. First, in terms of ascertaining the risk of prostate cancer, the follow-up time was short and the cohort was relatively small. Although this study had enough power to show the

TABLE 3. Characteristics of prostate cancer cases according to type of work schedule, Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 1988–1997

Characteristic	Work schedule			p value
	Daytime	Fixed night	Rotating shift	
No. of cases	21	3	7	
Death certificate only	1	0	0	
Mean age in years at baseline (standard deviation)	58.5 (6.4)	53.7 (4.0)	59.3 (5.4)	0.39*
Mean no. of years of follow-up (standard deviation)	6.7 (3.0)	5.6 (2.6)	6.3 (2.5)	0.82*
Mean age in years at endpoint (standard deviation)	65.2 (6.6)	59.3 (1.8)	65.6 (4.8)	0.27*
No. of cases with a family history of prostate cancer	1	0	1	0.60†
Mean body mass index‡ at baseline (standard deviation)	22.8 (2.0)	21.9 (0.9)	21.6 (2.0)	0.33*

* Derived from analysis of variance.

† Derived from the chi-square test.

‡ Weight (kg)/height (m)².

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文献レビューによる胃がん検診の受診率向上対策

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はじめに

胃がん検診の受診率向上対策を明らかにすることを目的として、胃がん検診の受診率について検討した内外の論文をレビューしたので、その結果を以下に記述する。

なお、大腸がん検診についても同時に検討したが、これについては他誌において発表することとなっているのでここには記載しない。

対象と方法

MEDLINE、CINHAL、医学中央雑誌、日本消化器集団検診学会雑誌及び日本消化器内視鏡学会雑誌の1985年1月～2005年2月の期間の胃がん検診関係論文を検索し、胃がん検診の受診率について報告された論文を選び出した。これらの論文の中で受診率向上対策が検討されているものと受診者の要因調査についての論文を最終的な検討対象とした。

Key Questionとして、「日本における胃がん検診受診率を向上させるにはどうすれば良いか？」を設定した上で、Check Listとして1) 目的は明確か(受診率の向上が目的とされているか)、2) 解析方法は無作為化比較対照試験か観察的手法か、3) 対象集団の定義と人数、4) 介入群と対照群は明確に定義されているか、5) 評価指標は明確に定義されているか、6) 結果、7) 研究の限界や偏り(Bias)が記載されているか、8) 結論、9) 結論は適切に評価されているか、10) 日本において適用可能かの10項目について整理した。

結 果

胃がん検診関係論文の検索の結果、胃がん検診の受診率について報告された論文は、27論文(英語論文1編、日本語論文26編)あった。これらの論文のうち、受診率向上対策についての3論文^{1)~3)}と受診者の要因調査についての5論文^{4)~8)}の合計8論文を検討対象とした。これら以外の19論文は、単なる実施報告のものが5論文、受診状況に関する調査についてのものが6論文、受診率の測定法についてのものが2論文、経済評価についてのものが3論文及びその他が3論文となっていた。

これらの8論文のそれぞれについてCheck Listの10項目を整理して表1～表8に示す。

表 1

著者	今井貴子、他
論文名	群馬県都市部における胃集検推進方式について — 前橋市医師会方式：胃癌個別検診について —
発表雑誌	消化器集団検診、88号、56-62、1990
目的（受診率向上）は明確か？	前橋市で実施されていた胃癌個別検診とチケット制の組合せ法を他都市部の車検診法と比較して、その長短所を明らかにすること。
解析方法（RCT／観察的）は？	観察的方法（無作為化されていない集団と集団の比較）
対象集団の定義？ 人数？	対照群（高崎市）と介入群（前橋市）、ともに人口約30万人
介入群と対照群は明確に定義されているか？	対照群：群馬県高崎市；S61年に精密検査が医師会委託となったが一次検診は車検診のままであった、介入群：群馬県前橋市；S59年より個別検診導入、S62年チケット制導入
評価指標は明確に定義されているか？	対照群（高崎市）と介入群（前橋市）と間の受診率の比較、介入群（前橋市）におけるチケット制導入前後での受診率の比較。なお、受診率の分母の定義は示されていない。
結果	受診率は、対照群（高崎市）：S58年3.1%、S59年4.9%、S60年6.0%、S61年4.0%、S62年5.5%、S63年6.7%、介入群（前橋市）S58年1.7%、S59年7.8%、S60年8.9%、S61年10.5%、S62年15.7%、S63年13.6%
研究の限界が記載されているか？ Bias は？	初回受診者の割合が不明であり、統計学的処理もされていないので偶然の結果であったかどうか不明で一般化することができないと考えられるが、そのような記載はなかった。
結論	個別検診とチケット制が導入された前橋市と車検診のままであった高崎市の受診率（検診率）の間で2倍の差が生じた。
結論は適切に評価されているか？	統計学的処理がなされていないので不適切と考えられる。
日本において適用可能か？	住民の多様な要望に対応できるという点については、日本での研究であり他の日本の地域においても適応可能と考えられる。

RCT：無作為化比較対照試験

表 2

著者	河村奨、他
論文名	胃集検受診率向上へ寄与するもの — 複合検診と直接撮影方式 —
発表雑誌	消化器集団検診、87号、11-19、1990
目的（受診率向上）は明確か？	検診の技術面としての検診システム、検査方法が胃集検受診率にどう影響しているかを検討した。
解析方法（RCT／観察的）は？	観察的方法（市町村・保健所別の受診率の年次推移の観察）
対象集団の定義？ 人数？	山口県内の市町村・保健所別受診率の推移の観察と従業員約900人の化学工業系の職域
介入群と対照群は明確に定義されているか？	胃がん検診と腹部超音波検査や基本健康診査等の併用の導入をを介入として、導入前後での比較を行っており、導入前が対照となっている。併用方法には様々な類型があり介入の定義は不明確である。
評価指標は明確に定義されているか？	受診者数、受診率が中心であるが、胃がん発見率も示されている。なお、受診率の分母の定義が明確でない。
結果	胃集検単独よりも複合検診の方が5-10%程度受者の増加が見られた。
研究の限界が記載されているか？ Bias は？	記載されていない。
結論	他のがん検診や基本検診と併せて胃がん検診を実施する複合検診は、胃集検受診者増に寄与している。
結論は適切に評価されているか？	統計学的検討がなされていないので偶然の結果であることを否定し得ない。この点で適切とは言えない。直接撮影法による胃がん検診にもふれられているが、きちんとした評価がされていない。（導入前の受診者数が示されていない。）
日本において適用可能か？	他のがん検診や基本検診と併せて胃がん検診を実施することは、論文の結果のいかに関わらずより望ましいと考えられ、他の地域でも適応されている。

表 3

著者	大滝隆子、他
論文名	川崎市民の胃がん検診の受診行動に関する調査
発表雑誌	消化器集団検診、35巻1号、89-93、1997
目的（受診率向上）は明確か？	市民が胃がん検診に関してどう行動しているかを把握する。
解析方法（RCT／観察的）は？	自記式調査の解析（過去3年間の胃の検査の受診についての横断調査）
対象集団の定義？ 人数？	性・年齢・行政区で層化無作為抽出された40歳以上の川崎市民3,000人
介入群と対照群は明確に定義されているか？	介入についての研究ではないので設定されていない。
評価指標は明確に定義されているか？	過去3年間のそれぞれの年の胃X線検査と上部内視鏡検査のそれぞれの受診率（受診者数／回答者数）
結果	回収は1,257人（回収率41.9%）。X線検査受診歴ありは85.6%であり年齢に関係なく80%を越えていた。X線検査の28.8%は医療として受診、残りの71.2%は検診として受診、うち市の検診は全体の16.8%。過去3年のいずれでもX線検査のみ受診約32%、内視鏡検査のみ受診約2%、両方受診約8%、合計約42%。過去3年間毎年受診28%、過去3年間1回以上受診61.2%。未受診の主たる理由は必要性を感じなかったため（60.5%）。
研究の限界が記載されているか？ Biasは？	41.9%の回答者における受診率であり、バイアスの影響を受け高く出ている点にふれている。
結論	地域胃集検受診者数の減少は、職域検診の普及と集検以外の個別検診の充実による。
結論は適切に評価されているか？	状況証拠としては適切な推論と考えられるが、直接的根拠としては弱いと思われる。
日本において適用可能か？	結果から、どうすれば受診率を向上させることができるかということは導き出せない。

表 4

著者	赤松直樹、他
論文名	住民調査からみた胃集検受診の実態第一報 胃集検受診に関連する要因
発表雑誌	産業医大誌 8(2)、177-183、1986
目的（受診率向上）は明確か？	胃集検受診の関連要因のみで、受診率向上に言及していない
解析方法（RCT／観察的）は？	縦断的研究
対象集団の定義？ 人数？	40歳以上の全住民3,660人（回答者2,404、回収率65.7%）
介入群と対照群は明確に定義されているか？	介入についての研究ではないので設定されていない。
評価指標は明確に定義されているか？	過去3年間の胃集検受診率（3年間に1度）
結果	検診受診率は男性24.1%、女性14.1%で男が有意に高かった。これは職域検診の影響によるもので、公務員の受診率は78.7%、無職の受診率は12.5%であった。受診に強く関連する因子として、家族のがん既往歴がもっとも大きかった。
研究の限界が記載されているか？ Biasは？	回答率が低い。論文の中ではあまりふれられていない。
結論	受診率向上のために「家族のがん既往歴よりも強い動機付けが必要」という結論であった。
結論は適切に評価されているか？	受診率向上対策に直接結びつけられるものではない。
日本において適用可能か？	日本における調査であり、応用は可能。

表 5

著者	坪野吉孝、他
論文名	地域胃がん検診の受診行動の心理的規定要因 — Health Belief Model による検討
発表雑誌	日本公衆衛生学会誌、40(4)、255-264、1993
目的（受診率向上）は明確か？	胃集検受診の心理学的分析である。受診率向上対策は考察の中で例示している。
解析方法（RCT／観察的）は？	アンケートを用いた後ろ向き観察研究
対象集団の定義？ 人数？	45-64歳の男女で老人保健法による胃がん検診対象者627人中、基本健康診査受診者400人、ここから無効回答を除外した337人。さらに1年前に行ったEPQ-Rによる性格調査の回答者278人を対象とした。
介入群と対照群は明確に定義されているか？	介入についての研究ではないので設定されていない。
評価指標は明確に定義されているか？	過去5年の胃がん検診受診回数
結果	健康への関心、胃がんに罹患する危険性の意識、胃がん検診の効果の認識が、胃がん検診の受診回数と正の相関。胃がんの深刻さの認識、胃がん検診受診上の障害の意識が負の相関
研究の限界が記載されているか？ Bias は？	Health Belief Model (HBM) の尺度の信頼性、後ろ向き研究であるデザイン上の問題。HBM の理論的妥当性
結論	HBM が、胃がん検診の受診行動を理解する理論的支柱となる可能性を示唆する。
結論は適切に評価されているか？	受診率向上対策に直接結びつけられるものではないが、胃がんの深刻さの認識を増長することはかえって受診率低下を来す可能性を示唆するなど、参考になる部分はある。
日本において適用可能か？	日本における調査であり、応用は可能。

表 6

著者	北 昭一、他
論文名	胃集検の精検受診率向上に関わる要因についての検討
発表雑誌	日本消化器集検学会誌、36(4)、461-467、1998
目的（受診率向上）は明確か？	精検受診率向上のための経験談
解析方法（RCT／観察的）は？	解析ではなく、実体験のレポート
対象集団の定義？ 人数？	定義されていない
介入群と対照群は明確に定義されているか？	定義されていない
評価指標は明確に定義されているか？	定義されていない
結果	要精検者を減少させることで、精検受診率は100%近くなった。受診勧奨は、検診の現場で医師が直接行っている。
研究の限界が記載されているか？ Bias は？	記載されていない
結論	日程計画、技師の撮影能力、医師の読影能力などが有機的に機能しないと、精検受診率は向上しない。
結論は適切に評価されているか？	精検受診率向上対策であり、検診受診率ではない。
日本において適用可能か？	日本の研究である。

表 7

著者	Y. Suwazono, et al
論文名	The factors related to undergoing stomach examination and through medical examination in Japanese male workers
発表雑誌	J Occup Health, 42(3), 144-146, 2000
目的（受診率向上）は明確か？	受診の要因調査
解析方法（RCT／観察的）は？	観察的研究
対象集団の定義？ 人数？	自動車工場勤務の男性466人
介入群と対照群は明確に定義されているか？	定義されていない
評価指標は明確に定義されているか？	胃がん検診受診のレセプト（症状受診も含まれていると思われる）
結果	多変量解析で差が出たのは、技術系職種・飲酒歴・時間の束縛・検査の知識。
研究の限界が記載されているか？ Bias は？	研究対象者数が少ない。後ろ向き研究。一般集団には応用できない。
結論	時間の束縛を改善させるために、ペプシノゲン法の導入も必要かもしれないという結論。
結論は適切に評価されているか？	受診関連要因であり、直接受診率向上につながるものはない。
日本において適用可能か？	日本の研究である。

表 8

著者	加藤育子、他
論文名	無既往・無自覚症状者の生活習慣の特徴
発表雑誌	日本公衆衛生学会誌、35(10)、556-561、1988
目的（受診率向上）は明確か？	ベースラインコホートの解析であり、無自覚無症状一般集団の特性分析である。
解析方法（RCT／観察的）は？	観察的研究（コホート研究）
対象集団の定義？ 人数？	40歳以上の全住民33,538例中、有効回答者30,070人（有効回答率92.8%）
介入群と対照群は明確に定義されているか？	観察的研究で、介入群は設けられていない。
評価指標は明確に定義されているか？	無自覚・無症状者の割合
結果	無症状・無自覚の健康群では、がん検診への参加が少ない。
研究の限界が記載されているか？ Bias は？	断面調査のため疾病や症状の結果も含まれる。
結論	何らかの疾患や自覚症状があるものが検診に参加しやすい。
結論は適切に評価されているか？	受診関連要因であり、直接受診率向上につながるものはない。
日本において適用可能か？	日本の研究である。

考 察

今回の検討対象となった8論文はすべて日本での研究論文であったが、胃がん検診を老人保健法という社会システムの中で実施している唯一の国であるのでこれも当然のことである。日本からの研究論文であるので、「日本における胃がん検診受診率を向上させるにはどうすれば良いか？」という Key Question にはそのまま

回答を与えることができるという点で有用ではあったが、無作為化比較対照試験による研究は皆無であり、質的に満足できるものではなかった。

受診率向上対策についての3論文から示唆されるのは、1) チケット制を含む個別検診は多様な住民の利便に答えることによって受診者数を増加させるかも知れないが、個別検診は既に

全国的に導入されつつある。2) 基本検診や他のがん検診等と併せて複合化(総合化)することは、多様な住民の利便に応えることによって受診者数を増加させるかも知れないが、これも既に全国的に導入されつつある。ということで新たな知見ではなかった。

受診者の要因調査についての5論文からは受診率向上に直接言及するものはなかったが以下のことが示唆された。すなわち、1) 胃がん検診受診率に関連する因子として、家族のがん既往歴が正の相関を示したが、一方無自覚・無症状の「健常者」の受診率は低く、検診の本来の対象者を受診につなげる動機付けができていなかった。2) 受診者の心理学的分析によれば、胃癌の深刻さの認識を増長することは、受診率低下を来す可能性が示唆された。禁煙指導のような心理学的アプローチが今後必要となるのかもしれない。

このように、胃がん検診の受診率向上対策としては、1) 個別検診、2) 他の検診・健診と一緒に実施すること、3) 心理学的アプローチを行うことが有用と考えられた。

おわりに

以上のような点を地域における胃がん検診システムに取り込んで行く必要があると考える。

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ORIGINAL ARTICLE

Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: A case-control study

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Abstract

Objective. Pepsinogen testing is widely used in Japan as a method of screening for gastric cancer. To evaluate the efficacy of this method, a case-control study was conducted in a rural town in Hiroshima prefecture, Japan, where no previous pepsinogen testing had been performed. **Material and methods.** Three age- and gender-matched control subjects were randomly selected for each of 41 individuals who had died of gastric cancer. The three control subjects were selected from individuals who were living in the same area as the patient when gastric cancer was diagnosed. **Results.** The odds ratios for death from gastric cancer among control subjects screened within 1 and 2 years before the individuals were diagnosed versus those not screened were 0.238 (95% confidence interval (CI): 0.061–0.929), and 0.375 (95% CI: 0.155–0.905), respectively. **Conclusions.** The study results suggest that gastric cancer screening using the pepsinogen method may reduce mortality from gastric cancer.

Key Words: Gastric cancer, mortality, pepsinogen, screening

Introduction

Gastric cancer is a major cause of cancer death in many countries, including Japan. However, the mortality rate for gastric cancer has been decreasing in Japan, partly because of the introduction of mass screening programs [1]. The validity of indirect photofluorography, which is the conventional screening method used in Japan, has been recognized [1–5], but indirect photofluorography is associated with certain drawbacks, such as exposure to radiation and the need for specially trained technicians and special equipment, which limit its use. Therefore, simpler and more effective screening strategies for gastric cancer are needed.

Helicobacter pylori (*H. pylori*) infection can cause gastric inflammation, and glandular atrophy [6,7],

which affects serum concentration of pepsinogen (PG), is the major risk factor for atrophic gastritis [8–10]. Many gastric cancers develop in areas of severe and extensive atrophic gastritis [11–14]. We have reported a high prevalence of gastric neoplasms in populations with atrophic gastritis diagnosed on the basis of the serum PG concentration [15]. Thus, serum PG measurement can be applied as a gastric cancer screening method [16–20]. The accuracy of PG testing in comparison with photofluorography or endoscopy or with follow-up study has been reported [15–20]; however, there have been no reports on the effectiveness of such screening in reducing the number of deaths from gastric cancer. In the present case-control study, we evaluated the relation between testing and mortality due to gastric cancer.

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